Evidence Report/Technology Assessment
Number 200

Safety of Probiotics to Reduce Risk and Prevent or Treat Disease

Agency for Healthcare Research and Quality
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Evidence Based Practice

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Number 200

Safety of Probiotics to Reduce Risk and Prevent or Treat Disease

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA 290-2007-10062-I

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AHRQ Publication No. 11-E007
April 2011

This report is based on research conducted by the Southern California Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2007-10062-I). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this report. Service as a Technical Expert Panel member or peer reviewer should not be construed as agreeing with or endorsing the content of the report.

Suggested citation: Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JNV, Suttorp MJ, Johnsen B, Shanman R, Slusser W, Fu N, Smith A, Roth E, Polak J, Motala A, Perry T, Shekelle PG. Safety of Probiotics to Reduce Risk and Prevent or Treat Disease. Evidence Report/Technology Assessment No. 200. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2007-10062-I.) AHRQ Publication No. 11-E007. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Available at: www.ahrq.gov/clinic/tp/probiotictp.htm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This review was jointly sponsored by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS), the NIH National Center for Complementary and Alternative Medicine (NCCAM), and the Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

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Acknowledgments

We wish to thank Marguerite Klein, M.S. (National Institutes of Health [NIH] Office of Dietary Supplements [ODS]); Linda Duffy, Ph.D. (NIH National Center for Complementary and Alternative Medicine); Dan D. Levy, Ph.D. (Food and Drug Administration Center for Food Safety and Applied Nutrition); and Anne Thurn, Ph.D. (ODS) for their guidance and support. We wish to thank the members of the Technical Expert Panel: Michael Cabana, M.D., M.P.H.; Cara Fiore, Ph.D.; Barry Goldin, Ph.D.; Patricia L. Hibberd, M.D., Ph.D.; David Mills, Ph.D.; Mary Ellen Sanders, Ph.D.; Maija-Liisa Saxelin, Ph.D.; Alain L Servin, Ph.D.; and Jon A. Vanderhoof, M.D., for their helpful suggestions and recommendations. We also would like to thank Louis M.A. Akkermans, Ph.D.; Marc Besselink, M.D.; Daniel Buijs, M.Sc., and Ger Rijkers, Ph.D., who provided peer reviews of the draft report.

Safety of Probiotics to Reduce Risk and Prevent or Treat Disease

Structured Abstract

Objectives. To catalog what is known about the safety of interventions containing *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and/or *Bacillus* strains used as probiotic agents in research to reduce the risk of, prevent, or treat disease.

Data Sources. We searched 12 electronic databases, references of included studies, and pertinent reviews for studies addressing the safety of probiotics from database inception to August 2010 without language restriction.

Review Methods. We identified intervention studies on probiotics that reported the presence or absence of adverse health outcomes in human participants, without restriction by study design, participant type, or clinical field. We investigated the quantity, quality, and nature of adverse events.

Results. The search identified 11,977 publications, of which 622 studies were included in the review. In 235 studies, only nonspecific safety statements were made ("well tolerated"); the remaining 387 studies reported the presence or absence of specific adverse events. Interventions and adverse events were poorly documented.

A number of case studies described fungemia and some bacteremia potentially associated with administered probiotic organisms. Controlled trials did not monitor routinely for such infections and primarily reported on gastrointestinal adverse events. Based on reported adverse events, randomized controlled trials (RCTs) showed no statistically significantly increased relative risk (RR) of the overall number of experienced adverse events (RR 1.00; 95% confidence interval [CI]: 0.93, 1.07, p=0.999); gastrointestinal; infections; or other adverse events, including serious adverse events (RR 1.06; 95% CI: 0.97, 1.16; p=0.201), associated with short-term probiotic use compared to control group participants; long-term effects are largely unknown. Existing studies primarily examined *Lactobacillus* alone or in combination with other genera, often *Bifidobacterium*.

Few studies directly compared the safety among different intervention or participant characteristics. Indirect comparisons indicated that effects of delivery vehicles (e.g., yogurt, dairy) should be investigated further. Case studies suggested that participants with compromised health are most likely to experience adverse events associated with probiotics. However, RCTs in medium-risk and critically ill participants did not report a statistically significantly increased risk of adverse events compared to control group participants.

Conclusions. There is a lack of assessment and systematic reporting of adverse events in probiotic intervention studies, and interventions are poorly documented. The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence.

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Executive Summary

Introduction

The Agency for Healthcare Research and Quality (AHRQ) commissioned the Southern California Evidence-based Practice Center based at RAND to carry out a systematic review on the safety of probiotics used in research to reduce the risk of, prevent, or treat disease. The evidence report was jointly sponsored by the National Institutes of Health (NIH) Office of Dietary Supplements, the NIH National Center for Complementary and Alternative Medicine, and the Food and Drug Administration Center for Food Safety and Applied Nutrition.

Probiotics (literally, "for life") are bacteria or yeasts considered to confer a health benefit on the host organism. The review objective was to catalog what is known about the safety of interventions containing organisms from six different genera used as probiotic agents (*Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and *Bacillus*), alone or in combination, used to reduce the risk of, prevent, or treat disease in research studies.

This evidence report has a broad scope and was not restricted to specific interventions, specific patient groups, or specific clinical outcomes. The large number of included studies allowed unique analyses to explore adverse events reported to date in research on probiotics.

Methods

We searched 12 electronic databases (DARE, Cochrane Database of Systematic Reviews, CENTRAL, PubMed, Embase, CINAHL, AMED, MANTIS, TOXLINE, ToxFile, NTIS, and AGRICOLA) and scanned the references of included studies and pertinent reviews for studies addressing the safety of interventions using products containing microorganisms purported to have probiotic properties (henceforth called "probiotics") from database inception to August 2010 without language restriction.

We systematically identified studies monitoring the presence or absence of participants' adverse health outcomes, without restriction due to study design, participant, or clinical field. Any studies that assessed the effect of microorganisms used as probiotic agents and reported on an adverse health outcome (its presence or absence) were included. Two reviewers independently screened studies for inclusion, extracted data, and assessed their quality. We differentiated studies that addressed a specific adverse event from those with nonspecific safety statements.

We investigated the quantity of adverse events (number of participants with adverse events per treatment group, number of adverse event incidences per treatment group), the quality of the adverse events (all adverse events, serious adverse events), and the nature of adverse events (e.g., gastrointestinal events, infections). The review aims to answer a large number of questions pertaining to product and participant factors. Studies reporting direct comparisons (e.g., between two different probiotic organisms) were primarily sought; in addition, indirect evidence was analyzed in stratified analyses and meta-regressions.

Results

The review demonstrates that there is a large volume of literature on probiotics. However, the literature provided only limited evidence to address the questions the review set out to answer.

The literature search identified 11,981 publications, of which 2,189 were ordered as full-text publications after title and abstract screening and 622 studies were included in the review. Of these, 235 studies made only nonspecific safety statements (e.g., "the intervention was well tolerated") without indicating what kind of adverse events were monitored. The remaining 387 studies reported the presence or absence of one or more specific adverse events; these studies were abstracted in detail and used to answer the Key Questions. Across all included studies and treatment arms, 24,615 participants used a probiotic product.

The review considered reports without study design restrictions and included a large number of randomized controlled trials (RCTs); however, the majority were not designed to address safety. The quality of included studies varied greatly within study design categories. Adverse events were poorly documented, and the parameters that were monitored were often not stated. Interventions were poorly documented, lacking detail, for example, on the specific probiotic strain administered. Very few of the identified studies investigated *Saccharomyces* or *Streptococcus*, and even fewer *Enterococcus* or *Bacillus*; the majority of identified studies used *Lactobacillus*, alone or in combination with other genera, most often *Bifidobacterium*.

To estimate the proportion of existing studies of probiotic organisms found in the literature that are included in this safety review, we noted all RCTs of probiotics that were found in our searches that reported on patient outcomes. Of this pool of potentially relevant RCTs, 58 percent met inclusion criteria for the review (i.e., made a nonspecific safety statement or reported the presence or absence of a specific adverse event). The remaining RCTs did not address the safety of probiotics as defined in this evidence review.

Key Questions

Key Question 1. What is the evidence that the active and lyophilized forms of probiotics (*Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus*) as single ingredients or in combination with other probiotics or prebiotics in all delivery vehicles (and formulations) when used to cure, treat, mitigate, or prevent a disease or reduce disease risk are safe in the short term? In the long term?

Case studies indicated that fungemia, bacteremia, sepsis, and other infections may be associated with administered probiotic organisms; the ability to reliably determine whether administered strains match the clinical isolate is now possible through DNA-based methods.

None of the identified case series, controlled clinical trials, or parallel and crossover RCTs reported an infection caused by the administered probiotic organisms. However, studies seldom reported that they monitored for infections of the types identified in case reports. In fact, most did not state what adverse events were monitored and did not systematically address the safety of the probiotic products.

Across parallel RCTs there was no indication that the quantity of reported adverse events was increased in short-term probiotic intervention arms compared to control groups, based on the relative risk (RR) of the number of participants with adverse events (RR 0.98; 95% confidence interval [CI]: 0.93, 1.04, p=0.537; 121 RCTs) as well as the number of adverse-event incidences reported in each treatment group (RR 1.00; 95% CI: 0.93, 1.07, p=0.999; 208 RCTs). The current available evidence does not suggest a widespread risk of adverse events associated with

probiotics, but future studies that explicitly monitor for the issues of concern are needed to quantify the actual risk of specific adverse events in intervention studies.

Key Question 2. What are characteristics and associations of the reported harms in Question 1?

Across all included studies, the most commonly reported adverse events were gastrointestinal in nature. This was followed by reported infections and infestations. The third most common category was the "other" category for symptoms that could not be assigned to a specific organ system or type of adverse event.

Across identified RCTs, there was no indication that participants using probiotic organisms experienced statistically significantly more gastrointestinal (RR 1.03; 95% CI: 0.89, 1.18, p=0.693; 126 RCTs), infections (RR 1.00; 95% CI: 0.87, 1.16, p=0.967; 65 RCTs), or other adverse events (RR 1.01; 95% CI: 0.91 1.12, p=0.923, 131 RCTs) compared to control group participants.

Studies rarely reported efforts to monitor adverse events specific to probiotic products. Hence, safety evaluations may change with future, more targeted assessment of adverse events in intervention studies.

Key Question 3. What is the evidence that harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* differ by product and delivery characteristics?

The lack of detail in the description of administered probiotic organisms in most studies hindered evaluations of the safety. Many studies did not specify which probiotic strains were investigated, nor was there indication that intervention preparations were tested for identity of the included organisms, quantity, viability, or contaminants.

Stratified analyses by probiotic genus showed no increased risk of adverse events among the probiotic group compared to a control group in RCTs using interventions reported to contain exclusively *Lactobacillus* (RR 0.98; 95% CI: 0.87, 1.11; p=0.785), *Bifidobacterium* (RR 0.92; 95% CI: 0.82, 1.03; p=0.141), *Saccharomyces* (RR 1.00; 95% CI: 0.46, 2.18; p=0.993), *Streptococcus* (0.99; 95% CI: 0.78, 1.25; p=0.907), *Enterococcus* (RR 0.85; 95% CI: 0.47, 1.54; p=0.588), or *Bacillus* (0.99; 95% CI: 0.44, 2.22; p=0.973) strains. A meta-regression comparing the relative risk ratio associated with the genera indicated a statistically significantly higher risk for *Streptococcus* strains compared with the other genera; however, this indirect comparison is based on a small number of studies that investigated *Streptococcus*, *Enterococcus,* or *Bacillus* interventions. Direct (head-to-head) comparisons of genera, species, strains, or delivery vehicles are largely absent in the literature.

There was some indication across studies that safety findings may differ by delivery vehicle. Intervention participants in studies in which yogurt or other dairy products were administered were more likely to experience adverse events compared with control group participants (RR 1.37; 95% CI: 1.05, 1.79; p=0.022) based on the number of adverse event incidences reported across groups in a subgroup analysis. However, studies directly comparing delivery vehicles are missing.

We did not find conclusive evidence in the existing literature that interventions with a mixture of different organisms reported more adverse events than studies using one probiotic strain only or evidence that synbiotics (mixtures of prebiotics and probiotics) differ from probiotics; however, there is a lack of direct comparisons.

Key Question 4. How do the harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* vary based on (a) dose; (b) timing; (c) mode of administration; (d) age, gender, ethnicity, disease or immunologic status; (e) relationship to efficacy?

Very few studies overall explored the effect of intervention or participant characteristics on safety. To summarize, in the few studies that reported on the time of onset of gastrointestinal effects, most effects were observed in the first 3 days of treatment. The onset of infections tended to occur 1 week to several weeks after initiation of probiotics use; however, this information is primarily derived from case studies and was not systematically reported.

In indirect comparisons across studies, we found no evidence that a particular mechanism or route of administration of probiotic organisms was associated with an increased risk of an adverse event in intervention participants relative to control group participants. Stratified analyses and meta-regressions showed no increased risk of adverse events for children (RR 0.96; 95% CI: 0.88, 1.04; p=0.296, 35 RCTs), adults (RR 0.97; 95% CI: 0.79, 1.19; p=0.745, 40 RCTs), or elderly (RR 0.94; 95% CI: 0.82, 1.08; p=0.367, 4 RCTs) participants compared with adverse events observed in corresponding control groups; however, it has to be noted that only very few studies were identified that reported on elderly participants.

There was some indication that health status is associated with the experience of an adverse event when using probiotics. Case studies reporting serious adverse events described health-compromised, not generally healthy participants who contracted (most often) a serious infection potentially caused by probiotic organisms. However, subgroup analyses of RCTs in medium health-compromised participants (RR 1.03; 95% CI: 0.94, 1.13; p=0.491) and critically ill patients (RR 0.79; 95% CI: 0.51, 1.22; p=0.286) did not show a statistically significantly increased risk of experiencing adverse events for intervention participants compared with control group participants with similar patient characteristics.

Key Question 5. How often does harm associated with *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* lead to hospital admission or lengthened hospitalization?

While several case studies reported hospitalizations associated with the consumption of a product including *Saccharomyces, Lactobacillus,* or *Bacillus* strains, none of the case series or controlled trials reported that a probiotics intervention led to a hospitalization in the intervention participants. However, the number of hospitalizations due to adverse events was only explicitly reported on in a few of the included studies, and older publications may not have associated a hospitalization with probiotics intake.

RCTs reporting on the presence or absence of serious adverse events showed that differences across probiotic and control group participants were not statistically significant (RR 1.06; 95% CI: 0.97, 1.16; p=0.201, 66 RCTs). However, this result is primarily based on *Lactobacillus* interventions, and a few studies investigating *Saccharomyces* and *Bifidobacterium*; there was a lack of studies reporting on the presence or absence of serious adverse events for other genera.

Key Question 6. How does harm associated with *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* relate to use of concomitant antibiotics, confounding diet therapies, corticosteroid use, immune suppressants, or other potential confounders?

We did not identify studies that addressed possible interactions or confounders of probiotics interventions. Although the risk of adverse events in general might be higher in individuals taking multiple medications, subgroup analyses of studies in which the intervention participants as well as the control group participants received antibiotics (RR 1.07; 95% CI: 0.94, 1.23; p=0.271) or corticosteroids (RR 1.04; 95% CI: 0.88, 1.22; p=0.650) found no statistically significant increased risk of adverse effects among intervention participants. There were too few studies to explore interactions with concomitant diet therapies, and studies in participants using immune suppressants were also largely absent from the existing literature.

Future Research

Future studies need to characterize the intervention preparations in more detail. As identification methods progress, the reporting should include verification with DNA-based methods to identify the individual strains included in preparation, their potency and viability, and any potential confounders. The majority of existing studies report on *Lactobacillus*, alone or in combination with other genera, most commonly *Bifidobacterium* strains, and more studies are needed to explore potential adverse events associated with interventions that include the genera *Enterococcus* and *Bacillus*, in addition to studies on *Streptococcus* species selected for their probiotic properties, as well as studies on the use of *Saccharomyces* in some patient groups.

Studies should describe which adverse events were monitored to allow a clearer understanding of the presence and absence of adverse events in probiotics intervention studies. The reporting of adverse events should follow reporting guidelines such as the extension of the CONSORT statement for harms. In addition, there are comprehensive systems for cataloging adverse events, such as the Common Terminology Criteria for Adverse Events system. Monitored harms should include infections with probiotics organisms as well as treatment failures in order to be able to quantify the risk for participants in intervention studies. Critical outcomes, such as all-cause mortality, should be assessed and reported in primary studies, and reviews should consider all studies measuring the outcome regardless of whether the study was conducted to evaluate the efficacy of the intervention or the occurrence of adverse events.

Long-term effects of probiotic interventions are largely unknown, and there is a need to evaluate long-term interventions. In addition, large cohort studies following self-selected use of probiotic organisms are needed to fully understand the efficacy and safety of probiotics among representative populations.

Currently, few studies address complex questions about probiotic safety, such as interactions of participant or intervention characteristics with the use of probiotic products. The effect of product, intervention, or participant characteristics should be addressed with appropriate multivariate analyses. There is also indication that participants with compromised health should be monitored closely for potential adverse events associated with the use of probiotic products. Studies evaluating effects on elderly participants are largely absent from the literature, and the effects of delivery vehicles should be investigated systematically.

Conclusions

There is a lack of assessment and systematic reporting of adverse events in probiotic intervention studies, and interventions are poorly documented. RCTs and case studies diverge in the outcomes they report. The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer specific questions on the safety of probiotic interventions with confidence.

Introduction

The Agency for Healthcare Research and Quality (AHRQ) has commissioned the Southern California Evidence-based Practice Center based at RAND to carry out a systematic review on the safety of products containing microorganisms believed to have probiotic properties (henceforth called probiotics or products containing probiotics). This review was jointly sponsored by the National Institutes of Health (NIH) Office of Dietary Supplements, the NIH National Center for Complementary and Alternative Medicine, and the Food and Drug Administration Center for Food Safety and Applied Nutrition.

Background

Probiotics (literally, "for life") are microorganisms purported to have a health benefit on the host organism. The definition of what is a probiotic has evolved as the sciences of microbiology, medicine, and the manufacturing industries have matured. According to one definition offered by an expert committee convened by the Food and Agriculture Organization of the United Nations and the World Health Organization, probiotic organisms are live microorganisms that when administered in adequate amounts confer a health benefit on the host (FAO/WHO, 2001). This definition explicitly restricts what can be considered a probiotic to live organisms. Other definitions do not emphasize the viability of the microorganisms and would include heat-killed preparations (e.g., Salminen, Ouwehand, Benno, & Lee, 1999). Defining probiotics is challenging because of the limits in our understanding of how organisms benefit the human host, the apparent variation in what may constitute a beneficial balance for digestion and other physiological processes, the effects of probiotic organisms on the normal gut environment, and our limited understanding of the gut ecosystem (Schmid, 2006).

The genera of bacteria and fungi that have been employed for their probiotic properties are most commonly species of *Lactobacillus* and *Bifidobacterium*; other bacterial genera, such as *Streptococcus, Enterococcus*, and *Bacillus*, and species of the yeast genus *Saccharomyces* have also been studied. Probiotic properties of genera, species, and strains may vary according to the indication. Related to probiotic organisms, prebiotics are food products defined as nondigestible food ingredients that benefit the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improve host health. Synbiotics are preparations in which probiotic organisms and prebiotics are combined, presumably to form a synergistic relationship.

The intentional use of microorganisms in the preparation of foods as well as the belief in their health-promoting properties has a long history. Species of the lactic acid bacterium genus *Lactobacillus* have been used for thousands of years to preserve dairy products by converting milk to yogurt; likewise, the yeast, *Saccharomyces cerevisiae*, has long been used for leavening bread and for fermenting grains and fruits to make spirits. Various other fungi (molds) have long been known for their use in cheesemaking. *Bacillus subtilis*, a soil bacterium, has long been used to ferment soy beans to make the Japanese staple food natto. Mixtures of microorganisms have been used to treat infections topically and systemically since ancient times. The use of probiotics to prevent and treat gastrointestinal disorders in particular has been proposed, for example, by Metchnikoff in the 1890s, using *Lactobacillus* strains to restore normal gastrointestinal microbial balance. The use of *Lactobacillus* strains to treat urogenital infections is often attributed to Newman, who published a paper in 1915 on this topic (McGroarty, 1993). More recently, the use

of the commensal bacterium, *Bifidobacterium*, has been advocated to promote immune and gastrointestinal function in infants. Probiotic strains of *Streptococcus* have been used in an attempt to prevent and treat dental disease and gastrointestinal disorders. Probiotic strains of *Enterococcus* have also been used to treat gastrointestinal infections. *Bacillus subtilis* has fungicidal properties and, for example, was used as a treatment for gastrointestinal complaints prior to the introduction of sulfur-based antibiotics. Regarding these last two examples, particular concerns have been raised about the safety of the genera *Enterococcus* and *Bacillus*, both of which include pathogenic species.

Depending on the form and the country in which they are administered or used, probiotic products are classified as any one of several different entities: dietary supplements, foods, food components, or pharmaceuticals. Each of these categories is subject to entirely different regulations and burdens of proof regarding the demonstration of a health benefit as well as safety, and these regulations and guidelines differ by country (Sanders, 2010; Venugopalan, 2010). Further complicating the current picture is that very little is known about the quantities required for the various genera, species, and strains to show probiotic properties.

The scientific and popular literature includes numerous reviews on the efficacy or effectiveness of probiotic organisms for treating or preventing a variety of conditions. However, despite their popularity, questions remain about the efficacy and effectiveness of probiotics; published reports for specific conditions often provide conflicting results, and the efficacy and effectiveness of probiotics is quite likely to be strain and indication specific. In 2010, the European Food Safety Authority denied the merit of multiple health claims filed on behalf of probiotic products, citing lack of scientific basis (EFSA, 2010).

Regardless of the evidence base for the efficacy and effectiveness of products containing probiotics, the widespread availability and popularity of products promoted as containing probiotic organisms indicate that their safety warrants further investigation. Probiotic organisms added to foods (i.e., yogurt and some infant formulas) have been described by some authors as "generally recognized as safe" (GRAS). Food ingredients considered GRAS are those affirmed or apparently affirmed by their manufacturers as meeting the requirements for the GRAS exemption from the requirement for regulation as a food additive. This term, defined in sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act, applies to any substance that is intentionally added to food and has been exempted from premarket approval because it is "generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use." Authors often cite the fact that lactic acid bacteria have been used for preservation of food by fermentation for thousands of years as evidence of their safety (World Gastroenterology Organisation, 2008). However, the GRAS designation can be applied only to specified uses of a specific ingredient. Other uses, particularly if they are based on higher exposure or exposure to an ingredient with very different properties, may not be included in the original GRAS designation.

Advances in microbiology and molecular biology, along with the adoption of organisms not previously used as probiotics, have contributed to a growing concern about the potential safety of these microorganisms. Specific concerns include the isolation of administered probiotic organisms from infection sites, and the possibility of gene transfer between probiotic organisms and bacteria or fungi dwelling in the digestive tract and antibiotic resistance shown in in vitro studies. A number of cases of infection have been documented that resemble closely the strains given as probiotic agents to the infected individuals or persons in their vicinity. Such concerns suggest that the pathogenicity, infectivity, toxicity, and intrinsic properties of the organisms may

require closer study (Ishibashi, 2001). Liong (2008) concluded from a review of the literature that translocation and infection reports associated with use of probiotics deserve further investigation and should become a part of safety assessments so that the negative effects of probiotics do not outweigh the benefits. Recent trials and reviews that failed to show the efficacy of probiotics and in some cases report an increased risk of undesirable effects associated with probiotic interventions (Besselink, 2008; Whelan, 2010) also point to a closer look into the safety of probiotics, in particular for patients with compromised health.

In order to make informed decisions about the use of probiotic organisms, it would thus appear helpful at this point to assess the evidence for their safety across clinical areas. To date, no comprehensive systematic review has synthesized the available evidence of adverse symptomatic health outcomes in human participants.

Project Purpose

The review set out to answer a number of research questions posed by the sponsors of the evidence review.

Key Questions

1. What is the evidence that the active (e.g., live or viable) and lyophilized forms of probiotics (*Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus*) as single ingredients or in combination with other probiotics or prebiotics in all delivery vehicles (and formulations) when used to cure, treat, mitigate, or prevent a disease or reduce disease risk are safe in the short term? Long term?
    a. What safety parameters are collected in clinical studies (Phases I-IV)?
    b. What harms are reported in clinical studies (Phases I-IV)?
    c. What harms are reported in case reports?
    d. What safety parameters are collected in population surveillance studies and other observational studies, and do these include only standard clinical safety parameters (e.g., standard blood chemistry profiles) or also expanded laboratory or clinical testing unique to the use of probiotics?
    e. What harms are reported in population surveillance studies and other observational studies?
    f. What harms are reported in human mechanistic studies?
    g. Do the studies describe an antibiotic therapy designed to treat unintended pathology caused by the administered organism?
    h. Do the studies describe methods for recovery of the administered organism from either the gastrointestinal tract or serum?
2. What are characteristics and associations of the reported harms in Question 1?
    a. What interactions between probiotics and medications are reported?
    b. What harms related to acquired antibiotic resistance and/or transferability are reported?
    c. What is the nature of harms (e.g., toxicogenic, immunologic, hematologic, deleterious physiologic or metabolic activity, allergic, blood infections, hematocytometric values, liver and renal function enterotoxin, production, proteases, or opportunistic infection, etc.), and do these include only standard harms or also harms that might be uniquely applicable to the use of a probiotic?

3. What is the evidence that harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* differ by product and delivery characteristics?
    a. What is the scientific evidence that harms differ by delivery vehicle including excipients or novel delivery vehicles?
    b. What is the scientific evidence that harms differ by genus, species, and strain (including intraspecies strain variations)?
    c. What is the scientific evidence that harms differ between active and lyophilized forms of probiotics?
    d. Does harm differ by products containing a single probiotic versus a mixture of probiotics?
    e. Does harm differ by products containing only probiotics and those containing a mixture of probiotics and prebiotics?
4. How do the harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* vary based on (a) dose (cfu); (b) timing; (c) mode of administration (e.g., catheter); (d) age (all ages, including infants), gender, ethnicity, disease or immunologic status of the patient; (e) relationship to efficacy?
    a. Is there a threshold or dose-response relationship between probiotics and harm? Does the duration of intervention relate to harm?
    b. Is there a relationship between time of onset of harm and time of probiotic administration (e.g., prior to onset of disease under study, after disease onset)? How does time of exposure affect harm? Is harm sustained after the intervention or exposure stops?
    c. Does the route of administration (e.g., orally, jejunostomy tube, central venous catheter) relate to harm?
    d. How does harm relate to subpopulations, including different age groups (specifically including neonates and infants under age 24 months), men and women, ethnic/race subgroups, or health status (healthy to high risk) individuals?
    e. Do randomized controlled studies that report harm show efficacy or no efficacy?
5. How often does harm associated with *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* lead to hospital admission or lengthened hospitalization?
6. How does harm associated with *Lactobacillus, Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* relate to use of concomitant antibiotics, confounding diet therapies, corticosteroid use, immune suppressants, or other potential confounders?

Scope

This review on the safety of probiotics is explicitly exploratory in nature. Therefore, a number of clarifications are warranted regarding what the review set out to achieve and what questions may have to be addressed in future research.

First, because little evidence currently suggests the kinds of potential harms that should be investigated in a review on the safety of probiotics, the safety outcomes considered for this review were explicitly not specified a priori; instead, all reported adverse events were included in the review. Theoretically, a selection of particular kinds of harms could be guided by the nature of the intervention—for example, the exposure to bacteria and yeasts suggests monitoring infections—and as a general research approach, serious adverse events should have priority. But given the lack of any prior synthesis on the specific risks of probiotic organisms for human

participants, a broad, unrestricted overview of what has been assessed in the literature and what has been reported appeared most informative. Thus, the review aimed to identify the adverse events reported in the literature, without restriction to specific outcomes of interest, as further outlined in the inclusion criteria, with one limitation: The focus was on health outcomes, that is, symptomatic outcomes and/or clinically relevant outcomes, rather than on intermediate outcomes or in vitro results. In this review we explore the quantity, the quality, and the nature of the adverse events as outlined in the methods section.

This report is not an efficacy or effectiveness review investigating the usefulness of probiotic organisms for preventing adverse events caused by other treatments such as antibiotic treatment. That is, studies in which efficacy outcomes were identical with adverse events (e.g., prevention of antibiotic-induced diarrhea) were not considered for this review, as further outlined in the inclusion criteria. This restriction required careful review of individual studies, but has also been imposed in other safety reviews (e.g., Pitrou, Boutron, Ahmad & Ravand, 2009), and an overview of the efficacy and effectiveness of probiotic organisms for the prevention of adverse events from other treatments was outside the resources and scope of this project. We considered failed effectiveness outcomes only in those cases where this was explicitly highlighted by the study authors as one of the main results of the study.

Throughout this report we use the term "harm" and "adverse event" interchangeably. We explicitly avoid the term "adverse effects," as it implies a causal relationship between harm and intervention. In most included studies, there are multiple alternative explanations for the encountered adverse events; hence we only list the encountered events per treatment group.

This review focuses on published literature. A substantial number of peer-reviewed articles reporting on studies of probiotics have been published in scientific journals. Although the pursuit of unpublished data (for example through approaching manufacturers of probiotic products) might be desirable, the approach taken for this exploratory review was to summarize the existing literature in the public domain to develop a clear picture of the readily available body of evidence. The data sources are outlined in the search strategy, and the implications of the search strategy are further addressed in the discussion section.

Furthermore, the review aimed to capture the safety of organisms—*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus,* and *Bacillus*—when used as probiotic agents, rather than the safety of any exposure to any member of these genera of microbiological organisms. The search strategy primarily aimed to identify *studies of probiotics*, rather than aiming to identify every study that investigated the effects of the above bacterial or fungal organisms, such as exposure to *Streptococcus* bacteria strains. Studies were included in the review if they were described as probiotic studies, without further restriction to particular dose; demonstrated health benefits; genera, species, or strains of known quality; rather, all studies investigating the effect of purposeful intake of probiotic organisms of the genera of interest were considered.

However, a reported intervention was part of the inclusion criteria for this review as outlined in detail in the inclusion criteria section. Publications reporting incidences of infections, such as documented cases of *Lactobacillus* infections, were included in the review only if an intervention prior to the infection was reported, e.g., the probiotic organisms were purposefully consumed or administered. Studies were not restricted to investigator-controlled studies; observational studies of participants using probiotic organisms were also eligible for inclusion. We also did not restrict the review to products that would be classified as dietary supplements, foods, food ingredients, or pharmaceuticals.

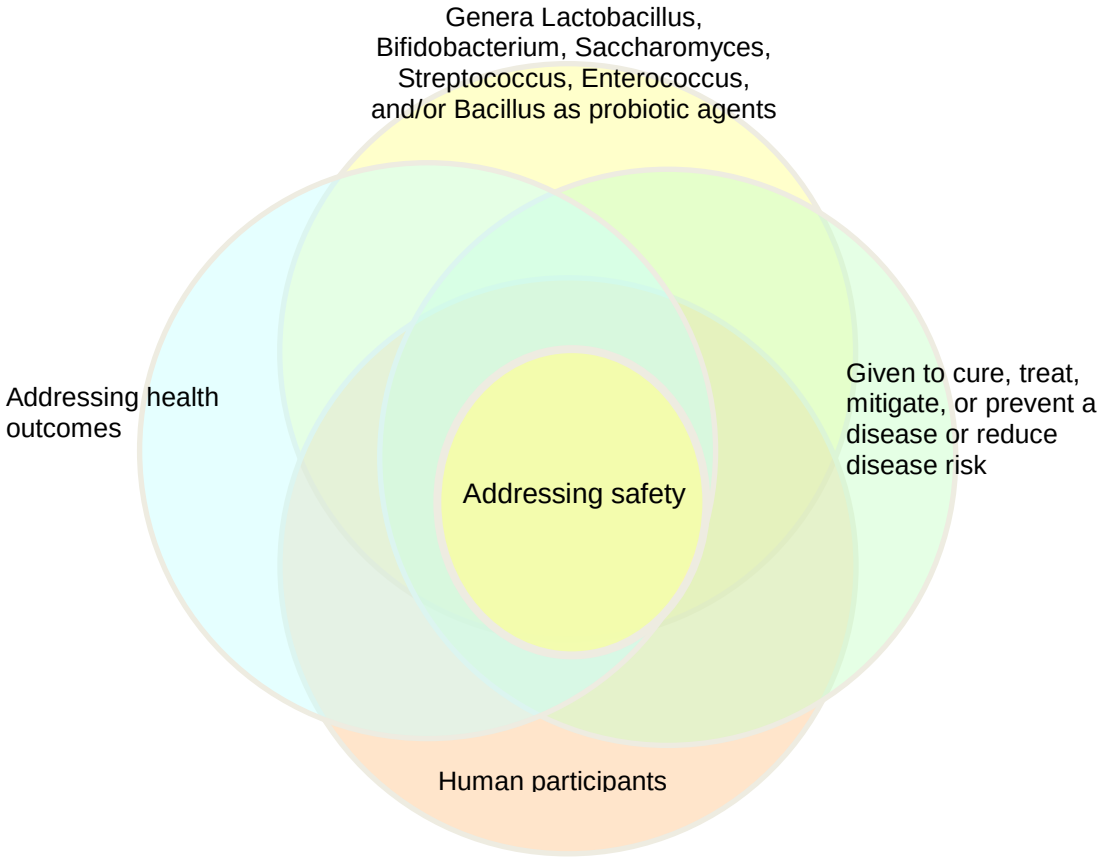
Finally, the review summarizes the existing evidence from studies in human participants only; animal studies and in vitro studies were outside the scope of the review. As outlined, the focus was on adverse events encountered in research studies that used probiotics to reduce the risk, prevent, or treat disease in human participants.

In summary, the review aimed to document what is currently known about the safety of probiotics in the existing *published* research literature on *interventions*, assuming an inclusive definition of *safety* and inclusive definition of *probiotics*. The purpose of the project was to catalog what is known about the safety of probiotics, in particular *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* organisms, used in research to reduce the risk of, prevent, or treat disease. The literature review also assessed the quality and completeness of the available information and our confidence in interpreting this information. The overview aimed to provide information relevant to practitioners, researchers, and regulators for assessing the safety of probiotic administration as well as to identify priorities or needs for future research.

Analytic Framework

Figure 1 shows the universe of studies from which the studies included in this review stem were drawn. Only studies in human participants; studies that used the genera *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus* as probiotic agents to cure, treat, mitigate, or prevent a disease or reduce the risk of a disease; and studies that addressed health outcomes were sought. Within these studies, we included those studies that addressed the safety of probiotics. All studies that contained vague safety statements as well as those that addressed specific harms, adverse events, adverse effects, side effects, or unintended effects were considered.

Figure 1. Included studies



All Key Questions were answered with studies within the above outlined universe of studies

Methods

Electronic Search for Literature Review

A pilot literature search undertaken at the outset of the project revealed that whereas safety aspects are not a research priority in the existing probiotics literature, many studies undertake a limited safety analysis as part of assessing efficacy. However, the inclusion of safety results in a publication was rarely indicated in the title or abstract of the publication or referred to in the keywords assigned by the individual electronic database (a finding that is not unique to the research field of probiotics). Although search filters exist for effectiveness studies in some clinical areas, filters to address adverse events tend not to be successful in reliably identifying relevant studies. And because the volume of literature on the efficacy of probiotics, both original research and reviews, was vast, it was necessary to conduct a careful review of the full text of a large number of publications to identify the relevant body of research results on the safety of probiotics.

The chosen search strategy was very inclusive in order not to miss potentially relevant publications. The truncated term "probiotic" and the term "synbiotic" were used to adequately reflect the scope of this project (see Appendix A). The term "prebiotic" also appeared initially useful and was added to the search strategy. The electronic search was not restricted to the genera specified in the key questions in order not to miss articles that did not mention the genus in the title, abstract, or keywords of the publication. The genera alone (without reference to their use as probiotics) were not useful search terms, as their inclusion added a very large number of irrelevant publications (e.g., all studies on *Bacillus* infections). Given the large number of probiotic and synbiotic products marketed as dietary supplements, foods, food ingredients, or drugs, the search also did not rely on product names. Many studies used mixtures that were not commercially obtained or available. Thus, an incomplete list of commercial product names might have introduced bias into the selection of studies for review. The identified manufacturers of probiotic products are listed in Appendix A.

The searches were performed without restriction by publication year or language, taking into consideration that a substantial proportion of research is published in Asian language publications. While uncertainty exists regarding whether the strains investigated in these studies are similar to those common in the U.S. market, these studies need to be assessed. The review also was not restricted with regard to study design; hence, no methodological search filter was applied. The review was restricted to studies in human participants. Rather than searching for studies that were indexed as studies in human participants, the electronic search was designed to exclude only publications that were indexed by the individual databases as studies in animals (where possible). The intent was to avoid missing studies that were not yet indexed accordingly or were misclassified.

Databases

The following databases were searched as sources for safety data on probiotics:

- DARE (Database of Abstracts of Reviews of Effects)
- Cochrane library of systematic reviews
- CENTRAL (Cochrane Central Register of Controlled Trials)

- PubMed (National Library of Medicine, includes MEDLINE) (Figure 2 depicts the PubMed search strategy)
- Embase (Biomedical and pharmacological bibliographic database)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- AMED (Allied and Complementary Medicine)
- MANTIS (Manual, Alternative and Natural Therapy Index System)
- TOXLINE (biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals)
- ToxFile (biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals)
- NTIS (National Technical Information Service)
- AGRICOLA (agricultural journals)

Figure 2. PubMed search strategy

PubMed – 1966-2010
probiotic* OR prebiotic* OR synbiotic*
NOT
animals NOT humans

Other Sources

The electronic search was complemented by screening the references of included studies and the references of relevant reviews. In addition, we hand searched the International Journal of Probiotics and Prebiotics. Clinicaltrials.gov was searched during the update searches. The database lists a number of registered probiotic trials. Personal files from Evidence-based Practice Center projects on related topics were also scanned to identify additional relevant studies. The safety data from MedWatch; the Web pages of the Food and Drug Administration (FDA), including Center for Food Safety and Applied Nutrition CFSAN and the Center for Biologics Evaluation and Reasearch; and the CFSAN Adverse Event Reporting System database were also explored but did not contribute studies eligible for inclusion in the review.

Inclusion Screening

This section describes the inclusion criteria for the review.

Inclusion Criteria

- Participants:
  - Studies in human participants were eligible for inclusion in the review; animal and in vitro studies were excluded
- Intervention:
  - Studies using probiotics or synbiotics to cure, treat, mitigate, or prevent a disease or reduce disease risk (including probiotic drinks or supplements “to boost immunity” or similar) were eligible for inclusion in the review. The organisms had to be taken purposefully, and documented cases of infections were included only if use of a probiotic or synbiotic intervention was reported
- Comparator and Study Design:

- Original research studies were considered without study design restriction, but uncontrolled studies were included only when they explicitly addressed the effect of probiotic or synbiotic intake. Studies primarily testing the effects of a combination of a probiotic and another medication that could also result in adverse events were included only if the study also reported on a group receiving that medication without probiotics or the study explicitly addressed the safety of probiotic intake:
    - Randomized controlled trials (RCTs), clinical controlled trials, and cohort studies with at least two arms comparing the use of probiotics or synbiotics to placebo, other treatment, or other types of probiotics or synbiotics
    - Before–after studies and time series with measurements before and after introducing probiotics or synbiotics
    - Case series (no comparator) that address the effects of probiotics or synbiotics
    - Case reports that explicitly address the effects of probiotics or synbiotics
    - Mechanistic probiotics or synbiotics studies of all designs addressing patient health outcomes
    - Case-control studies that focus on probiotics or synbiotics as predictors of an adverse event in participants
- Outcomes:
    - Studies that addressed adverse patient health outcomes, particularly symptomatic outcomes, were included in the review. Studies that reported only intermediate outcomes such as gene transfer or gastric colonization without reference to participants' negative health status were not eligible for inclusion in the review. Dislike or the taste of the product was not considered eligible adverse events. Studies where efficacy outcomes were identical to adverse events (e.g., efficacy of probiotics in the treatment of diarrhea; efficacy of probiotics in the prevention or reduction of negative health outcomes caused by antibiotic treatment) were excluded unless the safety of the probiotics was also explicitly addressed in the publication. As no effectiveness review was undertaken in conjunction with the safety review exacerbations of primary outcomes, such as exacerbation instead of improvement in allergy symptoms in some participants, compared to baseline or in comparison to a control group (treatment failures), were also not included in the review unless these results were one of the main findings of the publication and highlighted in the abstract of the publication
- Genus:
    - Studies investigating *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and/or *Bacillus* as probiotic agents alone or in combination with other ingredients were eligible for inclusion in the review. Studies were excluded if the genera used could not be verified. Studies administering yogurt or milk products containing only *Lactobacillus* and/or *Streptococcus* organisms as starter cultures were not included unless an additional probiotic strain was added to the product. We included studies regardless of whether authors stated that viable organisms were used but interventions of explicitly heat-killed or inactivated organisms were excluded, as the criterion of viability is part of the established definitions of probiotics and interventions using heat-killed forms rarely labeled these preparations "probiotics."

Title and Abstract Inclusion Screening

The initial relevance screening was performed using the reference manager software Endnote. Endnote allows the import of titles, abstracts, and keywords for each reference identified through electronic searches. All identified records were screened independently by two reviewers in order not to miss potentially relevant studies. Records deemed by at least one reviewer to potentially report safety information were ordered as full text copies for further scrutiny.

Identifying safety data is challenging since most publications focus on the clinical efficacy of the intervention in question with either no, sparse, or incomplete and nonsystematic reporting of safety aspects. The review team followed inclusive decision rules for ordering full paper copies of publications in order not to miss studies that might report on adverse events in the full publication but did not indicate so in the title, abstract, or keywords of the publication. In summary, we ordered all publications that targeted the safety of probiotics as full-text articles. In addition, all empirical studies on probiotics in humans that addressed health outcomes were ordered to check the full text publication for data on the safety of probiotics.

Publications that clearly addressed animal studies or in vitro studies, comments, opinion pieces without data, unsystematic reviews not specific to safety, and publications that did not address health topics were excluded.

Full Text Inclusion Screening

Two reviewers independently screened the selected full text publications using a standardized form outlining the inclusion criteria. Any disagreement was resolved through discussion, through consultation with the review team, or with other input such as the local content expert or the technical expert panel (TEP).

Studies identified through reference mining were included in the review if they met all the above mentioned inclusion criteria.

The inclusion screening process also identified all RCTs reporting patient health outcomes in human participants using probiotics or synbiotics of the genus *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* or *Bacillus* to cure, treat, mitigate, or prevent a disease or reduce disease risk compared to placebo, another probiotic, prebiotic or synbiotic, other, or no intervention. The number of such relevant RCTs was determined as a denominator for assessing the proportion of those that addressed safety.

Data Abstraction and Quality Assessment

This report considered two different kinds of publications. Our primary interest was in identifying publications that addressed specific adverse events. However, a number of publications were found that addressed the safety of probiotics but did not report the presence or absence of specific adverse events.

For papers that did not address specific adverse events but instead provided only general statements such as “well tolerated,” “no adverse events,” or “two participants dropped out due to adverse events” without specifying which adverse events were assessed, the data abstraction was minimal. These studies were included for reasons of completeness but their informational value for this evidence review is minimal due to the lack of outcome determination.

For studies addressing specific adverse events, detailed information was extracted regarding the type of study, the participants, the product containing probiotics or synbiotics, the assessed

adverse events, and the results of the study regarding the safety of the intervention (see abstraction form in Appendix B). The data were abstracted using defined categories where possible and appropriate, and, if not, using free text. These studies were the primary basis for answering the research question addressed in this review. All extracted information is documented for each study in the evidence tables (Appendix C).

Multiple publications of the same study were counted (and extracted, quality assessed and analyzed) as one study to ensure that the same participants did not enter the analyses multiple times. Publications of a particular study were defined by the investigated participant population. Publications that reported the results of two different studies were counted as different studies if both studies met the inclusion criteria of the review (human participants; eligible study design; report of an intervention; *Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus, Streptococcus,* and *Bacillus* used as probiotic agents; adverse health outcome addressed).

For studies with more than one arm, we selected a main treatment arm (arm 1 in evidence tables) and a control group that was most similar to the main treatment arm but did not receive probiotics or synbiotics if available (arm 2 in evidence tables). If additional probiotic and synbiotic groups (arms) were included in the study (including interventions of heat-killed or inactivated organisms), those data are shown as arm 3 and 4 in the evidence tables.

We extracted data on all *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* or *Bacillus* strains contained in the intervention preparations regardless of the probiotic qualities of the strain. If an intervention included a yogurt starter culture with a probiotic strain added, we listed the starter cultures alongside the probiotics strain, if that information was provided. Studies were inconsistent in differentiating strains with assumed probiotic properties from strains without assumed probiotics properties (the product was assumed to have probiotic effects, without attributing these effects to individual strains); hence, we recorded all reported strains. Initially, we had considered contacting authors of primary studies for missing information on the identity of probiotic organisms, that is, whether the administered probiotics strains were verified in the study. However, the quality of reporting on the administered probiotic organisms was rather poor overall, and our resources did not permit contacting what would have been the majority of study authors for this extensive literature review. Therefore, study details were extracted as reported.

Adverse events. Regarding safety data, we extracted any adverse event reported in the publication and assessed the quantity, quality, and nature of the adverse events. We considered reasons for dropouts as well as adverse events reported for participants finishing the study. We extracted all adverse events for all treatment groups, including those that study authors did not consider related to the intervention. Because such judgments are difficult to make and may depend on the development of the clinical field, we report the complete set of adverse events. Reports of individual treatment failures were not extracted, as these outcomes should be addressed systematically in an effectiveness review extracting all data for the selected outcome. We extracted the number of incidences of the individual adverse events and the number of participants with an adverse event per group if this information was clearly provided in the publication or could be derived with confidence from the reported information.

We extracted the number of participants with adverse events per group and the number of all individual incidences of adverse events per treatment arm.

The nature of the reported adverse events was explored by categorizing events with the Common Terminology Criteria for Adverse Events (CTCAE) classification system. The reported

adverse events and reasons for dropping out were classified according to the 27 areas specified in the CTCAE and, where possible, graded in their severity on a scale from 1 (mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated) to 5 (death from adverse event) according to the CTCAE system.

The reported adverse events were also assessed as to whether they constituted serious adverse events following the FDA definitions. Serious adverse events were defined as death, a life-threatening event, hospitalization, a disability-causing event, a congenital anomaly, or events requiring an intervention to prevent permanent impairment or damage. Sepsis was classified as a serious adverse event.

In trials where mothers and their children received probiotic interventions, only the adverse events for children were considered for pooled analyses because studies reported inconsistently on children and their mothers. The number of participants was calculated as the number of mother–child dyads randomized to the treatment groups.

Quality. Each study was also assessed regarding its quality. We considered a wide range of study designs in this review, and some quality dimensions were specific to the individual study design (e.g., concealment of treatment allocation for RCTs), while others were sources of bias that apply to all study designs (e.g., blinding of outcome assessors). The quality assessment incorporated the quality of the reporting of the product and probiotic genus, species, and strain; the methods; and the reporting of the assessment and the documentation of observed adverse events. Each quality indicator was scored using a three-point scale (0 = high risk of bias, 1 = unclear or possible risk of bias, 2 = low risk of bias).

The specific markers of quality were the quality of the probiotic description (genus, species, and strain), the quality of the reporting of the assessment of adverse events, the quality of the reporting of the adverse events themselves, selection bias, baseline comparability of groups, power calculation for harms, ascertainment of compliance and exposure, method of ascertaining adverse events, random treatment allocation, concealment of allocation, participant blinding, outcome assessor blinding, rate and description of dropouts, intention to treat analysis, presence or handling of confounders, and the potential conflict of interest.

Procedure. The data abstraction and quality assessment were performed in duplicate with two reviewers independently reviewing the publications using a standardized form. The numerical results for the eligible outcomes were abstracted and checked by a statistician. Any disagreements were resolved through discussion, through consultation with the review team, or with other input such as from the local content expert or the TEP.

Analysis

Several of the questions the review set out to address required only descriptive data (e.g., number of studies reporting adverse events, type of harms, etc.). For studies that reported the presence or absence of a specific adverse event, we extracted two different measures of the quantity of adverse events where possible: the number of participants who experienced adverse events and the number of incidences of individual, reported adverse events. For controlled studies, we extracted the number of participants with adverse events and the number of individual incidences for each intervention arm. In cases where the number of events was reported for one group within a study but not explicitly for the other group, we assumed that zero events occurred for this second group.

For each study, we extracted the total number of participants entering the study and the number of participants per treatment arm. The latter was the number of participants per group as randomized or initially entering the treatment group where stated; in nonrandomized and single group studies we used the number of participants in the treatment group as reported. In addition, we extracted the number of dropouts and the number of dropouts due to adverse events per group.

Where appropriate, we pooled results across studies in a meta-analysis to obtain a summary estimate. Studies were included in pooled analyses if they reported complete information on the total number of participants in each treatment group, as well as the number of participants with events in each group or the number of adverse event incidences per group. We identified a large number of RCTs and restricted the pooled analyses to parallel RCTs. Trials that did not randomize participants or that used a crossover design were used only for sensitivity analyses, where appropriate. When pooling studies with adverse event incidences, we excluded those trials where the total number of adverse events incidences exceeded the number of participants per treatment arm (this was very rare but not impossible as participants can experience more than one adverse event).

For parallel RCTs, we computed the relative risk for adverse events, comparing treatment and control groups, and the absolute risk per group and compared risk differences across groups. Where the number of cases with an adverse event for a treatment arm was zero, an increment of 0.5 was added, where required for the specific statistical analysis. Studies were pooled with random effects analysis using the DerSimonian-Laird procedure, using the metafor package, v1.4 (Viechtbauer, 2010) within R 2.10.2. We report the pooled relative risk and risk differences together with a 95% confidence interval (CI).

Pertinent results were depicted graphically in forest plots. Each forest plot indicates the point estimate and confidence interval associated with the data reported for each included study. The area of each square is proportional to the study's weight in the meta-analysis. Throughout, the forest plots show the log of the relative risk on the horizontal axis.

The evidence report set out to answer a large number of Key Questions pertaining to product and participant factors. We primarily sought studies that reported direct comparisons to answer Key Questions. For example, studies comparing two different delivery vehicles within the same study were used to address differences associated with the delivery vehicle. Where no direct comparisons or only few comparisons were identified, or where comparisons were unusual or inappropriate (e.g., comparing effects in children and in adults), we used subgroup analyses and metaregressions to investigate the factor in question. Subgroup analyses stratified RCTs by the factor in question. For example, a separate pooled analysis comparing intervention and control groups was undertaken for studies in children, in adults, and in elderly participants to investigate whether safety results vary by age. Metaregressions were undertaken to investigate the potential predictors (or moderators) of effects such as the age of the participants. In the metaregressions, we incorporated additional predictors into the model, assessing the 95% CI and p-value associated with the ratio of relative risk for the particular predictor. This type of analysis can identify interaction effects, that is, whether the risk compared to control is statistically significantly higher than compared to the risk seen in other study types. Where a categorical moderator had more than two levels, we first assessed the joint significance of the predictor before examining the univariate effects. Metaregressions and subgroup analyses are indirect comparisons across studies and were interpreted with caution, as they are confounded by many factors.

The proportion of RCTs that addressed adverse events was also determined relative to the total number of identified RCTs reporting patient health outcomes in human participants using probiotics or synbiotics of the genera *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, or *Bacillus* to cure, treat, mitigate, or prevent a disease or reduce disease risk compared to placebo, another probiotic or synbiotic, other intervention, or no intervention. This assessment answers the question of what proportion of high evidence level studies do and do not address the safety of using probiotics or synbiotics. This analysis is based on a literature scoping approach of the excluded literature and is an estimate only.

Rating the Strength of the Evidence

For each of the key research questions, a synopsis of the evidence was undertaken. The body of evidence consisting of all studies that were identified that contribute to answering the research question was rated according to the following criteria: risk of bias, consistency, directness, and precision.

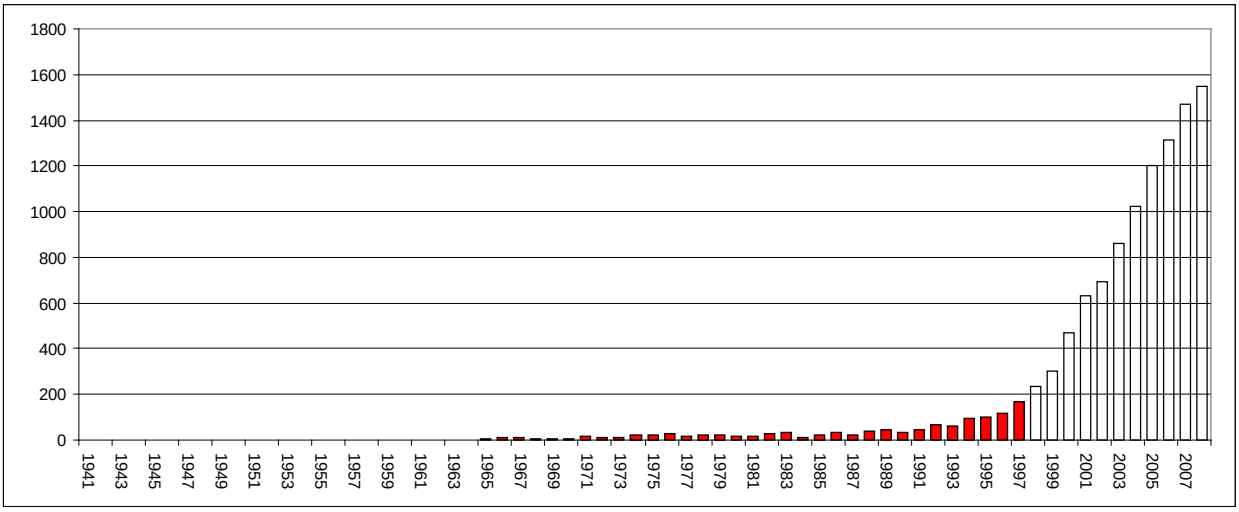
The risk of bias was assessed for each study by taking the study design and the results of the quality assessment of the individual study into account. The quality criteria are outlined above. In addition, the consistency of results across studies was considered. For this dimension, we checked whether the direction of results was similar across comparable studies. The directness of the evidence takes into account whether any head-to-head trials were identified that allowed a direct comparison (between two probiotic genera, for example) within the same study rather than having to rely on indications across studies. Across-study comparisons are confounded by many factors, results may be misleading, and conclusions from indirect comparisons have to be regarded with caution. The precision relates to the confidence intervals around a summary estimate, the range of values that have to be considered true based on the given data. In addition, this dimension considers, for example, whether the risk of adverse events in the intervention group is statistically significantly different from the risk of adverse events in a control group.

Finally, for each question we graded the strength of the evidence that was identified for the particular topic. The strength of evidence reflects the confidence in answering each Key Question. The following categories were used: high, moderate, low, or insufficient. High indicates that we have confidence that the evidence reflects the true effect; the research question can be sufficiently answered with the available evidence. Moderate indicates that we have only moderate confidence that the identified evidence reflects the true effect. A rating of low indicates that we have only low confidence that the identified evidence reflects the true effect and that it is likely that future research will change currently available estimates of effects. When the strength of evidence is rated as insufficient, it indicates that evidence to answer the research question is unavailable. The absence of evidence does not equal the absence of an effect; it indicates that there is insufficient evidence to answer the research question. A summary of the general approach is outlined in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (AHRQ, 2007).

Results

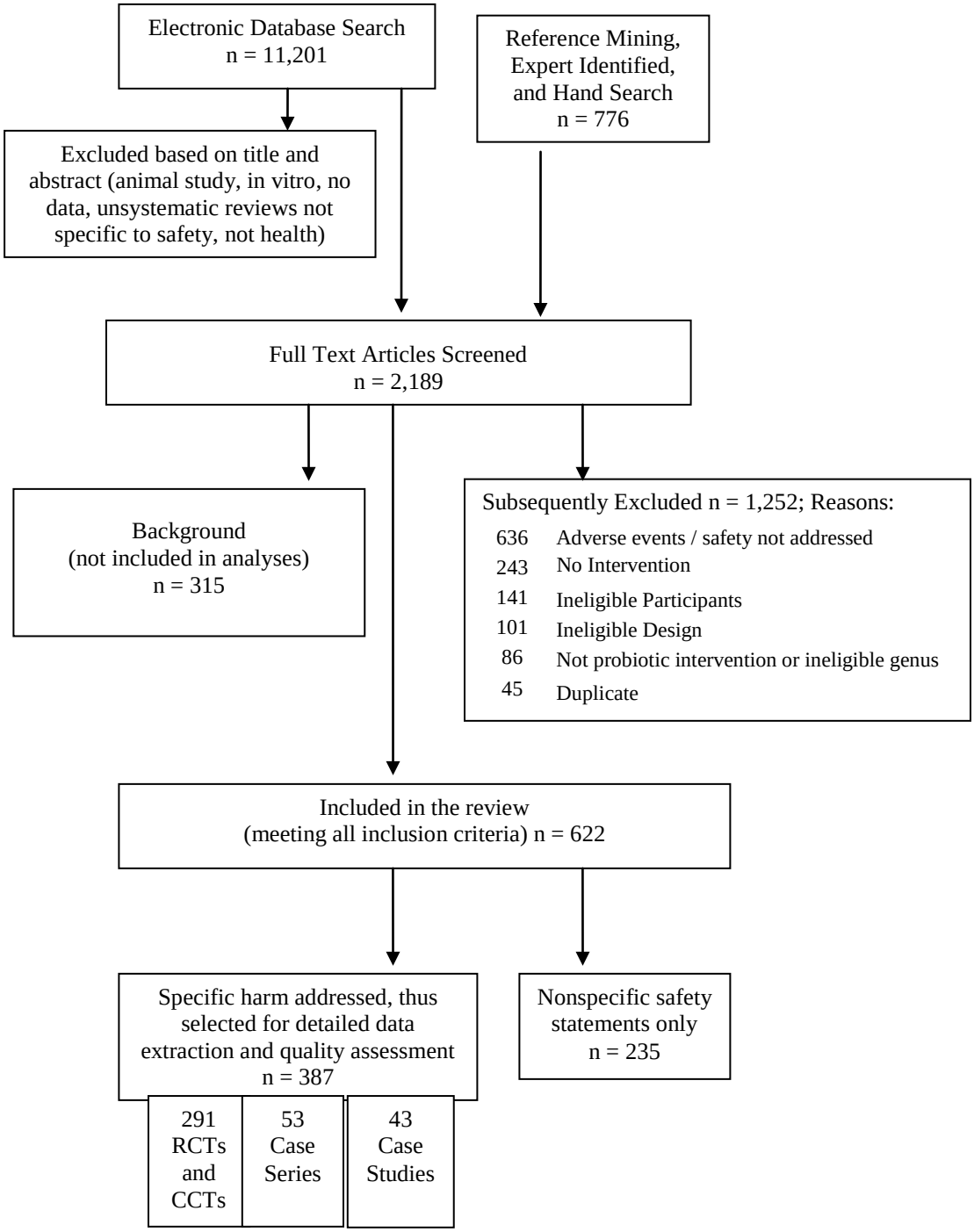
The literature search revealed a large research volume on the topic of probiotics, with a particular increase in research publications shown in recent years. All databases were searched from inception. Figure 3 plots the identified publications by the year of publication.

Figure 3. Literature volume



The literature search for the systematic review identified 11,977 publications. Of these, 11,201 publications were identified through searching electronic databases, and the remaining 776 came from reference mining included studies and background papers and hand searches. The literature flow for the review is shown in Figure 4.

Figure 4. Literature flow



Of all identified publications, 9,788 were excluded on title and abstract level where publications clearly addressed animal studies, in vitro studies, comments and opinion pieces without data, unsystematic reviews not specific to safety, and publications that did not address health topics. We ordered 2,189 full text articles for further scrutiny.

Applying the standardized form to inclusion screen full text papers by two independent reviewers, 1,252 publications were excluded. Excluded publications are listed in Appendix D with the primary reason for exclusion. The screening process considered, in this order,

monitoring and/or reporting of adverse events, participants, genus, design, intervention, and duplicates. Only one reason for exclusion was recorded, although most publications would have not passed two or three exclusion criteria. Also listed in the appendix are 315 studies that were classified as background papers. These were mostly reviews used for further reference mining or multiple publications of included studies.

Overall, 622 studies met inclusion criteria. The full list of included studies is shown in the appendix together with the source the publication was identified from. The electronic databases were searched in a particular order, starting with PubMed as outlined in the search strategy. The majority of included studies were indexed in PubMed. A substantial number of studies were identified through reference screening of included studies and background papers.

The included studies were then screened again in a further step to differentiate studies that addressed a specific adverse event from those that did not (nonspecific safety statements).

Potentially Relevant Studies Not Addressing Safety

To estimate the proportion of existing probiotics studies currently found in the literature that are included in this safety review, we enumerated the probiotics randomized controlled trials (RCTs) reporting on patient outcomes that were found in our searches. We then calculated the proportion of RCTs included in this review as an estimate of the proportion of currently available studies that were included.

RCTs are regarded as high evidence level studies, and of all published research studies, these should be more likely to adhere to good reporting practices, which include the reporting of adverse events. We have identified 774 RCTs in our literature searches that were potentially relevant for the Key Questions and were theoretically eligible to be included in this review based on the participant, intervention, genus, and study design criteria of this review.

Of these relevant RCTs, 446 (58 percent) met inclusion criteria for this review because they addressed the safety of probiotics. All other RCTs reported on relevant interventions, in relevant participant groups, but they did not address adverse patient health outcomes as defined in this evidence review. Of all published RCTs that we identified in our searches, 279 (36 percent) reported on the presence or absence of a specific adverse event.

Included Studies With Nonspecific Safety Statements

Evidence Table C6, Nonspecific Safety Statements,in Appendix C summarizes the 235 identified studies that made only vague safety statements indicating that “there were no adverse events” or that the intervention was “well tolerated” but gave no indication what kind of adverse events were screened for or did occur. The evidence table shows what the publication reported regarding the assessment of adverse events and the safety results.

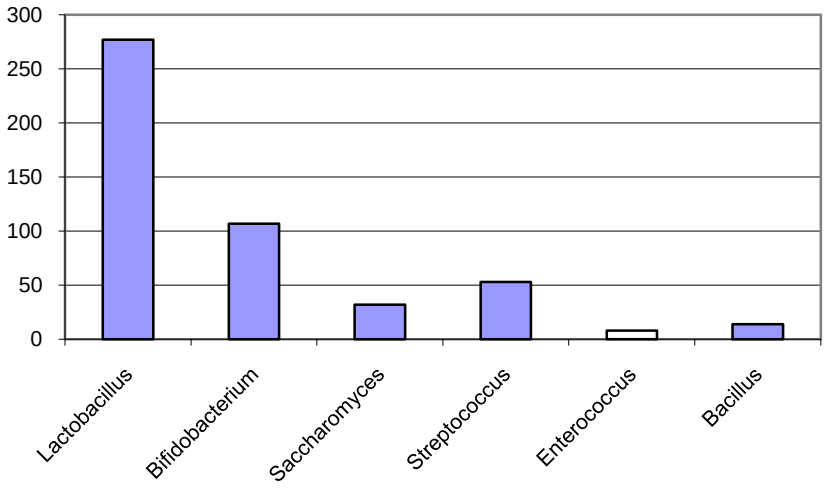
The majority of these studies were RCTs. Very few included studies were “mechanistic studies,” that is, specifically investigating the mechanism of action with which probiotic organisms potentially achieve effects. Mechanistic studies rarely addressed patient health outcomes, including adverse events.

Only few studies (67/235) provided details about the assessment procedure (e.g. “any side effects were also recorded,”), but no specific outcomes that were monitored in the study were reported. The large majority of studies did not refer to the assessment of adverse events.

The table also shows the investigated genus, species, strain, and form of probiotic organisms given, as well as the potency and the administered dose, and the product name, where applicable, for these studies. *Lactobacillus* was by far the most commonly investigated genus, and about

three-fourths of the identified studies used products that included *Lactobacillus* alone or in combination with other genera. *Enterococcus* and *Bacillus* studies accounted for less than 5 percent of the sample. Figure 5 shows the frequency of the genera of all strains used in the studies.

Figure 5. Included strains by genus in studies with nonspecific safety statements



Several publications reported the species and in some cases subspecies that were investigated. Common in this sample were *Lactobacillus rhamnosus*, *casei*, and *acidophilus*; *Bifidobacterium bifidum, lactis, and longum; Saccharomyces boulardii*/*cerevisiae*; *Streptococcus/Enterococcus faecium*; or *Bacillus coagulans*. One-third of the studies did not report the investigated strain. These studies provided no information on what exactly was studied or at least what was supposed to be studied. In addition, most studies did not state that any efforts were made to test the administered microorganism(s).

In more than half of the identified publications, the form of the organism was not described, such as whether the organism was active, lyophilized (freeze-dried), or heat killed. Most common was the description "live," "active," or "viable" (32 percent); reference to freeze-dried stored organisms was made in a quarter of the publications. No studies that employed heat-killed organisms and provided vague safety statements were identified using the search algorithm.

The potency of the studied probiotic strain was reported for a third of the articles (expressed as colony-forming units [cfu] for bacterial strains), although with rare exceptions, the potency does not appear to have been tested as part of the study. Thus, the reported potency information may have been that provided by the manufacturer of the product. The actual potency can deviate from the product label and can be influenced by the delivery vehicle that is employed in the study so the stated potency information is only a rough indicator. In addition, the dose information was usually not clearly documented or not linked to the potency information, or the potency and dose were reported only on the product, not at the individual organism level, so that in most cases the daily amount of exposure of the probiotic organisms remained unknown.

A third of these publications stated that the investigated intervention had "no side effects." The statements "no adverse effects," "well tolerated," and "no adverse events" were also, and all equally, common, each found in about 20 percent of the identified publications. The statement "safe" was a rarely used expression, accounting for fewer than 5 percent of the publications,

presumably acknowledging that this statement is very difficult to ascertain with a single study. The remaining studies used other expressions.

None of these publications clearly reported their basis for the conclusions related to the absence of harms. That is, they did not state the specific parameters they monitored, or characterize the encountered adverse events further. A small number of publications monitored specific harms according to the methods section but the results were not reported. Studies describing the presence or absence of a specific adverse event were eligible for detailed data extraction, are described in the next section, and were used to answer the Key Questions.

Included Studies Addressing Specific Harms

A total of 387 studies were identified that addressed a specific adverse event. These studies were used to answer the Key Questions posed by the sponsors.

Evidence Tables

Detailed information on the included studies is shown in five evidence tables in Appendix C. Table C1 lists the study details and participant information, table C2 shows the intervention details, Table C3 outlines the assessment and analyses, Table C4 summarizes the reported results and Table C5 shows the quality assessment. Studies appear in alphabetical order (by name of the first author) within study design categories. For this categorization, we differentiated three study design groups: controlled trials, observational studies, and case studies. The nonrandomized controlled trials and the crossover and parallel randomized controlled trials were extracted in the same category; the observational study design group included only uncontrolled case series.

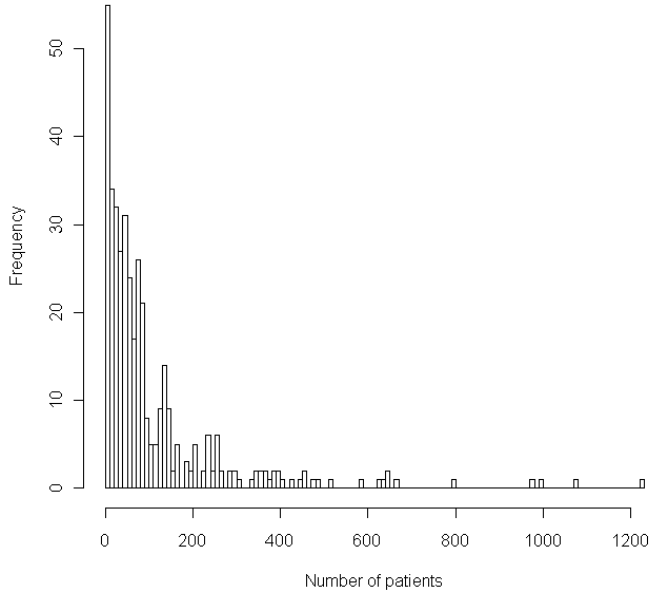
Study and Participant Details

Table C1: Study and Participant Details provides an overview of the type of study and the included participants. Almost all included studies were published as articles. Although abstracts and letters with data were eligible for inclusion in the review, these publications accounted for fewerthan 5 percent of the included publications. Multiple publications about the same study were extracted as one study, regardless of the number of publications employed to report the data. Publications reporting more than one study, in particular with different research designs, are shown as multiple studies. Fewer than one-third of studies reported that safety was one of the main aims of the publication. The efficacy of the intervention was the most common research question addressed by the included studies.

In all, 49 percent of included studies were conducted in European countries; Italian publications alone accounted for 10 percent of the sample. Studies were included regardless of the language of the publication. The number of U.S. studies included (11 percent) was similar to the number of Asian studies (16 percent). We determined the country by the study participants, not the authors of the publication. The individual countries are shown in the evidence table.

The majority of included studies employed a modest number of participants, that is, ranging between 11 and 100 participants. However, we also identified 111 larger studies (29 percent of all included studies) with more than 100 participants. Small studies with between 1 and 10 participants constituted 14 percent of the entire sample of included studies; most, but not all, were case studies. Figure 6 shows the number of participants included in the identified studies.

Figure 6. Number of participants in included studies



Across all studies and treatment arms, 24,615 intervention participants used a probiotics product, of which 21,403 were in the main treatment group. Across all studies, 16,574 participants were allocated to a nonprobiotic control group.

In terms of study design, parallel RCTs accounted for two-thirds of the entire sample addressing specific adverse events. We only classified those studies as RCTs that explicitly stated the random allocation to treatment and control group. All other trials were categorized as clinical controlled trials (CCT). We distinguished parallel and crossover RCTs, because with a crossover design, a carryover effect from the intervention phase cannot be ruled out and may lead to misinterpretation of the data. These trials included all studies where the intervention was under the control of the investigator. Cohort studies comparing two cohorts or case-control studies that addressed the safety of probiotics were not found. Cohort studies compare groups of participants using probiotic organisms with a group of participants not using probiotics; the intervention, that is, the use of probiotic organisms, is not controlled by the investigator but self-selected by the participant, and the data obtained are purely observational. Case-control studies are defined by the outcome, that is, a specific harm, and the intervention, the use of probiotic organisms, is investigated as a possible risk factor for the outcome in question. The remaining studies we included were case series and case studies, which represented 14 percent and 11 percent respectively. Case series report on a number of patients receiving the same intervention without a control group. Some case series were before–after studies, but for this safety analysis, these studies were not differentiated from other case series, because the preintervention data for safety aspects were typically missing so there was no baseline that allowed a comparison. The included case studies reported on one or more cases of adverse events attributed to probiotic organisms.

We also categorized the health status of the participants taking part in the included studies. We differentiated generally healthy, critically ill or high-risk patients, and participants with medium or indeterminate risk on the continuum from generally healthy to critically ill. Two-thirds of studies were in participants who were neither generally healthy nor critically ill. These participants were suffering from a variety of health complaints such as diarrhea, ulcerative colitis, or bacterial vaginosis. Some of the participant samples were generally healthy

participants (81/387). The smallest group of included participants was critically ill or high-risk patients, for example patients currently being treated in an intensive care unit or babies with very low birth weight. The participants' specific health problems were also extracted. We also noted whether participant groups of interest to the Key Questions were systematically excluded from each study, such as newborn and very young children; elderly participants; or immune-compromised, critically ill, or high-risk patients. In all, 52 studies explicitly reported that immunocompromised patients were excluded from the study. Another 73 studies excluded pregnant women, and 36 excluded breastfeeding or lactating women.

For each study, we noted the reason for which the probiotic organisms were given. Seventy-nine percent of studies used probiotic organisms in an attempt to either treat or prevent a specific condition. Although probiotic organisms can be administered in the form of a food or food ingredient, a drug, or a dietary supplement, and our search or inclusion criteria did not favor one particular form over another, the probiotic organisms were administered in a clinical context in the vast majority of identified studies, that is, testing the efficacy or effectiveness of the preparation to treat or prevent a clinical indication. On a related note, although definitions of drugs vary across countries (as reflected in the international literature), the vast majority of interventions were not commercial food or dietary supplement products (see also Evidence Table C2, Intervention). The evidence table also lists pertinent cotreatments such as antibiotics, immunosuppressants, steroids, or dietary therapies. Of all included studies, 28 percent reported that participants also took antibiotics while participating in the probiotics study.

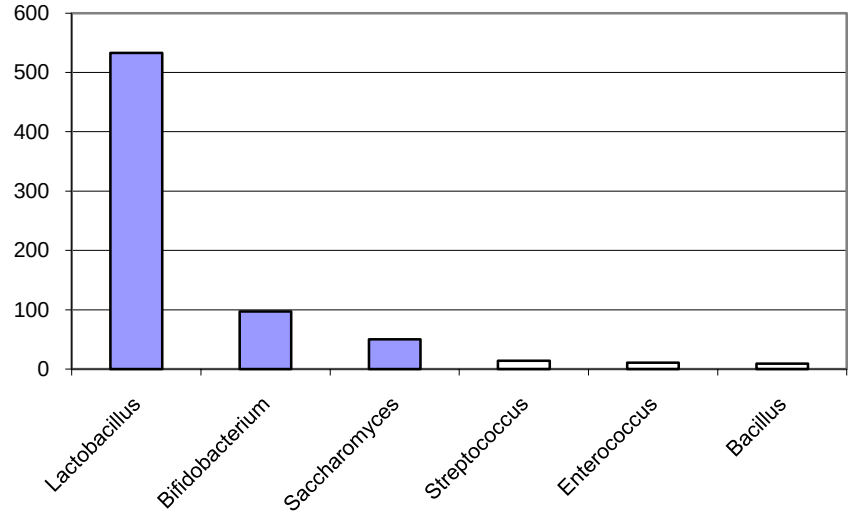
Intervention

The Evidence Table C2, Intervention presents an overview of the specific interventions evaluated in the included studies. When provided, the name of the product under evaluation was extracted. Furthermore, we extracted the delivery vehicle for the probiotic organisms where reported: in one-quarter of all included studies, the delivery vehicle was a pill or capsule. We also extracted the target of the intervention, since we identified somestudies that gave probiotic organisms to pregnant women, their babies after delivery, or both.

We also categorized the studies as to whether they investigated only one probiotic strain or several (i.e., a mixed product). A single-genus product was investigated in 55 percent of studies. In 39 percent of studies, more than one strain was included in the intervention preparation. The latter studies included those in which the probiotic agents were given in yogurt or other milk products, and we have included *Lactobacillus* and *Streptococcus* in this evaluation where reported, even when the study did not claim any probiotic characteristics for the yogurt strains (studies were inconsistent in differentiating strains with assumed probiotic properties or attributing probiotic properties to the studied product in its entirety).

We carefully avoided searching by the names of particular strains, species, or genera. However, the majority of identified studies targeted at least one *Lactobacillus* strain (73 percent). In all, 34 percent of studies included at least one *Bifidobacterium* strain. The other genera of interest to the report were represented in only 18 percent (*Streptococcus*), 12 percent (*Saccharomyces*), 4 percent (*Enterococcus*), and 3 percent (*Bacillus*) of studies, respectively. Figure 7 shows the number of strains by genus that were investigated in the included studies in the various treatment groups. Many studies used exclusively one *Lactobacillus* strain and many studies included more than one *Lactobacillus* strain but no other genera in the intervention.

Figure 7. Included strains by genus



We also categorized studies according to whether the intervention included only probiotics, or a combination of probiotics and prebiotics, that is, synbiotics. Fewer than 10 percent of studies stated clearly that they used a synbiotic product or reported the addition of ingredients with assumed prebiotic properties.

Details of the interventions were documented only sketchily. Studies reported the investigated genus and often the species but strain information was often not reported, as indicated by the large number of "not available (n/a)" entries in the evidence table. The evidence tables include the species as reported regardless of reclassifications on genus, species, or strain level based on new evidence. Apart from the genera *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus*, some intervention products also included the genera *Clostridium, Lactococcus, Leuconostoc, Pediococcus*, and *Propionibacterium*. The studied intervention products included the *Lactobacillus* species *acidophilus, bifidum, brevis, buchneri, bulgaricus, casei, caucasicus, coryniformis, crispatus, delbrueckii, fermentum, gasseri, (GG), helveticus, johnsonii, lactis, leichmannii, paracasei, plantarum, reuteri, rhamnosus,* and *salivarius* as reported by the authors. The reported *Bifidobacterium* species were *animalis, bifidum, breve, clausii, infantis, lactis*, and *longum*. The *Saccharomyces* interventions were described as *boulardii, cerevisiae,* or *cerevisiae boulardii,* and one study used the *Saccharomyces florentinus*. The reported *Enterococcus* species were *faecalis* and *faecium*. The reported *Streptococcus* species were described as *mitis, oralis, rattus, salivarius, sanguis,* and *thermophilus*, and some organisms were described as *Streptococcus faecium*. The studied *Bacillus* species were described as *clausii, coagulans, IP, licheniformis, oligonitrophilus, stearothermophilus*, and *subtilis*. Of all included studies, 43 percent did not report on included strains.

The form of the probiotic strain was also often not reported: 62 percent of studies did not report whether the organisms in the various intervention arms were in active, lyophilized, or heat-killed form, and/or whether the tested organisms were viable.

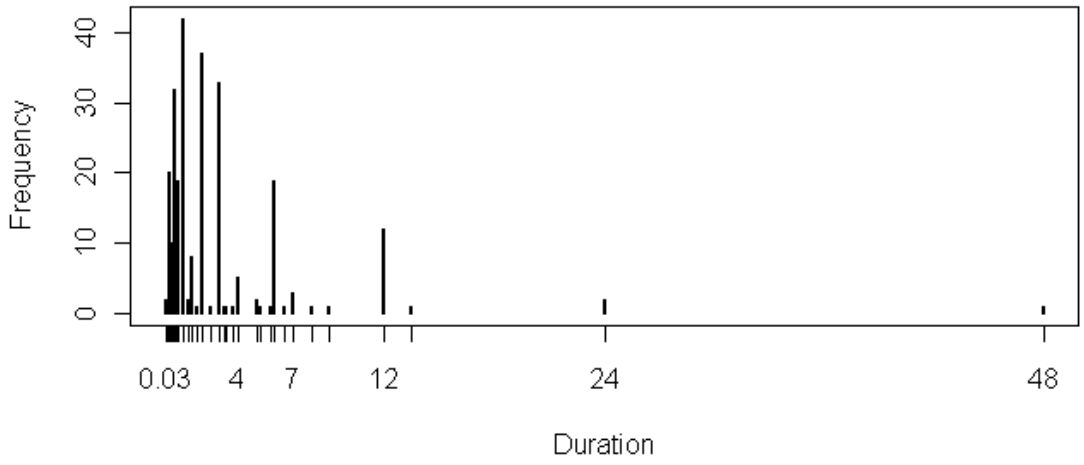
For studies that reported using a commercial product, we extracted only the intervention detail as reported by the authors, that is, we did not search for information from manufacturers to determine the composition of the product. The review covers the international literature and was

searched without restriction by publication year; it is possible that the product compositions vary across countries and have also changed over time. Fewer than 10 percent of studies clearly reported that they verified the probiotic strains that were given to participants as part of the study. The verification checked for the included strains, whether any contaminants were identified, and/or the number of active organisms.

The evidence table also shows the dose information as reported by the individual study authors. For each study, we extracted the daily intake of probiotic products where possible. The dose information was often incomplete, that is, the information provided was insufficient to calculate participants' actual daily or overall study exposure.

The evidence table also reports the length of the intervention in months. Many intervention periods in the included studies were of short duration, often lasting for only 1 week. We categorized studies by short-term, medium, and long-term use. Defining short-term use as 1 month or less and long-term use as 1 year or longer, we note that almost half of the included studies (46 percent) reported an intervention period of 1 month or less, and only 5 percent of studies explicitly investigated the long-term use of probiotic organisms, that is, use of probiotic products for 1 year or longer. In the remaining studies, medium intervention durations were studied (more than 1 month but less than 12 months) or in some cases, it could not be established how long the probiotic product was taken. Figure 8 shows the individual study durations in months.

Figure 8. Intervention duration in months



We also differentiated the route of administration of the probiotic product. In two-thirds of studies, probiotic organisms were administered orally. In 10 percent of these studies, enteral feeding tubes were used, owing to the fact that a number of studies evaluated probiotics in critically ill patients (see Evidence Table C1, Study and Participant Details).

In controlled studies, the probiotic intervention was most commonly compared to a placebo, or a group receiving probiotic organisms in addition to another medication, product, or treatment (the standard intervention) was compared to a group receiving only the standard intervention without the probiotic addition. For studies with multiple interventions, we chose as the primary intervention arm the one that differed from the control group only in the administration of a probiotic.

Assessment

We distinguished descriptions of the assessment of adverse events from the reported events. Evidence Table C4, Results lists all reported events; however, the Evidence Table C3, Assessment lists the specific adverse events that were reportedly assessed according to the methods section of the publication. We noted all reported published systems used to record, categorize, and grade adverse events; however, this information was not very common in the included studies. The assessed safety parameters of controlled trials are summarized in Key Question 1a. The information on observational studies is summarized in Key Question 1d.

We also categorized the duration of followup. In particular, in studies with multiple publications, this categorization was based on the longest reported followup period. In terms of short-, medium-, or long-term effects of probiotics use, outcomes were often elicited immediately after the end of the intervention period. The use of the probiotic product had either recently stopped, or in some instances was still ongoing at the time of the followup assessment. One-third of included studies assessed the effects of a probiotic intervention within 6 months after the intervention. Very few studies assessed long-term effects of probiotic use, i.e., effects reported more than 1 year after the treatment had stopped.

Results

Evidence Table C4, Results lists the reported results separately for each treatment group in the included studies (arm 1 to 4). The table documents the quantity, the quality, and the nature of the reported adverse events. For each study, we also extracted the total number of participants per study, the number of participants in each group at the time of randomization where applicable, the specific reported adverse events, the number of dropouts, and the number of dropouts due to adverse events.

In terms of the quantity of adverse events, we extracted the number of adverse event incidences separately for each treatment arm. In addition, we extracted the number of participants who experienced one or more adverse events per treatment arm. Since participants could experience multiple adverse events, the number of participants with adverse events and the total number of individual adverse events do not coincide and were extracted individually.

In terms of the nature of the adverse events, as outlined in the Methods section, we extracted the exact adverse events as reported by the authors of the publication, and in addition, we applied the Common Terminology Criteria for Adverse Events (CTCAE) system and categorized the events according to 27 categories. The Roman numerals in the evidence table refer to the CTCAE category, e.g., VII is gastrointestinal disorders, XII is infections and infestations, and XXVII is a miscellaneous category for events not covered by the CTCAE system or where adverse events were reported in a way that did not allow the assignment to a single category. In brackets after the individual adverse event, we added a characterization where possible (e.g. mild, or classified as 1 according to the CTCAE system). However, this information was usually not available. For each individual adverse event, we extracted the reported number of instances of the event.

In terms of the quality of the adverse events, we assessed for each reported adverse event whether it represents a serious adverse event (SAE) as outlined in the Methods section to distinguish the large number of minor complaints from the serious events. In the evidence table, the latter are noted as “(SAE)” for each applicable adverse event.

We also extracted a number of additional variables pertinent to the Key Questions such as the number of hospitalizations and the duration of hospitalization, where reported. Whether the

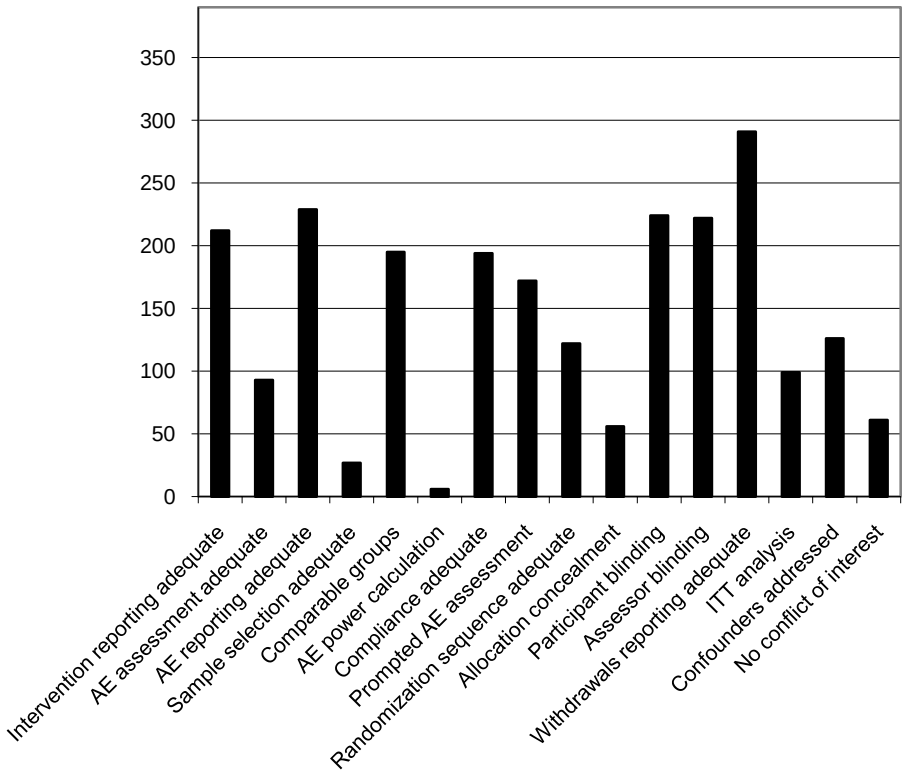
administered organism was recovered from the gastrointestinal tract, serum, mouth, or vagina (indicator of efficacy or safety); the need for antibiotic therapy to treat an infection; and occurrences of antibiotic resistance were also extracted and are explained in detail in the following sections.

We noted that the quality of the reporting seems to have increased in recent years; however, it is challenging to quantify this subjective observation. A logistic regression of the number of individual adverse events (including zero events, i.e., reporting on the presence or absence of adverse events) showed that the reporting of gastrointestinal events increased (B=0.048; p=0.010), however, there was a larger increase in the reporting of infections and infestations (B=0.014; p<0.0010).

Quality

Evidence Table C5, Quality summarizes the quality of the individual included studies, as judged by two independent reviewers. We applied a number of quality criteria covering the quality of the reporting as well as internal validity criteria for the study design. Only "met criteria" or "possibly met/not enough information to judge the quality" are displayed in the table, to allow an easy overview of the entire sample. Figure 9 synthesizes the quality of the reporting and the risk of bias for all assessed variables for the included 387 studies meeting all inclusion criteria.

Figure 9. Quality of the reporting and risk of bias in included studies



AE=adverse event; ITT=intention-to-treat

For each study, we evaluated the quality of the intervention reporting: Only studies reporting the administered strain as well as the genus and species met the criterion (211/387 studies). The assessment of adverse events was judged as clear and well reported by the two independent reviewers in 93/387 studies. The reporting of the adverse events themselves was judged adequate in 229/387 studies.

We also assessed the selection of the sample: 27/387 studies were judged to protect adequately against selection bias, for example, through the use of consecutive patients or explicitly representative samples drawn from the study population. Also, for controlled trials, we assessed the comparability of the groups allocated to the probiotics and to the control interventions. Of all controlled trials, 195/291 relevant studies were classified as adequate; these studies reported basic baseline information on both groups, and the data were considered comparable. As a quality measure for the study, we also judged whether the study reported a power calculation that considered any adverse event. Of all included studies, six studies assessed in advance whether their study would be adequately powered to show a statistically significant difference in adverse events between treatment arms, should they occur. Because we expected to find a number of case-control studies, we also assessed the studies for exposure ascertainment. In 194/387 studies, the reviewers were relatively certain that the probiotics were used as described, for example, because studies reported on the compliance of the participants, or it was assumed that the probiotic organisms were taken as indicated because studies took place in a controlled hospital environment (i.e., most likely administered by hospital staff).

The reviewers also judged the method of harms surveillance. Reported adverse events can differ across studies due to the method used to elicit adverse events. We differentiated passive surveillance, such as health care providers recording adverse events when spontaneously disclosed by participants, from active surveillance, for example, mention of a structured assessment of harms that was part of the study protocol as evidence that participants were explicitly prompted to report adverse events. In total, 172/387 studies were classified as using active surveillance, while for the other studies only passive surveillance could be assumed, or it was unclear from the reporting of the study.

Among the included studies were a large number of RCTs. In total, 121 studies described as randomized had a randomization sequence approach that was described and considered adequate (e.g., use of table of random numbers, computer generated sequences). We also judged the concealment of treatment allocation—whether study personnel were able to predict the study arm in which the participant would end up or whether the allocation to treatment groups was concealed. Only 56 out of all 266 parallel RCTs reported treatment allocation concealment. Finally, we assessed participant and outcome assessor blinding. In 223 studies, the participants were blinded to the treatment they received; they did not know whether they consumed or were exposed to the probiotic organisms in question, a placebo, or another control preparation. In a similar number of studies (221/387), the outcome assessor was described as blinded: it was assumed that the person eliciting the study outcomes was not aware whether the participant was taking probiotic organisms or not.

When assessing the risk for adverse events in a particular study, it is important to identify the number of dropouts (withdrawals). Whereas participants completing the intervention may report no adverse events, adverse events can lead to withdrawal (and might or might not be accounted for). In 290/387 studies, the numbers of withdrawals and dropouts were reported and the reasons for dropping out were described, or it was clearly reported that there were no dropouts and all participants were followed up. Of all parallel RCTs, 75 percent were judged by two independent

reviewers to report adequately on withdrawals. As a general quality measure, we also assessed whether studies reported an intention-to-treat analysis. In all, 99 included trials reported that they analyzed participants according to the treatment group to which they were originally assigned regardless of whether they completed the intervention or switched to another treatment. We also assessed whether studies reported any attempts to investigate or to avoid upfront confounding factors. Of all included studies, 126 were classified as attempting to address confounders, either through statistical analyses (e.g., multivariate analyses) or by features of the study design (e.g., matching control groups).

We also assessed the potential for conflicts of interest. We differentiated studies that were funded by a manufacturer of probiotics and studies where the conflict of interest was somewhat unclear because of lack of reporting or because the researcher's affiliation indicated no conflict of interest but the article reported that the study products were donated by a manufacturer. In 61/387 included studies, the authors explicitly stated in the publication that they had no conflict of interest.

Key Question 1. What is the evidence that the active (e.g., live or viable) and lyophilized forms of probiotics (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus*) as single ingredients or in combination with other probiotics or prebiotics in all delivery vehicles (and formulations) when used to cure, treat, mitigate or prevent a disease or reduce disease risk are safe in the short term? Long term?

All 387 studies meeting criteria for full data abstraction were considered to answer Key Question 1. Studies were considered, regardless of the genus, species, or strain; form; and delivery vehicles. Probiotics as well as synbiotics are included in the summary.

We have identified only very few studies that investigated *Enterococcus* or *Bacillus* strains and that could be included in this review, despite an extensive and unrestricted search. The following results primarily pertain to *Lactobacillus*, alone or in combination with other genera, most often *Bifidobacterium* strains.

Very few included studies (nine in total) investigated long-term effects defined as reporting on followup periods of one or more years.

(1a) What safety parameters are collected in clinical studies (Phases I–IV)?

The monitored safety parameters of the included CCTs and parallel and crossover RCTs are shown in Evidence Table C3, Assessment in Appendix C. We distinguished assessed harms from actually reported adverse events. Evidence Table C3, Assessment lists only outcomes that were explicitly monitored according to the publication.

The majority of publications reported little information on the assessment of adverse events, including what adverse events were monitored. Safety was one of the primary outcomes in only 55 publications out of all 291 identified CCTs, and parallel and crossover RCTs.

Often, adverse events were not specified a priori. Many trials did not mention safety or adverse events in the study outcome section (103 trials). A substantial number of publications reported in the methods section of the publication that 'adverse events' were monitored but did not define these outcomes further and reported no examples of what kind of events would be monitored (55 studies). The "AE Non-specific" category in Evidence Table C3, Assessment

includes those studies that explicitly monitored for any adverse event that occurred during the study period.

The trials rarely reported the use of a protocol or a systematic approach for the assessment of adverse events. Some publications used published tools to categorize adverse events. Allen (2010) recorded all untoward medical occurrences and these were then independently reviewed. The authors referred to the Directive 2001/20/EC and the ICD10 criteria. Aso (1992 and 1995) evaluated adverse reactions according to the criteria of the Japan Society for Cancer Therapy (Furue et al., 1986). Chouraqui (2008) and Dylewski (2010) reported that adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Hemmerling (2009) used the DAIDS Toxicity Table Addendum for Vaginal Microbicide Studies, WHO/CONRAD colposcopy manual 1994, and DAIDS Adult Toxicity Table (Division of AIDS, 2007) . The severity of adverse reactions was assessed using the CTCAE, version 2.0 in the trial by Naito (2008). The Common Toxicity Criteria of the National Cancer Institute of Canada scale version 2 was used by Osterlund (2007) to assess and grade any adverse events. Sykora (2005) used a tool for H. pylori treatment side effects (de Boer, 1996) and assessed the causal relationship of the encountered side effects to the treatment. Wind (2010) also used published tools to assess safety (Gastrointestinal symptom rating scale, Svedlund et al., 1988; King's stool chart, Whelan et al., 2004).

When specified, the assessment of adverse events was either by provider assessment at the time of clinical examination (165 trials), by patient diary (68 trials), by questionnaire (24 trials), or explicitly by telephone interview (21 trials), and some trials used lab tests (24 trials), but a substantial number of trials (52 trials) did not specify how adverse events were elicited. In studies with provider assessment, it was usually unclear whether participants were prompted to report adverse events, whether clinicians routinely checked for particular events, or whether it was left up to the participants to mention events that they noticed. We suspected that studies that completed an Investigational New Drug (IND) application were more likely to report a systematic approach to assessing harms, but only one publication (McFarland, 1994) reported on the completion of an IND application.

Individual outcomes that were frequently explicitly monitored were “diarrhea” (37 trials), “vomiting” (27 trials), “constipation” (22 trials), “flatulence” (13 trials), “abdominal pain” (12 trials), “bloating” (10 trials), and “nausea” (9 trials) (see Evidence Table C3, Assessment in Appendix C). Signs of infections were rarely explicitly monitored in the included trials. The outcome “sepsis” or signs of sepsis was assessed in 11 of the included trials. Nine trials reported that “infections” were monitored, two trials explicitly monitored for bacteremia, and none of the trials stated in the methods section that fungemia was monitored. The outcome “death” was specified as a monitored adverse event in nine trials (this number does not include studies assessing mortality as an efficacy or effectiveness measure). Data on hospitalizations are presented in detail in Key Question 5.

All studies eligible for full data extraction had to report on a specific adverse event. All specific adverse events that were recorded are presented in Evidence Table C4, Results in Appendix C. These adverse events were reported in the publication, even though the study might not have stated upfront that safety was assessed or defined what would be considered an adverse event. The table covers the presence as well as the absence of adverse events (zero events). In other words, the publications that reported identified no instances of a particular harm.

The specific outcome most commonly reported on across studies was “diarrhea.” In total, 59 studies reported the absence or presence of diarrhea incidences in the treatment arms. This was

followed by “vomiting” (39 studies). Incidences of “death” or the absence of incidences was reported in 36 studies. The outcome “nausea” was recorded in 24 studies. “Sepsis” or “septicemia” was reported on in 21 studies. Twenty-three studies reported on “abdominal pain” and 30 on “constipation.” “Headache” was reported on in 22 studies. Flatulence was reported on in 19 studies, and 16 studies reported on the presence or absence of “bloating” incidences. All other outcomes were addressed in fewer than 10 studies.

In almost all included studies, the outcome assessment took place shortly after probiotic organisms were given (assessing short- and medium-term effects), and the intervention period was less than one year long (studying short- and medium-term use).

(1b) What harms are reported in clinical studies (Phases I–IV)?

For all CCTs and parallel and crossover RCTs, we recorded which adverse events were reported and how many participants per treatment group experienced the presence or absence of this particular outcome. In the evidence tables, the study arms appear in this order: main treatment group, control group, and additional treatment groups to which probiotics were given.

Exact adverse events as reported were extracted and are shown in Evidence Table C4, Results, in Appendix C. We extracted all reported results, including zero events (e.g., zero cases of sepsis). We classified the adverse events according to the CTCAE system and added the corresponding codes I to XXVII. Where possible, we graded the severity of the symptom on a scale from 1 to 5 or characterized the adverse event further if additional information was provided (in brackets after the harm). Studies reported on the presence or absence of a very large number of individual outcomes.

The number of reported adverse events per study varied greatly, presumably depending in part on the thoroughness of the adverse event recording and potentially in part on the type of study; for example, most studies whose primary aim was to assess the efficacy of probiotics reported one or more cases of each of a small number of adverse events encountered. Other studies, the primary aim of which was to specifically investigate the safety of probiotics in substantial participant samples, compared the incidence of relatively common occurrences such as colic in infants. Finally, this review also considered studies of “failed effectiveness,” that is, studies that assessed the efficacy or effectiveness of probiotics in preventing a particular condition (e.g., antibiotic-induced diarrhea or allergic dermatitis), where, unexpectedly, the risk for the condition actually increased in the probiotics group (rather than decreasing, as was hoped); thus, the primary outcome (efficacy, or lack thereof) became the safety issue.

Frequent Individual Adverse Events

The most commonly reported individual adverse events were “death,” “‘diarrhea,” “constipation,” “nausea,” “respiratory infections,” “spitting up,” “abdominal discomfort,” “dyspepsia,” “colic,” “abdominal fullness,” “allergy sensitization,” and “pain on micturition.” This analysis considers only the exact wording; similar symptoms or syndromes were not grouped. A categorization of reported adverse events is undertaken in response to Key Question 2c. Only data that indicated the treatment group in which the adverse event occurred were considered.

Across all trials, 177 incidences of “deaths” were reported in probiotic treatment groups, and 174 incidences were reported in a control group. Mortality was recorded in 32 trials, and each contributed one or two cases to the total number, with the exception of Kerac (2009), Besselink (2008), and Awad (2010). Kerac (2009) monitored deaths in children with severe acute

malnutrition and reported 108/399 deaths in a group receiving synbiotics compared to 119/396 in children using a control formula. The PROPATRIA trial reported by Besselink et al. (2008), a study of failed effectiveness, reported on 24 deaths in a treatment group compared to 9 cases in the control group in patients with acute pancreatitis. The deaths were not directly associated with cases of sepsis caused by the administered organism (0 incidences). Awad (2010) reported 5/60 deaths in a *Lactobacillus acidophilus* intervention group for the prevention of necrotizing enterocolitis and sepsis compared to 6/30 neonates receiving placebo; however mortality was 14/60 in the heat-killed *Lactobacillus acidophilus* group.

Of the other trials that reported on the group the deceased participant was originally allocated to, eight recorded more death incidences in one or more probiotic or synbiotic treatment groups compared to a control group (Bajaj, 2008; Beausoleil, 2007; Correa, 2005; Frohmader, 2010; Ishikawa, 2005; Manley, 2007; Naito, 2008; Puccio, 2007). Nine trials reported more deaths in control groups (Alberda, 2007; Basu, 2007; Chui, 2009; Dylewski, 2010; Honeycutt, 2007; Klarin, 2008; McFarland, 1994; Reuman, 1986; Sazawal, 2010). Three trials reported an equal number of deaths across groups (Dewan, 2007; Klarin, 2005; Tempe, 1985). Several studies reported that no deaths occurred in either treatment group of the trial (Anukam, 2008; Delia, 2002; Gibson, 2008; Knight, 2007; Lata, 2009; Luoto, 2010; Merenstein, 2009; Merenstein, 2009; Rio, 2002).

In total, 130 cases of diarrhea were reported in probiotics treatment groups, compared to 126 cases in a control group; the outcome was assessed in a large number of studies. Individual study results varied, sometimes favoring the probiotics treatment group, sometimes the control group, or reporting an equal number of incidences as documented in the Evidence Table C4, Results. Constipation was assessed in a large number of studies that contributed 1 or 2 cases of constipation in each of the treatment groups to the total number of 78 cases in a probiotics intervention and 73 cases in a control group. McFarland (1994) reported eight cases of constipation in the treatment group and two in the placebo group. Nausea was assessed in many studies, and several contributed 1 or 2 cases to the total number of 58 in probiotics users and 52 across control groups. However, Besselink (2008) reported 20 cases of nausea in the treatment group and 23 in the control group.

Respiratory infections were assessed in a number of studies, but 47 out of all 58 reported infections in a treatment group, and 49 out of all 59 control group incidences were reported by Gibson (2008), investigating the safety of a probiotic infant formula.

The 52 cases of “spitting up” in participants taking probiotics compared to 45 control group cases were almost all reported in a study by Abrahamsson (2007) (2 control group cases were reported by Maldonado (2009) investigating a probiotics intervention in the prevention of eczema).

There were 46 cases of “dyspepsia” in the probiotics group across studies and 3 in control group participants. As 45 cases came from one study that did not explicitly report on the control group (Turchet, 2003), the interpretation of the difference in results has to be regarded with caution. The adverse event with the next highest incidence was that of “constipation” (76 cases vs. 71 cases among control). In all, 44 cases of “abdominal discomfort” were reported across probiotics intervention groups (compared to the same number in a control group) where the number of adverse events was clearly stated. The symptom was assessed in a number of studies but the cases primarily came from one study (Kukkonen, 2007) that evaluated a synbiotic infant formula (35 cases in treatment, 37 in control group).

Colic was assessed in a number of studies, but 17 out of the 38 treatment group cases and 15 out of all 33 incidences of colic in control group infants were reported in Vlieger (2009), who investigated the tolerance and safety of a probiotic infant formula. There were 36 recorded incidences of abdominal fullness in a probiotics intervention group and 43 incidences across the control groups, all reported in one study (Besselink, 2008). All 35 cases of 'allergy sensitization' in the treatment group compared to 21 cases in the control group were identified in a failed effectiveness study (Taylor, 2007) that investigated the role of probiotic infant formula in the prevention of atopic dermatitis. The 31 cases of pain on micturition compared to 42 control group incidences were reported by Naito (2008) investigating adverse events in patients with transurethral resection of bladder cancer. All other events occurred in fewer than 30 participants across the 291 trials; all individual study results are shown in the Evidence Table C4, Results.

Number of Adverse Events

To quantify the risk of adverse events, we extracted two measures from individual studies, the number of participants with adverse events and the number of incidences of adverse events. This review included studies in generally healthy as well as critically ill participants with multiple morbidities. The listed adverse events are primarily of interest only in relation to a control group. Only controlled studies allow a comparison of the natural occurring rate of adverse events, the rate that can be expected with patients suffering from a particular condition, or that are caused by cointerventions.

Number of participants with adverse events. For each included study, we extracted the number of participants who experienced an adverse event in each group, where available. There were 121 studies that reported this number for a group with probiotics intake and a control group not receiving probiotic organisms as part of the intervention. The pooled relative risk effect for the number of adverse events was 0.98 (95% confidence interval [CI]: 0.93, 1.04, p=0.537) indicating that the risk to experience any adverse event was not higher in the probiotic group than in a control group not taking probiotics. The pooled risk difference was -0.001 (95% CI: -0.005, 0.003, p=0.993), indicating no difference between treatment and control groups.

The included controlled trials used a variety of control interventions. For comparisons between treatment groups, we considered all control interventions that were characterized by the absence of probiotics use. In a further sensitivity analysis, we restricted the comparison to parallel placebo-controlled RCTs. There was also no indication of an increased risk of adverse events relative to placebo control group participants (relative risk [RR]: 0.98; 95% CI: 0.92, 1.05; p=0.654; risk difference [RD] -0.003; 95% CI: -0.009, 0.004; p=0.386.

Number of incidences of adverse events. Not all studies reported explicitly the total number of participants who experienced any adverse event in each treatment group. The majority of studies reported one or more instances of adverse events that occurred in each group. From the publication it was not always clear whether these events were the only adverse events encountered and how many participants experienced an adverse event, as a participant can experience more than one adverse event. An alternative way to approach the risk for adverse events is to synthesize across all mentioned adverse event incidences. Studies where the total number of adverse event incidences exceeded the number of participants were excluded from this analysis, but 208 studies entered the analyses. The pooled relative risk for probiotics groups relative to control groups was 1.00 (95% CI: 0.93, 1.07, p=0.999) in this analysis, indicating an

equal risk of adverse events in the intervention group and the control group. The risk difference between intervention and control groups was 0.002 (95% CI: -0.002, 0.007, p=0.303). The small difference was not statistically significant; despite the large number of RCTs, no difference across treatment arms in the quantity of adverse events could be observed.

Considering only parallel placebo-controlled trials, there was also no evidence for a statistically significantly increased risk of adverse events based on the number of adverse event incidences (RR 1.02; 95% CI: 0.94, 1.10; p=0.659; RD 0.0010; 95% CI: -0.004, 0.006; p=0.659).

These quantitative analyses consider only the total number of adverse events reported in the main treatment group and the main control group, regardless of the type of outcome, including mild side effects such as bloating as well as serious adverse events such as sepsis and death. In section 2c we explore the nature of reported adverse events further, and Key Question 5 summarizes the evidence on serious adverse events.

A detailed analysis of the genera-specific safety reported in controlled trials is provided in Key Question 3b, additional intervention factors are also explored in Key Question 3.

Long-Term Effects

Of all included controlled trials, six addressed long-term effects of probiotics intake, meaning the studies reported followup assessments of one year or more. All investigated *Lactobacillus* strain interventions, alone or in combination with *Bifidobacterium*.

Abrahamsson (2007) investigated a short prenatal exposure and then 1 year of intake of probiotic organisms (*Lactobacillus reuteri* ATCC 55730) in infants to prevent eczema and found no differences in gastrointestinal problems between groups (spitting up, colic, or constipation), the last followup was at two years, one year after the original treatment had stopped, and no other adverse events were reported. Kopp (2008) investigated a short prenatal exposure and then six months of probiotics intake (*Lactobacillus rhamnosus* GG ATCC 53103) in infants to prevent atopic dermatitis and pointed out that children with recurrent episodes of wheezing bronchitis were more frequent in the probiotics treatment group (13 vs. 4 cases, p=0.03) at the 2-year followup, 1.5 years after the original treatment had stopped; the authors reported that no other notable adverse effects attributable to the probiotics supplementation were observed. Kuitunen (2009) (see also Kukkonen, 2007) investigated a short prenatal exposure and then 6 months of probiotics intake (*Lactobacillus rhamnosus* GG ATCC-55 103) in infants to prevent allergic diseases and found similar rates of abdominal discomfort, vomiting, excessive crying, and difficulty swallowing the product across groups, but infants in the probiotic group had significantly lower hemoglobin values than the placebo group. The followup period was 2 years; the last followup was 1.5 years after the intervention had stopped. Ljungberg (2006) followed children with genetic risk for type 1 diabetes mellitus for two years to evaluate the feasibility of using *Lactobacillus rhamnosus* GG in the first 6 months of life to decrease the appearance of Type 1 diabetes-associated autoantibodies. At the 2-year followup, the study found two samples positive for autoantibodies (3 across all followup periods), but the treatment group allocation was not specified, and other adverse event results were not reported. Naito (2008) investigated a 1-year probiotic supplementation (*Lactobacillus casei* Shirota) of participants on chemotherapy and reported no statistically significant differences between pain on micturition, urinary frequency, gross hematuria, constipation, or diarrhea across groups in the 3-year followup period, 2 years after the intervention stopped.

Niers (2009) investigated a short prenatal exposure and then 1 year of *Bifidobacterium* and *Lactobacillus* intake of mothers and their high-risk children to prevent allergic disease and

followed these dyads for 2 years. The flow diagram shows that the rate of dropouts for health problems of the child or the mother, feeding difficulties, or gastrointestinal colic were similar across groups.

No other trials were identified that reported on long-term effects of probiotics. The effects of long-term use of probiotics (defined as intervention durations of 1 year or more) are described in Key Question 4a.

(1c) What harms are reported in case reports?

In total, 43 case studies were identified that reported 1 case (Barton, 2001; Bassetti, 1998; Burkhardt, 2005; Cesaro, 2000; Cherifi, 2004; Conen, 2009; De Groote, 2005; Fredenucci, 1998; Henry, 2004; Hwang, 2009; Jensen, 1976; Ku, 2006; Ledoux, 2006; Lestin, 2003; Lolis, 2008; Lungarotti, 2003; Mackay, 1999; Munakata, 2010; Niault, 1999; Oggioni, 1998; Oh, 1979; Ohishi, 2010; Perapoch, 2000; Piarroux, 1999; Piechno, 2007; Pletinex, 1995; Presterl, 2001; Rautio, 1999; Rijnders, 2000; Tommasi, 2008; Trautmann, 2008; Viggiano, 1995; Zein, 2008; Zunic, 1991), 2 cases (Force, 1995; Kunz, 2004; Land, 2005; Riquelme, 2003), 3 cases (Kniehl, 2003; Munoz, 2005), 4 cases (Hennequin, 2000; Richard, 1988) or 6 cases (Lherm, 2002) of individuals who experienced an adverse event potentially associated with administered probiotic organisms. Only patients reported to have taken probiotic organisms purposefully (intervention study criterion) were eligible for inclusion in the review; hence, Perapoch et al. (2000) and Piarroux et al. (1999) contributed only one case each to the evidence tables, Munoz (2005) three cases, and Lherm (2002) six out of seven discussed cases. The identified case studies reported on 62 cases in total.

The participant details are abstracted in Evidence Table C1, Study and Participant Detail; the product details are abstracted in Evidence Table C2, Intervention. We extracted details for all included case studies that reported adverse events. We extracted the exact reported adverse event(s) and classified them using the CTCAE classification system. Although the reporting of adverse events tended to be more detailed in case studies, it was nonetheless rarely possible to grade the severity of the individual symptoms. The adverse events are shown in Evidence Table C4, Results.

The safety of probiotics was the main aim of all included case studies; the topic was an adverse event potentially associated with the intake of probiotic organisms. The case reports considered the adverse event to have potentially been caused by the intake of probiotic organisms.

The majority of publications presented the finding as a rare event of clinical importance encountered in clinical practice (Barton, 2001; Bassetti, 1998; Burkhardt, 2005; Cesaro, 2000; Cherifi, 2004; Conen, 2009; De Groote, 2005; Force, 1995; Fredenucci, 1998; Hennequin, 2000; Henry, 2004; Hwang, 2009; Jensen, 1976; Ku, 2006; Kunz, 2004; Land, 2005; Ledoux, 2006; Lestin, 2003; Lolis, 2008; Lungarotti, 2003; Mackay, 1999; Munakata, 2010; Niault, 1999; Oggioni, 1998; Oh, 1979; Ohishi, 2010; Perapoch, 2000; Piechno, 2007; Pletinex, 1995; Presterl, 2001; Rautio, 1999; Rijnders, 2000; Riquelme, 2003; Tommasi, 2008; Trautmann, 2008; Viggiano, 1995; Zein, 2008; Zunic, 1991).

Other cases were identified by following up a particular infection and then investigating whether it might be linked to exposure to probiotics. Lherm (2002) describe seven cases of fungemia in an intensive care unit, 6 of which could be linked to pretreatment with *Saccharomyces boulardii* [*cerevisiae*]. Munoz (2005) observed three patients with *Saccharomyces cerevisiae* fungemia in an intensive care unit for whom a review of the medical

records identified the treatment with Ultralevura as a risk factor. Piarroux (1999) retrospectively analyzed case histories of 437 observed cases of fungemia and concluded that *Saccharomyces* accounted for 16 cases. The authors described a *Saccharomyces boulardii* [*cerevisiae*] intervention for one patient but provided no further details on the other cases. Richard (1988) followed up all encountered cases of bacteremia caused by a *Bacillus* strain in a 6-year period and concluded that four of eight cases of *Bacillus subtilis* bacteremia were associated with the absorption of an oral preparation containing *Bacillus subtilis* spores.

The most commonly reported single outcome in the case studies was fungemia. Fungemia or presence of *Saccharomyces cerevisiae*/*boulardii* in blood cultures was reported for 33 cases in 21 publications (Bassetti, 1998; Cesaro, 2000; Cherifi, 2004; Force, 1995; Fredenucci, 1998; Hennequin, 2000; Henry, 2004; Lherm, 2002; Lolis, 2008; Lungarotti, 2003; Munoz, 2005; Niault, 1999; Perapoch, 2000; Piarroux, 1999; Piechno, 2007; Pletinex, 1995; Rijnders, 2000; Riquelme, 2003; Trautmann, 2008; Viggiano, 1995; Zunic, 1991). In addition, one publication reported the spread of fungemia to another infant who had not consumed probiotic organisms (Perapoch, 2000). All studies reported that the infection was associated with the administered organism *Saccharomyces boulardii* [*cerevisiae*]; however more details on the reliability and validity of the recovery methods are given in section 1h.

Eight cases of bacteremia associated with *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus GG*, and *Bacillus subtilis* were reported in six publications (Barton, 2001; De Groote, 2005; Ledoux, 2006; Richard, 1988; Tommasi, 2008).

Sepsis was reported for nine cases described in seven publications (Burkhardt, 2005; Kunz, 2004; Land, 2005; Lestin, 2003; Oggioni, 1998; Ohishi, 2010; Zein, 2008). The authors associated the outcome with the intake of *Saccharomyces boulardii* [*cerevisiae*], *Lactobacillus GG*, *Bacillus subtilis*, *Bifidobacterium breve*, or a blend of *Bifidobacterium* and *Lactobacillus* strains, but more details are reported in section 1h.

D-lactic acidosis was reportedly associated with *Lactobacillus acidophilus* in one case, a blend of *Lactobacillus acidophilus* and *Bifidobacterium infantis* in one other, and a product containing *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Streptococcus faecalis*, and *Streptococcus faecium* in three publications (Ku, 2006; Munakata, 2010; Oh, 1979). Endocarditis was reported in two publications reporting on two total cases (Mackay, 1999; Presterl, 2001), associated with a blend of *Lactobacillus* and *Streptococcus* strains. The development of an abscess associated with *Lactobacillus rhamnosus* was reported in two publications describing one case each (Conen, 2009; Rautio, 1999). Fever as the main adverse event after *Saccharomyces boulardii* [*cerevisiae*] use was described in one publication describing one patient (Jensen, 1976). One case of food protein-induced enterocolitis syndrome was associated with a *Saccharomyces boulardii* [cerevisiae] intervention (Hwang, 2009). Kniehl et al. (2003) reported 3 cases of diarrhea in patients who took a *Bacillus* product, but concluded that probiotics medication may result in diagnostically misleading results when stool specimens are taken (pseudo-outbreak of *Bacillus cereus*).

Twelve of the 59 patients described above died: 1 patient due to neurological complications (Richard, 1988), 1 due to pulmonary infection (Richard, 1988), 1 due to complications of anorexia nervosa (Cherifi, 2004), 1 due to multiple organ failure after bypass operation (Lestin, 2003), 2 presumably primarily sepsis related (Oggioni, 1998; Rijnders, 2000), and 6 patients due to causes not further specified (Lherm, 2002; Munoz, 2005).

Long-Term Effects

Three studies reported on the clinical course of the presented case studies and followed the patient for 1 year or more.

Oh (1979) reported on an incidence of d-lactic acidosis in a patient with short-bowel syndrome taking *Lactobacillus acidophilus*. After treatment with neomycin, the patient remained free of acidosis and neurologic dysfunction in the reported 1-year followup period. Presterl (2001) reported on a case of endocarditis initially associated with the intake of *Lactobacillus rhamnosus* after possible long-term consumption of probiotic yogurt (exact duration not reported, DNA-based methods showed no match of organisms). After treatment with penicillin for the infection and other medical procedures for further morbidities, the patient was well at the 3-, 6-, and 12-month checkups.

Cesaro (2000) reported on a case of *Saccharomyces cerevisiae* fungemia in a neutropenic patient. After treatment with amphotericin-B, bone marrow transplantation, and chemotherapy to treat leukemia, the patient was well at least 3 years after the fungemia incidence.

(1d) What safety parameters are collected in population surveillance studies and other observational studies, and do these include only standard clinical safety parameters (e.g., standard blood chemistry profiles) or also expanded laboratory or clinical testing unique to the use of probiotics?

None of the included studies in this review is a traditional population surveillance study. None of the screened studies followed participants who chose to take probiotics or synbiotics, and hence would have been a self-selected intervention group. With the exception of some case studies, all of the included studies were part of a research study investigating the effects of probiotics or synbiotics chosen by the study investigators. We identified no cohort study comparing a group of participants who used probiotics with a group of people who did not. We also did not identify case-control studies that met all our inclusion criteria, that is, studies that identify cases by the outcome and look for potential risk factors, of which taking probiotics might be one. Hence there is no evidence from traditional population surveillance studies.

We identified 53 case series, studies that followed a group of participants who were given probiotics or synbiotics. Case series do not compare the results of the treatment sample to a control group, so this evidence is typically classified as observational and limited in its power to allow inferences from observed adverse events to the received intervention. Two thirds of the identified studies used medium sample sizes. Only 8 large studies (reporting on 100 or more participants) were identified (Bellomo, 1979; Cobo Sanz, 2006; Colecchia, 2006; Di Pierro, 2009; Dughera, 2007; Fukuda, 2008; Gniwotta, 1977; Luoto, 2010). Eight studies reported on 10 or fewer participants (Benchimol, 2004; Berman, 2006; Bruce, 1988; Elmer, 1995; Garrido, 2005; Hensgens, 1976; Malkov, 2006; Reid, 2001; Weiss, 2010).

Nineteen of the case series indicated that investigating the safety of the intervention was one of the main aims of the publication (Bibiloni, 2005; Bruni, 2009; Colecchia, 2006; Elmer, 1995; Fukuda, 2008; Gabrielli, 2009; Huynh, 2009; Karimi, 2005; Kitajima, 1997; Lamiki, 2010; Lombardo, 2009; Luoto, 2010; Mego, 2005; Nobuta, 2009; Rosenfeldt V, 2003; Uehara, 2006; Yim, 2006; Zahradnik, 2009). However, almost half of the case series did not report that they assessed adverse events as part of their treatment evaluation, as can be seen in Evidence Table C3, Assessment.

Where studies stated that adverse events were monitored, they typically did not define what would be considered an adverse event and what exactly was monitored. Where specified, studies mentioned that they monitored gastrointestinal symptoms or blood chemistry results.

To assess any adverse events that may occur during the treatment period, some studies used a patient diary (Barrett, 2008; Bekkali, 2007; Gionchetti, 2007; Huynh, 2009; Lamiki, 2010; Lombardo, 2009; Zahradnik, 2009) or a questionnaire (An, 2010; Barrett, 2008; Cobo Sanz, 2006; Colecchia, 2006; Dughera, 2007; Gruenwald, 2002; Nobuta, 2009), but in most cases, the assessment was done by a health care professional. It was often not clear whether the assessment of adverse events was prompted or whether the health care professionals recorded only adverse events that participants chose to mention. Colechia (2006) reported the use of a published questionnaire (Neri, 2000) for the harms assessment. The measure was designed to discriminate irritable bowel syndrome and gastrointestinal diseases from food allergies; however it also covered drug tolerance. Mego (2005 and 2006) graded toxicity according to the National Cancer Institute Common Toxicity Criteria (version 2.0), designed to report results of cancer treatment.

We also extracted which adverse events were reported on by the authors, regardless of whether the harm occurred or it was reported that no incidence of the harm was found. The most frequently recorded individual adverse event was diarrhea or watery stool (recorded in nine studies); gas, meteorism, or flatulence (nine studies); bloating or fullness (seven studies); abdominal pain or gastralgia (five studies); and nausea (six studies).

(1e) What harms are reported in population surveillance studies and other observational studies?

As described under Key Question 1d, we did not identify conventional population surveillance studies that met our inclusion criteria. The only evidence that can be described here stems from case series. In this review, a case series was defined as a study reporting on a single group of participants using probiotics or synbiotics. In total, 53 case series were identified reporting on 3,473 participants. The majority investigated *Lactobacillus* strain interventions, mainly alone or in some cases in combination with strains of other genera. Five studies investigated an intervention including *Bifidobacterium*, four used *Saccharomyces*, three *Enterococcus*, two *Streptococcus*, and two *Bacillus* organisms. All included genera are indicated in the Evidence Table C4, Results, details of the individual interventions are shown in Evidence Table C2, Intervention.

For all case series, we extracted which adverse events were reported in the publication, using the exact wording from the articles. In addition we classified the adverse events using the CTCAE classification system and graded events where possible; however the reported detail of adverse events rarely permitted grading the severity. We also indicated for each outcome whether it was considered an SAE. The details of each study can be seen in Evidence Table C4, Results.

The most frequently reported incidence of an individual symptom across the case series was bloating or fullness (25 participants, recorded in 7 studies) followed by diarrhea or watery stools (22 participants across studies, 16 studies recorded the outcome). Flatulence or gas (20 participants, 9 studies recorded the outcome) and nausea (18 participants, recorded in 13 studies) were also recorded in more than 10 participants.

In total, the case series reported 12 deaths across studies, and the outcome was recorded in 3 studies. During the study reported by Carlsson (2009), two dementia patients using *Lactobacillus* and *Lactococcus* among other medications died. Malkov (2006) reporting on a sample of 10

cancer patients using, among other medication, a *Bacillus oligonitrophilus* KU-1 containing product, all of whom died from unspecified causes, liver failure, pulmonary edema, and stroke. Mego (2006) reported that no deaths occurred (*Enterococcus faecium* M-74 containing intervention).

In the absence of a control group and multiple alternative explanations for the reported adverse events, it is not possible to attribute the events to the probiotics intervention.

Long-Term Effects

None of the included case series reported on long-term treatment effects (a followup of 1 or more years after the administration of probiotic organisms).

(1f) What harms are reported in human mechanistic studies?

Of the included studies that reported a specific adverse event, none could clearly be described as a mechanistic study. Studies primarily investigating possible mechanisms of action of probiotics are either not published in the peer-reviewed literature and databases we searched, which concentrated on health research, or they do not consider patient health outcomes, the focus of this review. We also identified only a very small number of studies that reported nonspecific safety statements and that could be described as mechanistic studies (see Appendix C, Evidence Table C6, Nonspecific Safety Statements).

A study focusing in part on a mechanistic question (Garrido, 2005) investigated how the ingestion of different amounts of *Lactobacillus johnsonii* La1 influences the main bacterial populations of the fecal microbiota in eight symptomatic volunteers. The study stated that the participants showed good tolerance for the product and noted only mild increases of borborygmi. Johansson (1998) investigated the survival of *Lactobacillus plantarum* DSM 9843 (299v) after ingestion in a RCT and reported that five participants in the probiotic and (the rose-hip drink) control group experienced transient abdominal discomfort, nausea, or flulike symptoms. Songisepp (2005) studied the fecal lactoflora composition, *Lactobacillus fermentum* ME-3 recovery, intestinal lactoflora, and oxidative stress markers of blood in healthy volunteers and reported one acute respiratory viral infection (treatment group unclear) and no changes in gastrointestinal functions or other adverse effects on general welfare.

A case series by Biblioni (2005) that investigated the composition of biopsy-associated microbiota in patients with ulcerative colitis among other questions reported that no biochemical adverse events occurred with VSL#3, but 29 percent of participants reported increased bloating. Satokari (2001) published an additional article on polymerase chain reaction and denaturing gradient gel electrophoresis monitoring of fecal *Bifidobacterium* populations in a prebiotic and probiotic trial, and reported one incident of abdominal discomfort in the control group and one control group participant who did not complete the study due to antibiotic treatment.

(1g) Do the studies describe an antibiotic therapy designed to treat unintended pathology caused by the administered organism?

Of the 387 included studies, 40 case studies (of all 43 case studies) described an antibiotic or antifungal therapy designed to treat unintended pathology potentially caused by the administered organism (Barton, 2001; Bassetti, 1998; Burkhardt, 2005; Cesaro, 2000; Cherifi, 2004; Conen, 2009; De Groote, 2005; Force, 1995; Fredenucci, 1998; Hennequin, 2000; Henry, 2004; Ku, 2006; Kunz, 2004; Land, 2005; Ledoux, 2006; Lestin, 2003; Lherm, 2002; Lolis, 2008; Lungarotti, 2003; Mackay, 1999; Munakata, 2010; Munoz, 2005; Niault, 1999; Oggioni, 1998;

Oh, 1979; Ohishi, 2010; Perapoch, 2000; Piarroux, 1999; Piechno, 2007; Pletinex, 1995; Presterl, 2001; Rautio, 1999; Richard, 1988; Rijnders, 2000; Riquelme, 2003; Tommasi, 2008; Trautmann, 2008; Viggiano, 1995; Zein, 2008; Zunic, 1991). Details of the case studies are described in section 1c.

None of the other studies (i.e., case series, CCTs, parallel and crossover RCTs) reported the use of antibiotics to treat unintended effects of the probiotics treatment.

However, causes for antibiotic or antifungal therapy were neither always clearly stated nor easy to establish, and authors might not have associated the treatment with the probiotic intervention. Hence, we extracted any mention of antibiotic treatment in the included studies. This summary does not include studies where all participants received antibiotics as a cotreatment or studies where the reduction or prevention of antibiotics use was an efficacy outcome. Only studies were considered that reported that a course of antibiotic or antifungal treatment was required to treat an adverse event of individual participants during or after the intervention period.

Two case series reported that a participant required antibiotic treatment during a probiotic intervention. One study reported antibiotic treatment for febrile neutropenia (Mego, 2006). The other study reported treatment for a case of bronchitis (Reid, 2001).

Seventeen RCTs in total reported explicitly that a participant required antibiotic treatment during or after the intervention. In none of the RCTs did the authors relate the infections requiring antibiotic treatment to the probiotic, and antibiotic treatment was required in treatment and control group participants.

One study reported that participants receiving the probiotic had more otitis media, and it was then treated with an antibiotic (Abrahamsson, 2007). Allen (2010) reported more respiratory infections in the probiotic treatment group compared to placebo, and nine cases across arms were treated with antibiotics. Basu (2007) reported that two participants in each group were treated for septicemia (presumably with antibiotics, although not explicitly stated). Another study reported that two participants received antibiotics for abscesses that the authors attributed to Crohn's disease, specifically stating that they were "not caused by LGG," or *Lactobacillus* GG (Bousvaros, 2005). Gerasimov (2010) reported that three preschool children (two treatment group and one control group) treated for atopic dermatitis were lost to followup due to respiratory tract infections requiring antibacterial therapy. Two of the RCTs reported unanticipated antibiotic use required during probiotic and placebo treatment but did not specify what it was treating (Chouraqui, 2008; Krasse, 2006). Haschke-Becher (2008) reported that one child in a probiotic intervention and three children in control groups withdrew due to antibiotic intake. One of the RCTs reported a gastrointestinal infection in the probiotics treatment group, without identification of the causative organism (Mimura, 2004). In another study, one case of perineal Candida was found in both arms and was treated with antibiotics (Millar, 1993). Niers (2009) reported that three mother-child pairs out of each treatment group discontinued a trial on prevention of allergic diseases due to use of antibiotics. Satokari (2001) reported that one control group participant did not complete the study because of an antibiotic treatment (details not reported). Sullivan (2003) reported that one participant in the probiotics group developed diarrhea, with no causative organism confirmed and was later treated with antibiotics. Tursi (2006 and 2008) reported that one case in a probiotics group was admitted to a hospital due to acute bronchial pneumonia and treated with antibiotics.

Larsson (2008) reported that 10 participants received antibiotics for upper respiratory infections or other reasons, at least 4 of whom were in the probiotic group. De Preter (2006)

reported that 1 participant withdrew from a crossover trial comparing *Saccharomyces boulardii* [*cerevisiae*], lactulose, and placebo intake but the group to which the participant was assigned was not reported.

(1h) Do the studies describe methods for recovery of the administered organism from either the gastrointestinal tract or serum?

To be included in the review, studies had to report an adverse patient health outcome; the recovery of the administered organism alone was not a sufficient outcome to be eligible for inclusion in the review. Nonetheless, a large number of included studies reported recovery of *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus* in the gastrointestinal tract, serum, mouth, or vagina. In most cases, the attempt to recover the organism was used as an efficacy measure, an indicator of a successful intervention and quality check that the organism was indeed consumed.

None of the case series, CCTs, or parallel or crossover RCTs reported an infection or other significant clinical signs and the recovery of the administered organism. Some of the trials reported that infections and/or the recovery of the administered organisms in the blood were monitored but that no cases occurred. A description of the methods was not reported; however, any suspected positive identification may have changed that.

Evidence From Controlled Trials

In total, 36 trials reported that sepsis, bacteremia or fungemia, infections, or blood cultures were monitored to investigate associations with the administered organism as a safety precaution.

A small number of trials reported explicitly on the absence of probiotics-associated sepsis, bacteremia or fungemia. Alberda (2007) reported no cases of *Lactobacillus*-induced sepsis. Bin-Nun (2005) reported no cases of sepsis due to administered probiotics (*Bifidobacterium* and *Streptococcus* strains). Forestier (2008) reported no cases of *Lactobacillus*-related sepsis. Jirapinyo (2002) reported no cases of sepsis due to *Lactobacillus* or *Bifidobacterium*. Kerac (2009) reported no cases of probiotics-related sepsis (*Lactobacillus, Leuconostoc, and Pediococcus*). Li (2004) reported no cases of sepsis due to *Bifidobacterium*. Lin (2005) reported no cases of sepsis due to probiotics (*Lactobacillus* and *Bifidobacterium*). Lin (2008) reported no cases of sepsis due to probiotics (*Lactobacillus* and *Bifidobacterium*). Manzoni (2006) reported no cases of sepsis due to LGG. Millar (1993) reported no cases of sepsis or infections attributable to LGG. Rouge (2009) reported no cases of sepsis due to *Lactobacillus* and *Bifidobacterium*. Barraud (2010) reported no cases of bacteremia due to *Lactobacillus*. Honeycutt (2007) reported no cases of *Lactobacillus* bacteremia. Morrow (2010) reported no cases of *Lactobacillus* bacteremia. Song (2010) reported no cases of fungemia due to *Saccharomyces*.

A small number of trials reported on the absence of probiotic-associated infections or signs of infections. Allen (2010) reported no infections due to *Lactobacillus* or *Bifidobacterium*. The PROPATRIA trial (Besselink, 2008) reported no infections caused by the administered probiotics (*Lactobacillus* and *Bifidobacterium* strains). Frohmader (2010) reported no infections due to probiotic strains (*Lactobacillus, Bifidobacterium,* and *Streptococcus* strains). Kotzampassi (2006) reported no cases of infections due to *Lactobacillus* species contained in formula. Lawrence (2005) reported no cases of *Lactobacillus* infections. Salminen (2004) reported no cases of infections due to *Lactobacillus*. Awad (2010) reported no probiotic bacteria were found

in blood (*Lactobacillus*). Osterlund (2007) reported no cases of *Lactobacillus* growth in blood. Peral (2009) reported that the administered *Lactobacillus* organism was not recovered in peripheral blood or wound samples. Samanta (2008) reported no blood cultures grew *Lactobacillus* or *Bifidobacterium*. Wolf (1998) reported that all cultures for bacteria in blood samples showed no growth after seven days of incubation (*Lactobacillus*).

Finally, some studies reported on the absence of infectious incidences without reference to the administered probiotic. Anukam (2008) reported no cases of bacteremia (*Lactobacillus* and *Streptococcus* strain intervention). Delia (2007) reported no cases of bacteremia or sepsis (intervention with *Lactobacillus, Bifidobacterium*, and *Streptococcus* strains). Kianifar (2009) reported no cases of bacteremia or fungemia (*Lactobacillus* and *Bifidobacterium* intervention). Luoto (2010) reported no cases of sepsis (*Lactobacillus* and *Bifidobacterium* intervention). Merenstein (2010) reported no cases of viral infections causing fever in the treatment group (*Lactobacillus* and *Streptococcus* strains). Panigrahi (2008) reported no cases of sepsis (*Lactobacillus* intervention). Reid (1992) reported no cases of superinfections (Lactobacillus strains). Saint-Marc (2010) reported no cases of infections (*Saccharomyces* intervention). Songisepp (2005) reported no infections (*Lactobacillus* intervention). Wada (2010) reported no cases of bacteremia (*Bifidobacterium* intervention). Knight (2007) reviewed whether any deaths in the samples were attributable to probiotic organisms and reported also on colonization of *Leuconostoc* in tracheal aspirate which may indicate that they also looked for the administered organisms. McFarland (1994) reported no cases of *Staphylococcus* sepsis, which may indicate that they also looked for the administered organisms.

Evidence From Case Series

Of the case series, Luoto (2010) reported no cases of LGG sepsis. Mego (2005) reported that the seven cases of bacteremia were mainly caused by coagulase-negative *Staphylococcus* and concluded that no infection was induced by the tested strain (*Enterococcus faecium* M-74). In a second study, Mego (2005) described a test for colonization of the gut by *Enterococcus* bacteria and in addition stated that bacteremia or infection caused by the tested probiotic strain (*Enterococcus faecium* M-74) was not found. Schneider (2005) described stool analyses and reported that no fever or fungemia occurred but did not mention a specific test (*Saccharomyces boulardii [cerevisiae]* intervention. Srinivasan (2006) explicitly stated that cultures did not show a pathologic growth of *Lactobacillus* bacteria (in surface cultures or sterile body fluids).

Evidence From Case Studies

Most case studies reported the recovery of an organism that resembled the administered probiotic strain (see Evidence Table C4, Results). The years of publication of the case studies encompass almost 40 years, during which time methods of identification have evolved. In several cases, there remained some doubt whether the recovered strain was identical to the administered organism. In most publications, authors suspected that there was an association rather than being able to show conclusively that the administered and the recovered organism were identical.

Several case studies did not report on an identification method, used phenotypic identification alone, or used other indicators such as the temporal closeness to the reaction (Burkhardt, 2005; Cesaro, 2000; Cherifi, 2004; Force, 1995; Henry, 2004; Hwang, 2009; Jensen, 1976; Ku, 2006; Ledoux, 2006; Lestin, 2003; Lungarotti, 2003; Mackay, 1999; Munakata, 2010;

Niault, 1999; Oh, 1979; Piechno, 2007; Pletinex, 1995; Rijnders, 2000; Spinosa, 2000; Tommasi, 2008; Trautmann, 2008; Viggiano, 1995; Zein, 2008; Zunic, 1991)

Other studies, in particular more recent ones, described a genetic fingerprinting approach to match species or strains.

Lactobacillus. Conen (2009) reported that *Lactobacillus rhamnosus* species recovered from an abscess were identical to the intervention species according to not further specified genetic sequencing pattern and resistance testing. De Groote (2005) used sequencing of the ribosomal operon region and strain typing of the isolates with pulsed field gel electrophoresis to show identity of the intervention organism and the *Lactobacillus rhamnosus* blood stream isolates. Kunz (2004) used PFGE to identify *Lactobacillus* GG from blood culture isolate in a case of sepsis and intervention isolates. Land (2005) used repetitive element sequence-based polymerase chain reaction DNA fingerprinting to match *Lactobacillus* GG isolates from bacteremia and sepsis cases and the intervention isolate. Rautio (1999) used pulsed-field gel electrophoresis (PFGE) to identify *Lactobacillus rhamnosus* species.

Presterl (2001) used randomly amplified polymorphic DNA polymerase chain reaction (RAPD)-PCR assays to distinguish pathogens and the probiotic strain and concluded that the *Lactobacillus rhamnosus* isolate causing endocarditis and septic arthritis was not identical with the probiotic yogurt *Lactobacillus rhamnosus* isolate as initially suspected.

Bifidobacterium. Ohishi (2010) used polymerase chain reaction analysis and strain-specific identification by a randomly amplified polymorphic DNA analysis to confirm the identity of sepsis isolates and the *Bifidobacterium breve* BBG-01 intervention.

Saccharomyces. Bassetti (1998) used pulsed field gel electrophoresis (PFGE) to match *Saccharomyces cerevisiae* species seen in fungemia with the intervention species. Fredenucci (1998) used electrophoretic patterns and variations in DNA-band patterns to establish the identity of the administered *Saccharomyces boulardii [cerevisiae]* organisms and fungemia isolates. Hennequin (2000) used mitochondrial DNA patterns to compare fungemia isolates and intervention *Saccharomyces boulardii [cerevisiae]* organisms. Lherm (2002) used a comparison of the polymorphism of nuclear and mitochondrial DNA with 13 restriction enzymes from the *Saccharomyces boulardii [cerevisiae]*) isolated in patients and the intervention. Lolis (2008) used sequencing analysis on the DNA of the fungemia strain isolated as *Saccharomyces cerevisiae* and the isolate obtained from the intervention product and reported 98 percent correspondence. Munoz (2005) reported that *Saccharomyces cerevisiae* isolates were compared in PCR fingerprinting profiles. Perapoch (2000) used molecular identification based on mitochondrial DNA restriction analysis and chromosomal DNA profiles to show that *Saccharomyces cerevisiae* isolates were identical. Piarroux (1999) used DNA sequences to compare *Saccharomyces boulardii [cerevisiae]* isolates. Riquelme (2003) used PFGE clonality banding patterns to match *Saccharomyces cerevisiae* isolates.

Streptococcus. No case studies associated with *Streptococcus* strains used as probiotics were identified.

Enterococcus. No case studies associated with *Enterococcus* strains used as probiotics were identified.

Bacillus. Oggioni (1998) used randomly amplified polymorphic DNA technique for two *Bacillus subtilis* strains.

Summary and Strength of Evidence Key Question 1

What is the evidence that the active (e.g., live or viable) and lyophilized forms of probiotics (*Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and *Bacillus*) as single ingredients or in combination with other probiotics or prebiotics in all delivery vehicles (and formulations) when used to cure, treat, mitigate or prevent a disease or reduce disease risk are safe in the short term? Long term?

Volume: 387 studies

Risk of bias: Medium

The evidence to answer this Key Question stems from a variety of study designs and quality. Although a large number of RCTs have been identified, the majority was not designed to systematically assess safety outcomes.

Consistency: Inconsistent

The RCTs, CCTs, and case series show very different results from case studies.

Directness: Direct

The evidence base includes a large number of RCTs directly comparing intervention and control group participants.

Precision: Imprecise

The majority of included studies use a moderate sample size; very few large studies have been identified. The studies are not powered to detect differences in adverse event incidences.

The identified evidence is insufficient to answer the Key Question with confidence.

The current literature is not sufficient to allow statements on the safety of probiotics in research studies if the term "probiotics" comprises the genera *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus*. The currently available literature describes primarily *Lactobacillus* interventions, alone or in combination with other genera, most often *Bifidobacterium*, and some interventions use *Saccharomyces* organisms. The available literature includes only a few reports on the genera *Streptococcus, Enterococcus,* and *Bacillus*. The absence of case reports of serious adverse events potentially caused by products containing *Streptococcus* or *Enterococcus* strains cannot be used as an indicator that the risk of serious adverse events is absent: the overall identified body of literature reporting on the presence and absence of harms indicates absence of relevant literature. The microorganisms have not been used in research studies, which may indicate less use in clinical practice.

Few studies indicated what adverse events were monitored. The clinical studies such as controlled clinical trials, and parallel and crossover randomized controlled trials and observational case series that reported on monitoring of adverse events listed gastrointestinal adverse events such as diarrhea, vomiting, and constipation as explicitly monitored.

Individual outcomes that were often reported on were death, diarrhea, constipation, and nausea, seemingly equally frequent across treatment arms. Individual outcomes such as mortality

and allergy sensitization should be assessed in a risk-benefit analysis including the outcome regardless of whether it was investigated as a safety concern or efficacy measure according to reports of failed effectiveness.

We have identified a number of case studies reporting cases of fungemia and some bacteremia cases that are likely to have been caused by the administered probiotic strain. The number of cases is small considering the volume of the literature searched; however, the studies indicate that probiotic strains can be associated with serious adverse events and that they can be linked to the use of probiotic products. To quantify the risk, study designs other than case studies are needed (e.g., RCTs). Even though the risk potential has been documented in the literature, studies do not routinely state that they assessed the risk of infections caused by the administered strain. None of the identified case series, CCTs, or crossover and parallel RCTs reported an infection caused by the administered probiotic strain.

In the absence of a control group and multiple alternative explanations for the adverse events reported in case series, it is not possible to attribute the events to the probiotics intervention.

Across RCTs, there was no evidence for a statistically significantly increased relative risk of the quantity of adverse events for intervention participants compared to control based on two alternative measures: the number of participants with adverse events per treatment arm (RR 0.98; 95% CI: 0.93, 1.04; p=0.537) and the number of adverse event incidences per treatment group (RR 1.00; 95% CI: 0.93, 107; p=0.999) in short and medium followup studies.

The review did not identify comparative population surveillance studies that systematically assessed safety. Very few publications were identified that reported on long-term effects of probiotics use.

Key Question 2. What are characteristics and associations of the reported harms in Question 1?

All 387 studies meeting criteria for full data abstraction were considered to answer Key Question 2.

The overview presented at the beginning of this chapter and Key Question 1 show the literature is incomplete with regard to the assessment of adverse events potentially associated with probiotics interventions. The evaluation of the characteristics and associations is limited to adverse events as currently reported in research studies.

(2a) What interactions between probiotics and medications are reported?

None of the included studies reported a formal interaction analysis for safety data. A number of studies commented on interaction effects for efficacy outcomes, but none of the studies investigated statistically whether medication leads to differential safety results

For the purpose of this review, we recorded whether participants in included studies used antibiotics, corticosteroids, immune suppressants, dietary therapies, or other pertinent cotreatments (e.g., chemotherapy) that might possibly influence the adverse events experienced by participants. We found a large number of parallel RCTs where participants systematically used additional treatments apart from the probiotics preparation under review. To address the question of an interaction between probiotics and medications, we differentiated RCTs broadly into those that reported a pertinent cotreatment and those that did not and added this factor to a meta-regression predicting effect size. This analysis compares the risk ratio between intervention and control group participants for studies with cotreatments and for studies without cotreatments, and determines whether this difference in risk is statistically significant.

Using the number of participants with adverse events, we found that the relative risk to experience an adverse event for studies with cotreatments was slightly higher but not statistically significantly different from studies without pertinent cotreatments (RR 1.12; 95% CI: 0.99, 1.26; p=0.074). This interaction analysis is based on 106 RCTs for which data were available for pooling. In total, 44 of these RCTs reported pertinent cotreatments. These numbers are based on the number of participants experiencing an adverse event. Using the total number of events across groups as a sensitivity analysis for the robustness of the result, we find a very similar result: the relative risk for studies with cotreatments was 1.04 times higher than for studies without cotreatments (95% CI: 0.90, 1.20; p=0.627), also indicating no evidence for a statistically significant difference in the relative risk of probiotics for studies with and without cotreatments. This interaction analysis is based on 195 studies; 86 included cotreatments. Methodologically it is problematic trying to identify an interaction signal across studies rather than having information that stems from within studies, so this result has to be interpreted with caution.

It is noteworthy that the included case studies that reported harms such as fungemia and bacteremia appear to be primarily in patients with multiple morbidities. Although the concomitant medications were not explicitly listed in all studies, the underlying conditions make it very likely that these patients were taking other medications (see Evidence Table C1, Study and Participant Details in the appendix for a description of patients). Whether an interaction between probiotics and medications contributed to the observed adverse events, and whether this interaction exists independent of a possible interaction between the underlying condition and probiotics cannot be determined in case studies.

Key Question 6 reports stratified analyses for the individual reported cotreatments.

(2b) What harms related to acquired antibiotic resistance and/or transferability are reported?

We included reports of acquired antibiotic resistance as well as antifungal resistance, given that the scope of the review included *Saccharomyces* strains. However, only studies reporting on patient health outcomes were eligible for inclusion in the review; hence this Key Question considered antibiotic or antifungal resistance and transferability incidences as a patient health outcome with clinical significance. Reports of laboratory tests showing antibiotic or antifungal resistance of microbial strains in isolation are outside the scope of the review.

None of the parallel or crossover RCTs, CCTs, or case series reported an incidence of antibiotic resistance and/or transferability. With regard to monitoring antibiotic resistance or transferability, one RCT (Reid, 1992) explicitly reported that none of the participants with urinary tract infections in a *Lactobacillus* suppository intervention showed any evidence of super-infection.

Antibiotic or antifungal resistance was addressed in six case reports. Conen (2009) report that *Lactobacillus rhamnosus* strains recovered from an abscess were resistant to cephalosporin classes I through IV and carbapenems but the patient improved with imipenem, clindamycin, and fluconazole. Oggioni (1998) describe an immunocompromised patient with recurrent septicemia. The patient's condition deteriorated despite antibiotic therapy. *Bacillus subtilis* strains isolated during fever episodes showed resistance to penicillin, erythromycin, rifampin, and novobiocin in two samples. Ohishi (2010) describe a neonate with omphalocele who developed *Bifidobacterium* septicemia. The isolated strain was susceptible in vitro to penicillin and ampicillin sulbactam but not to meropenem or amikacin. Piechno (2007) described a case of

fungemia in a cancer patient; one of the blood cultures showed the presence of *Saccharomyces boulardii* [*cerevisiae*] and indicated resistance to amphotericin B and possibly fluconazole. The patient recovered after a course of voriconazole. Trautmann (2008) reported on an intensive care patient who developed fungemia and presented with fever after initial clinical improvement while on fluconazole. The patient was able to leave the intensive care unit after administration of caspofungin. Zein (2008) reported on a diabetic patient who developed *Lactobacillus rhamnosus* septicemia; an antibiogram indicated resistance to nalidixic acid, vancomycin, and teicoplanin. The patient recovered after amoxicillin treatment.

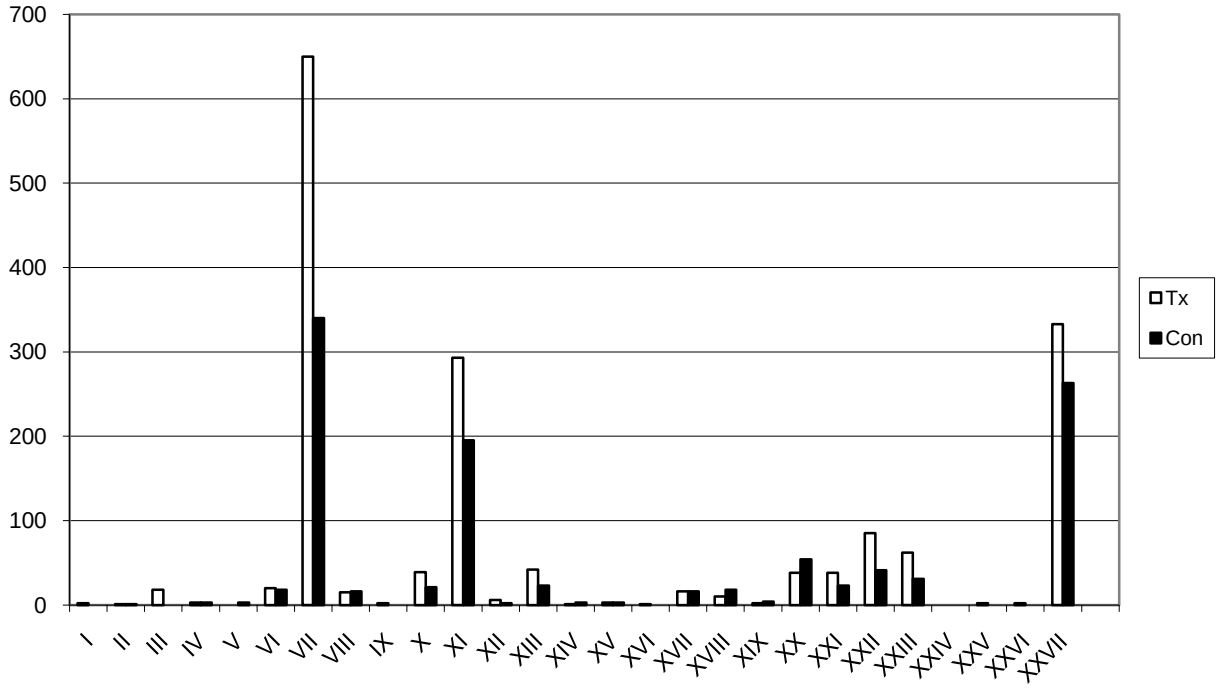
(2c) What is the nature of harms, and do these include only standard harms or also harms that might be uniquely applicable to the use of a probiotic?

Key Question 1 addressed primarily the quantity of adverse events and specific harms that were monitored and / or reported. The adverse events reported in the included studies were found within many organ systems. To explore the nature of the adverse events, we used the CTCAE system to differentiate adverse events and added an additional category, 'other,' so that all harms could be classified. The categorization system can be seen in Appendix B (data extraction form).

By far the most commonly reported incidence across all included studies was a gastrointestinal symptom (category VII in the Evidence Table C4, Results), followed by the category Infections and Infestations (category XI), and the "other" category (category XXVII). The last category included deaths not further specified, unclear adverse events (e.g., "collapse," "general health problems"), and summary incidences ("ear, nose, throat symptoms").

The graph shows the distribution of adverse events within the categories for all probiotic intervention arms (up to three per study) across studies and study designs. For studies that included a control group, frequencies are also shown. Figure 10 shows data from all included studies, both controlled and uncontrolled.

Figure 10. Adverse events per CTCAE category for participants using probiotics and control participants (up to 3 probiotics intervention groups, 1 control group



The categories VII (Gastrointestinal disorders), XI (Infections and infestations); and also XXVII (Other) are the most common categories describing the observed adverse events. Some encountered adverse events were included in categories X (Investigations), XX (Renal and urinary disorders); XXII (Respiratory, thoracic and mediastinal disorders), and XXIII (Skin and subcutaneous tissue disorders). The other categories (Blood and lymphatic system disorders; Cardiac disorders; Congenital, familial and genetic disorders; Ear and labyrinth disorders; Endocrine disorders; Eye disorders; General disorders and administration site conditions; Hepatobiliary disorders; Immune system disorders; Injury, poisoning and procedural complications; Metabolism and nutrition disorders; Musculoskeletal and connective tissue disorders; Neoplasms benign, malignant and unspecified (including cysts and polyps); Nervous system disorders; Pregnancy, puerperium and perinatal conditions; Psychiatric disorders; Reproductive system and breast disorders; Social circumstances; Surgical and medical procedures; and Vascular disorders) rarely described the reported adverse events.

The following sections report the risk of adverse events separately for each of the three established domains (gastrointestinal, infections, and 'other'). The 'other' category was analyzed together with all other observed incidences, excluding only categories VII and XI.

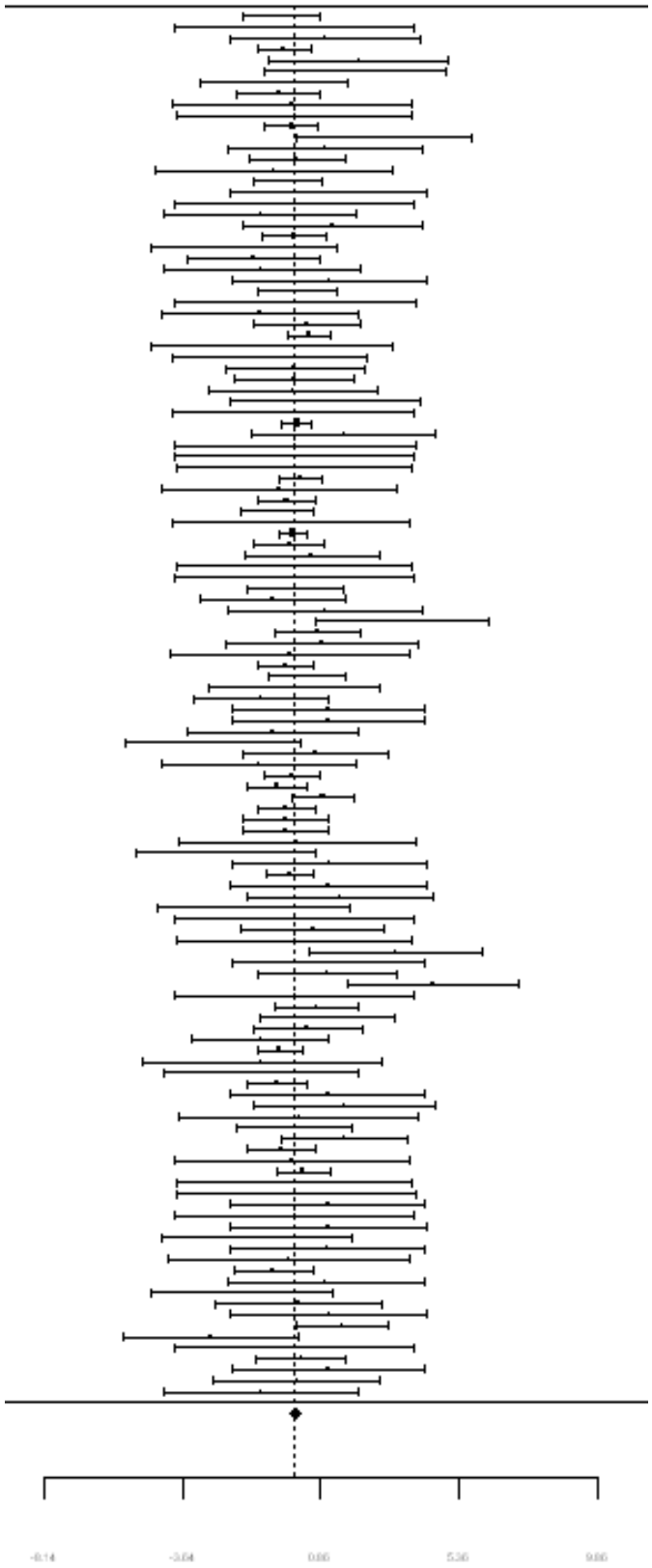
Gastrointestinal Adverse Events

To investigate the relative risk for a gastrointestinal adverse event to occur, we pooled the parallel RCTs that reported on the presence or the absence of these adverse events. The risk for participants in probiotics intervention groups, relative to non-probiotics control group participants, was 1.03 (95% CI: 0.89, 1.18, p=0.693) indicating that the probiotic interventions were not associated with a statistically significantly increased risk of gastrointestinal adverse events. Overall, there was no evidence across the included RCTs for a statistically significantly

increased risk to experience a gastrointestinal symptom in the probiotic group compared to another group from the same participant population with similar co-interventions and the presence or absence of underlying diseases. The control groups either received a placebo, no treatment, or the co-medication or infant formula without the probiotic supplement.

The analysis was based on 126 parallel RCTs. Studies comparing two probiotic or synbiotic treatments were excluded from this analysis and only one probiotic group was selected per study so that each study entered the meta-analysis only once (the main treatment group, most similar to the control group apart from the probiotic addition). This analysis included 104 studies that use *Lactobacillus* strains alone or in combination, indicating that *Lactobacillus* organisms were most commonly used in the included RCTs. Figure 11 graphically represents individual and pooled point estimates and 95% CIs obtained in included RCTs. Due to the large number of studies, numerical estimates and study identifiers of individual RCTs could not be displayed.

Figure 11. Graphical representation of the RR of the number of gastrointestinal adverse events across RCTs



The forest plot demonstrates that individual results differed across studies, sometimes favoring the control group and sometimes the intervention group, with no clear trend in either direction. Confidence intervals were wide in the large majority of studies, and very few individual studies reported a statistically significant difference between intervention and control group participants. The pooled risk difference between groups for gastrointestinal adverse events was 0.006 (95% CI: -0.001 0.012, p=0.071). The small difference between intervention and control group participant incidences was not statistically significant at the 5 percent level.

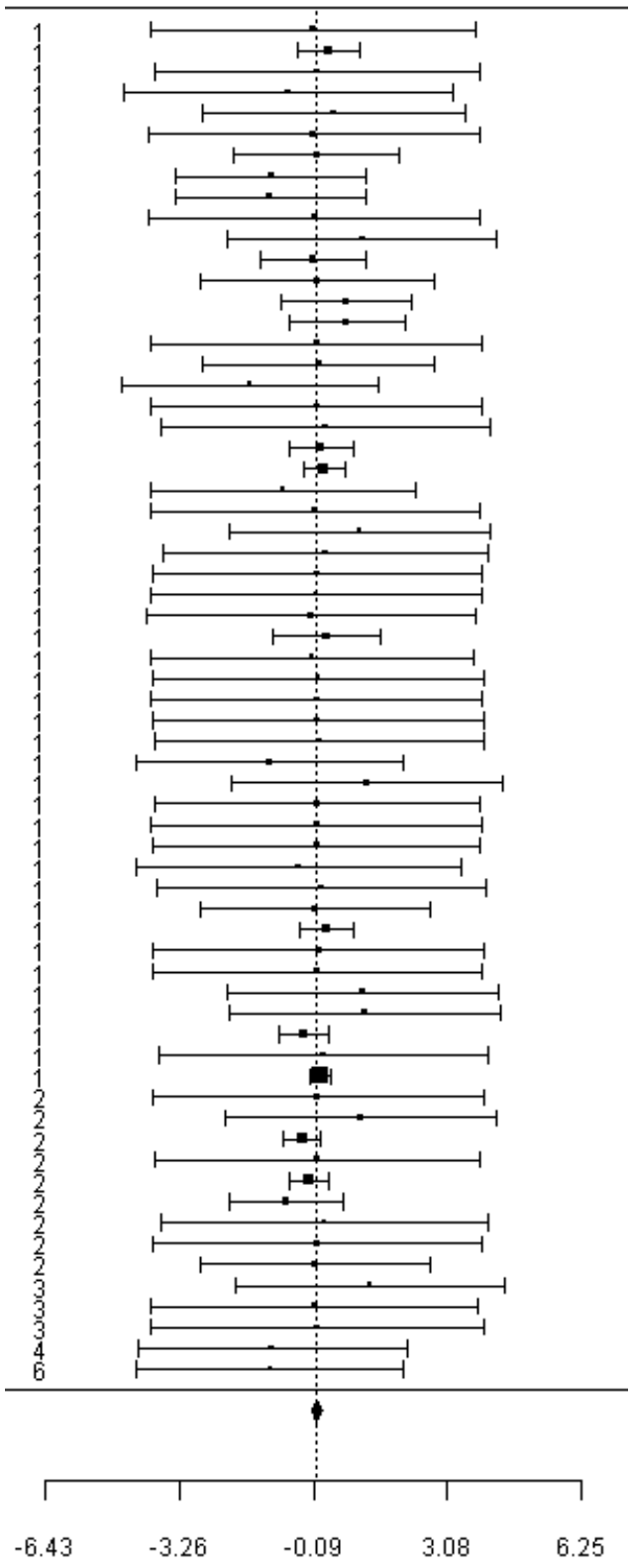
All individual study results are shown in the Evidence Table C4, Results. Stratified analyses for individual genera, participant characteristics or other intervention characteristics are reported in the following sections.

Infections and Infestations

We also pooled all incidences of infections and infestations (CTCAE category XI) across the included 65 parallel RCTs that reported the presence or the absence of these adverse events. The relative risk for individuals in probiotics groups, relative to a control, was 1.00 (95% CI: 0.87, 1.16, p=0.967). Across all included studies, genera, participant groups, and interventions, there was no difference in the risk of experiencing infections and infestations.

Figure 12 graphically represents individual and pooled point estimates and 95% CIs obtained in included studies. The numbering on the left hand side of the forest plot indicates the investigated genus. The number 1 indicates that a *Lactobacillus* strain was part of the intervention. In total, 39 percent of studies investigated blends and most often the blend included a *Lactobacillus* strain. The number 2 indicates that *Bifidobacterium* was present without *Lactobacillus*. Number 3 indicates that *Saccharomyces* organisms were present without *Lactobacillus* and *Bifidobacterium*. The number 4 indicates that *Streptococcus* or *Enterococcus* strains were present without *Lactobacillus*, *Bifidobacterium*, or *Saccharomyces* strains. The number 6 indicates that the intervention included *Bacillus* strains, but no *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, or *Enterococcus* strains. Due to the large number of studies, numerical estimates and study identifiers of individual RCTs could not be displayed.

Figure 12. Graphical representation of the RR of the number of infection and infestation adverse events across RCTs



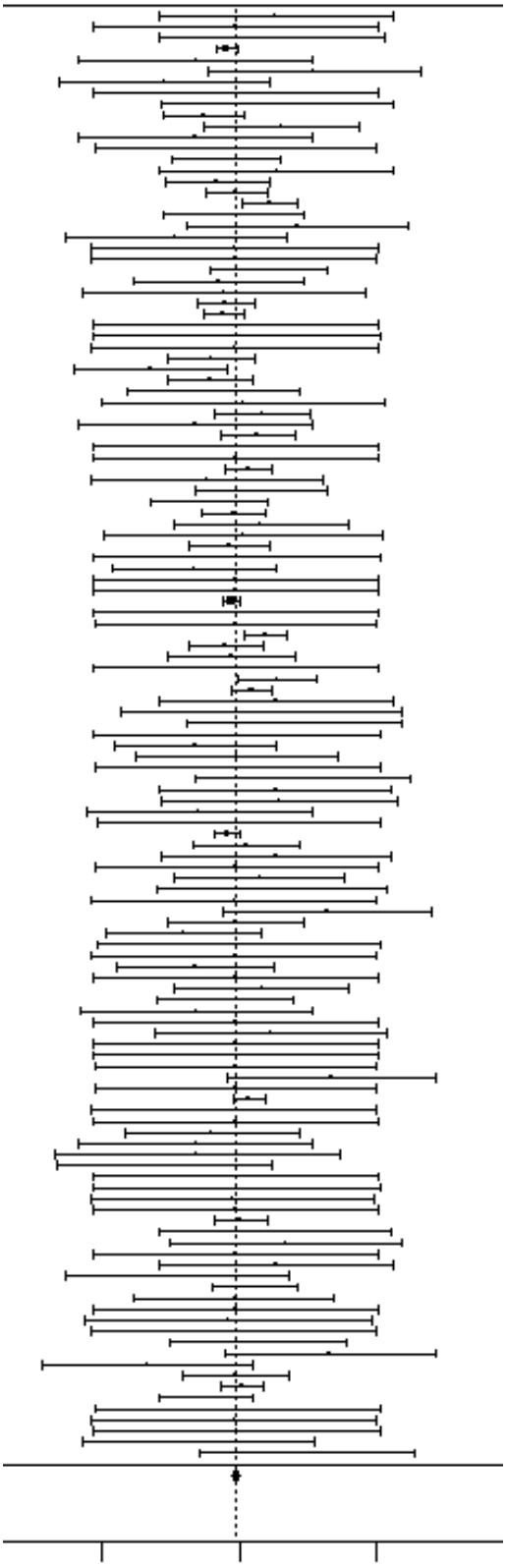
The forest plot demonstrates that individual results differed across studies, sometimes favoring the control group and sometimes the intervention group, with no clear trend in either direction. Confidence intervals were wide in the large majority of studies, and no individual study reported a statistically significant difference between intervention and control group participants. Considering the absolute risk difference model, the risk difference across treatment and control groups was not detectable (RD 0.000; 95% CI: -0.002, 0.002, p=0.918). There was no indication that reported infections and infestations were more common in probiotics groups compared to a comparable participant sample per group across all included parallel RCTs. All individual study results are shown in the Evidence Table C4, Results. Stratified analyses for individual genera, participant characteristics, or other intervention characteristics are reported in the following sections.

Other Adverse Events

The relative risk for individuals in the intervention group compared to the controls was 1.01 (95% CI: 0.91 1.12, p=0.923). In total, 131 RCTs were included in this analysis. The category 'other' contains all other adverse event incidences that were not categorized as gastrointestinal in nature or part of the infections and infestations adverse event domain. This category included the number of deaths, when the cause of death was not specified and attributed to a specific organ system.

Figure 13 graphically represents individual and pooled point estimates and 95% CIs obtained in included RCTs. In this analysis, the majority of included trials contributing data on other adverse events (107/131) used a *Lactobacillus* strain alone or in combination with other genera. Due to the large number of included studies, numerical estimates and study identifiers of individual RCTs could not be displayed.

Figure 13. Graphical representation of the RR of the number of other adverse events across RCTs



The forest plot demonstrates that individual results differed across studies, sometimes favoring the control group and sometimes the intervention group, with no clear trend in either direction. Confidence intervals were wide in the large majority of studies, and very few individual studies reported a statistically significant difference between intervention and control group participants. The risk difference to experience any of the other adverse events (not gastrointestinal or infections) across treatment groups relative to control was 0.001 (95% CI: -0.003, 0.004; p=0.713). There was no indication that the adverse event incidences were more frequent in a group using probiotic organisms.

All individual study results are shown in the Evidence Table C4, Results. Stratified analyses for individual genera, participant characteristics or other intervention characteristics are reported in the following sections. Evidence pertaining to serious adverse events is documented in Key Question 5.

Unique Harms

Generally, the identified literature was not very specific with regard to the adverse events that were monitored. The assessment and results evidence table shows, for example, that several studies analyzed blood chemistry variables, but researchers rarely reported exactly what they monitored, and none of the included studies highlighted incidences of unusual or unique results.

Harms unique to probiotics were primarily infections attributed to the administered organism. Several case studies reported a DNA-based identification of strains (see section 1c). Of all other included studies, only a few reported explicitly that infections, bacteremia, or sepsis incidences could possibly be attributed to the administered probiotics strain (see response to Key Question 1h). In the studies that monitored the incidence of infection, none was observed to have been caused by probiotic organisms. Some trials explicitly reported that no incidences of serious infections occurred (see Evidence Table C4, Results). Other trials reported only the number of incidences of sepsis as an adverse event, and it was not clear whether the administered probiotic strain was considered as a possible cause of the infection.

The frequency of reported gastrointestinal symptoms in the existing literature is noteworthy; however, neither the quantity nor the quality is unique to probiotics intake; similar symptoms in a similar quantity were also encountered in control groups.

Summary and Strength of Evidence Key Question 2

What are characteristics and associations of the reported harms in Question 1?

Volume: 387 in total, but varied across subquestions and analyses

Risk of bias: Medium

The evidence to answer this Key Question stems from a variety of study designs and quality.

Consistency: Inconsistent

The RCTs, CCTs, and case series show different results from case studies.

Directness: Varies across subquestions

The evidence base includes a large number of RCTs.

Precision: Precise

The majority of included studies use a moderate sample sizes but studies were pooled in a meta-analysis.

The identified evidence is moderate to low with regard to being able to answer the Key Question with confidence.

As described, the interventions and adverse events are not well documented and studies were not designed to assess adverse events systematically. The majority of studies investigated *Lactobacillus* interventions, alone or in combination with other genera, most often *Bifidobacterium*. Studies rarely reported efforts to monitor adverse events specific to probiotic products. Hence, evaluations of the safety might change with future, more targeted, assessment of adverse events.

Across all included studies, by far the most commonly reported adverse events were gastrointestinal in nature, followed by reported infections and infestations. The third most common category was the "other" category for symptoms that could not be assigned to one of the organ systems outlined in the applied CTCAE system. While the case studies primarily reported infections suspected or confirmed to be caused by an administered probiotics strain, the majority of other studies reported gastrointestinal incidences.

Across identified RCTs, there was no indication that participants using probiotic organisms experienced statistically significantly more gastrointestinal adverse events, infections and infestations, or other adverse events compared to control group participants. Individual comparisons were based on a large number of RCTs.

There is a lack of individual studies assessing interaction effects of medication affecting adverse events. An indirect comparison of RCTs in participants with pertinent co-medications compared to studies not describing these comedications indicated a slightly increased, but not statistically significantly different, relative risk ratio of adverse events between treatment and control group participants.

We identified only a very small number of studies addressing acquired antibiotic resistance as a patient outcome with clinical relevance. Evidence for potential harms came from case studies in patients with multiple morbidities. Resistance was reported only to selected antibiotics.

Adverse events other than infections potentially caused by the administered probiotics strain and unique to probiotics were not addressed in the literature. Evidence for infections came from case studies; included trials did not report on this outcome and/or did not find any cases and did not highlight adverse events unique to probiotics use.

Key Question 3. What is the evidence that harms of *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and *Bacillus* differ by product and delivery characteristics?

Very few studies were identified that explicitly investigated the effects of a commercially available food product (see Evidence Table C2, Intervention). The majority of identified studies appeared to provide a probiotic intervention prepared especially for the particular research study to investigate a beneficial health effect in participants with moderate health impairments.

Most included studies investigated *Lactobacillus* and/or *Bifidobacterium* preparations. In particular there were few reports on the genera *Enterococcus*, and *Bacillus*.

The reporting of the interventions was insufficient. A large number of studies did not report the strain that was investigated. The lack of reporting is a safety concern.

(3a) What is the scientific evidence that harms differ by delivery vehicle including excipients or novel delivery vehicles?

We extracted the investigated product name where reported in the publication. Different products such as Actimel, Culturelle, Infloran, or Yakult were described. However, the majority of studies did not state any product name and reported only the genus, such as *Lactobacillus*, that was given to participants.

By far the most common delivery vehicle was a pill or capsule, used in 101 included studies (see Evidence Table C2, Intervention). We also identified 29 studies of probiotic organisms in a dairy drink (Arunachalam, 2000; Barrett, 2008; Beausoleil, 2007; Boge, 2009; Cobo Sanz, 2006; Conen, 2009; Felley, 2001; Gotteland, 2003; Guillemard, 2010; Guyonnet, 2009; Hensgens, 1976; Ishikawa, 2003; Kajander, 2008; Merenstein, 2010; Newcomer, 1983; O'Mahony, 2005; Rautio, 1999; Rio, 2002; Salminen, 2004; Seppo, 2003; Simren, 2010; Songisepp, 2005; Spanhaak, 1998; Srinivasan, 2006; Sykora, 2005; Turchet, 2003; Wang, 2004; Yang, 2008). Twenty-one studies used enriched yogurt (Anukam, 2008; Bajaj, 2008; Carlsson, 2009; de Roos, 1999; Fukuda, 2008; Higashikawa, 2010; Kajimoto, 2002; Kim, 2008; Manley, 2007; Martinez-Canavate, 2009; Miyaji, 2006; Olivares, 2006; Parfenov, 2005; Parfenov, 2005; Presterl, 2001; Sakamoto, 2001; Salminen, 1988; Sullivan, 2003; Tomoda, 1991; Wheeler, 1997; Xiao, 2003). Among all identified studies, 29 added probiotic organisms to an infant formula (Bin-Nun, 2005; Chouraqui, 2008; Chouraqui, 2004; Cooper, 2006; Correa, 2005; Dupont, 2010; Gibson, 2009; Haschke-Becher, 2008; Kirjavainen, 2003; Langhendries, 1995; Lin, 2008; Maldonado, 2009; Millar, 1993; Petschow, 2005; Puccio, 2007; Reuman, 1986; Ruiz-Palacios, 1996; Saavedra, 2004; Scalabrin, 2009; Stratiki, 2007; Urban, 2008; van der Aa, 2010; Vendt, 2006; Vlieger, 2009; Weizman, 2006; Weizman, 2005; Ziegler, 2003).

Other studies used less common delivery vehicles such as vaginal suppositories; powder, often to be dissolved in water; chewing gum; drops; spray; or cultures on gauze pads as the Evidence Table C2, Intervention shows. Where available, we extracted the information on the delivery vehicle, such as whether the preparation was diluted with water or juice (Champagne, 2005) or mixed with breast milk (Lin, 2005). However, most studies did not describe exactly how the preparation was taken and whether it varied across participants.

Only one study was identified that compared two different delivery vehicles directly (Isolauri, 1991), that is, providing direct evidence on the effect of delivery vehicles. In this study, a group of children given a *Lactobacillus* casei GG fermented milk product was compared to a group of children using *Lactobacillus* GG as a lyophilized powder to promote recovery from acute diarrhea. The study reported that on day one, 58 percent of children in the milk product group vomited compared to 43 percent in the powder group; on day two, 21 percent versus 22 percent vomited; on day three, 0 versus 9 percent vomited, and after that, no more vomiting occurred. One other study (Metts, 2003) randomized participants to vaginal suppositories of *Lactobacillus acidophilus*, suppositories and oral capsules containing *Lactobacillus* and *Bifidobacterium* strains, and placebo; one participant in the oral and vaginal suppository group and one in the placebo group reported vaginal discharge. These individual study results do not allow any conclusions regarding the effects of one delivery vehicle over the other.

Metaregression: Delivery Vehicle

In the absence of direct comparisons, we investigated the delivery vehicle further in a meta-regression. A metaregression adding the factor “delivery vehicle” to a meta-analysis model indicated that adverse events results differ by delivery vehicle based on the number of

participants with adverse events (p=0.0157) as well as based on the number of adverse event incidences (p=0.040). The risk ratio between probiotic group participants and control group participants appeared to vary based on the chosen delivery vehicle. Hence, we investigated individual delivery vehicle further in stratified analyses.

Pill/Capsule

First, we compared the relative risk seen in a probiotics group using a pill, capsule, or gelcap compared to the risk of adverse events seen in a group across the included parallel RCTs. This subgroup represents the majority of included studies, as this delivery vehicle was most commonly used. We excluded all studies where the vehicle was described as a "tablet," as it was not clear from the original publication whether this was equivalent to a pill that was meant to be swallowed or a chewable tablet or a tablet that dissolves in water, for example.

Compared to controls, participants in a probiotics group were not more likely to experience adverse events, based on the number of participants with adverse events (RR 1.02; 95% CI: 0.92, 1.14; p=0.654; RD -0.001; 95% CI: -0.006, 0.004; p=0.746) or based on the number of adverse event incidences (RR 0.94; 95% CI: 0.0.80, 1.1.10; p=0.439; RD -0.001; 95% CI: -0.009, 0.008; p=0.888) in this subgroup of studies using pills, capsules, or gelcaps as the probiotics delivery vehicle.

Exploring the nature of the reported adverse events across probiotics and control groups in these studies, there was also no difference in gastrointestinal complaints (RR 1.02; 95% CI: 0.76, 1.36; p=0.898; RD 0.001; 95% CI: -0.007, 0.009; p=0.868), a trend but no statistically significant effect for infections and infestations (RR 1.24; 95% CI: 0.92, 1.67; p=0.151; RD 0.001; 95% CI: -0.004, 0.006; p=0.702), or for other adverse events (RR: 0.89; 95% CI: 0.72, 1.10; p=0.292; RD -0.001; 95% CI: -0.013, 0.011; p=0.868).

Yogurt/Dairy

Secondly, we undertook a stratified analysis for studies that delivered the probiotic organisms in a yogurt or dairy drink. It is conceivable that probiotic organisms react to the delivery vehicle; hence participants in probiotics groups might have an increased risk of adverse events in dairy or yogurt studies. Infant formulas were excluded from this analysis in order not to add another confounder (all infant formula studies have infants as participants).

Compared to controls, participants in a probiotics group were not more likely to experience adverse events, based on the number of participants with adverse events (RR 1.01; 95% CI: 0.90, 1.13; p=0.847; RD 0.001; 95% CI: -0.016, 0.017; p=0.921). However, based on the number of adverse event incidences in the 24 studies that used this delivery vehicle and reported data, the relative risk was 1.37 (95% CI: 1.05, 1.79; p=0.022), indicating that participants in the probiotics groups experienced more adverse events than control group participants. The absolute risk difference between studies was 0.023; it was not statistically significant (95% CI: -0.003, 0.049; p=0.078).

Exploring the nature of the reported adverse events in this subgroup of studies across probiotics and control groups, there was a trend for more gastrointestinal complaints (RR 1.30; 95% CI: 0.83, 2.04; p=0.245; RD 0.032; 95% CI: -0.006, 0.070; p=0.098), a trend for more infections and infestations (RR 1.99; 95% CI: 0.51, 7.80; p=0.321; RD 0.004; 95% CI: -0.004, 0.011; p=0.307), and a trend for more "other" adverse events (RR: 1.81; 95% CI: 0.98, 2.32; p=0.063; RD 0.003; 95% CI: -0.004, 0.011; p=0.388). However, none of the results showed a

statistically significantly increased relative risk or absolute risk difference for adverse events in dairy or yogurt studies comparing treatment to control group participants.

There were too few studies to investigate systematic differences between yogurt and dairy studies or to differentiate less common delivery vehicles further in a meta-analysis. Infant formula study results are presented in the response to Key Question 4d in the section on children. Results of all individual studies are shown in the Evidence Table C4, Results.

Overall, there was an indication that safety results may differ by delivery vehicle. However, given the type of analysis (an indirect analysis across studies), this result has to be regarded with caution and cannot replace evidence from direct, within study comparisons. In addition, chosen delivery vehicles can in part be confounded with participant characteristics (e.g. infant formula).

(3b) What is the scientific evidence that harms differ by genus, species, and strain (including intraspecies strain variations)?

The interventions in the included studies were not well documented. In many cases it was not reported what strains of organisms were used; only the genera, and sometimes, but not always the species, were stated. To meet inclusion criteria for the review, studies had to report a specific genus contained in the tested intervention.

Genus

The available research volume differs for the six investigated probiotic agents. A *Lactobacillus* strain was part of the intervention in 215 (68 percent) of the included studies, thereby being the most commonly studied genus. This number includes *Lactobacillus* strains not explicitly used as a probiotic agent but included in the product, for example as a starter culture for yogurt. *Bifidobacterium* was included in 32 percent of studies. *Saccharomyces* organisms were investigated in 13 percent of studies. *Streptococcus* strains were included in 15 percent of studies; this number includes studies investigating *Streptococcus* strains explicitly as probiotic agents as well as other uses such as part of a yogurt starter culture. *Enterococcus* strains were investigated in 16 studies only (5 percent of included studies). Preparations containing *Bacillus* strains were investigated in 10 studies (3 percent).

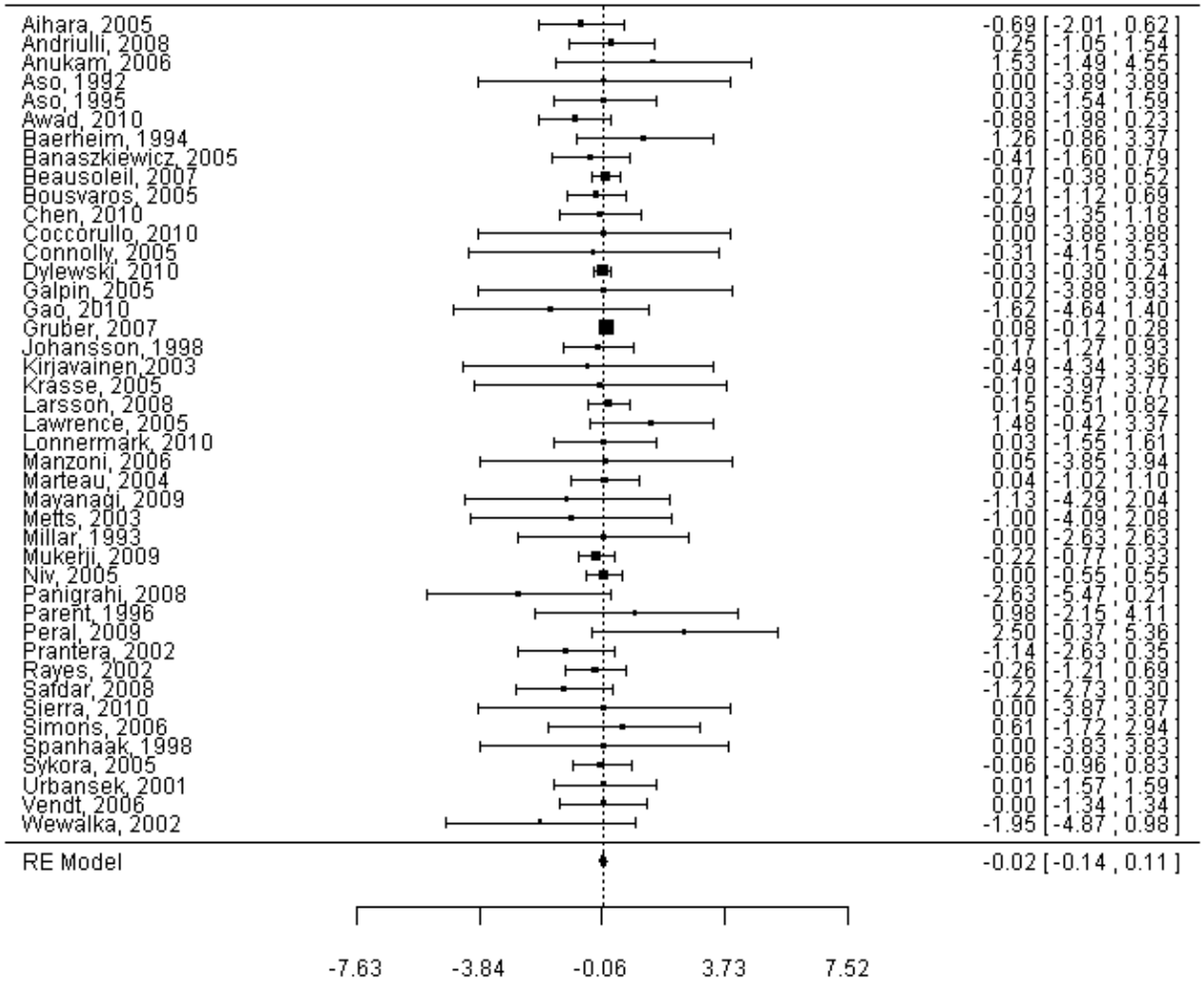
With regard to direct comparisons of genera across the included controlled studies, only very few studies were identified that directly compared the effects of two different genera within the study. Cui (2004) compared *Bacillus coagulans* and *Bifidobacterium longum* in the treatment of acute and chronic diarrhea and reported that body weight, body temperature, respiratory rate, heart rate, blood pressure, routine blood tests, and liver and renal function were within normal limits after treatment, and no adverse reactions were found. Dekker (2009) compared the safety of *Lactobacillus rhamnosus* HN001 and *Bifidobacterium animalis lactis* HN019 in a study of infants with asthma, hay fever, or eczema and found a rate of 19.6 percent versus 18.5 percent of hospitalizations in the two groups (17.6 percent for placebo) and found no statistically significant differences in gastrointestinal adverse events (diarrhea, reflux, abdominal pain, or vomiting) across groups. De Simone (2001) compared a commercial product containing *Streptococcus thermophilus, Bifidobacterium* strains, *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus delbrueckii bulgaricus,* and *Streptococcus faecium* to a product containing *Enterococcus faecium* in the treatment of irritable bowel syndrome and found no significant changes in blood counts and chemistry in the groups.

Margreiter (2006) compared a Lactobacillus gasseri and *Bifidobacterium longum* intervention with *Enterococcus faecium* and reported no lab abnormalities in either group.

O'Mahony (2005) found no changes in blood counts, serum chemistry, or serum immunoglobulins across groups receiving *Lactobacillus salivarius salivarius* UCC4331, *Bifidobacterium infantis* 35624, or placebo. There was one case each of epistaxis, unstable angina, and chest pain due to anxiety, but the group was not specified. Weizman (2005) stated that there was no difference between growth parameters, behavior, or stooling patterns, and there was no difference in the incidence of bloody stools or hospitalization across a *Bifidobacterium lactis* BB-12, *Lactobacillus reuteri* ATCC 55730, and placebo group.

Lactobacillus. Probiotic studies often used *Lactobacillus* strains in combination with other genera, but we also identified a substantial number of studies using exclusively *Lactobacillus* strains. The identified case studies describing harms potentially associated with this genus are described in Key Question 1. To quantify risks, we compared participants in parallel RCTs where one group received a *Lactobacillus* intervention and the other group received no or nonprobiotic treatment. In parallel RCTs, the relative risk for intervention participants to experience an adverse event was 0.98 (95% CI: 0.87, 1.11; p=0.785) compared to the nonprobiotic control group, based on all studies that used exclusively *Lactobacillus* strains and reported the number of participants with adverse events. Figure 14 shows the risk differences observed in individual RCTs.

Figure 14. RR number of participants with adverse events *Lactobacillus* RCTs



Individual study results varied, and there was no indication that the number of participants with adverse events differed systematically between groups on a *Lactobacillus* strain intervention and an equivalent group of control participants. The risk difference was -0.003 (95% CI: -0.014, 0.009; p=0.668). Using the alternative measure, the number of incidences per group, the relative risk was 0.96 (95% CI: 0.88, 1.06; p=0.421) and the corresponding risk difference was 0.002 (95% CI: -0.007, 0.011; p=0.746).

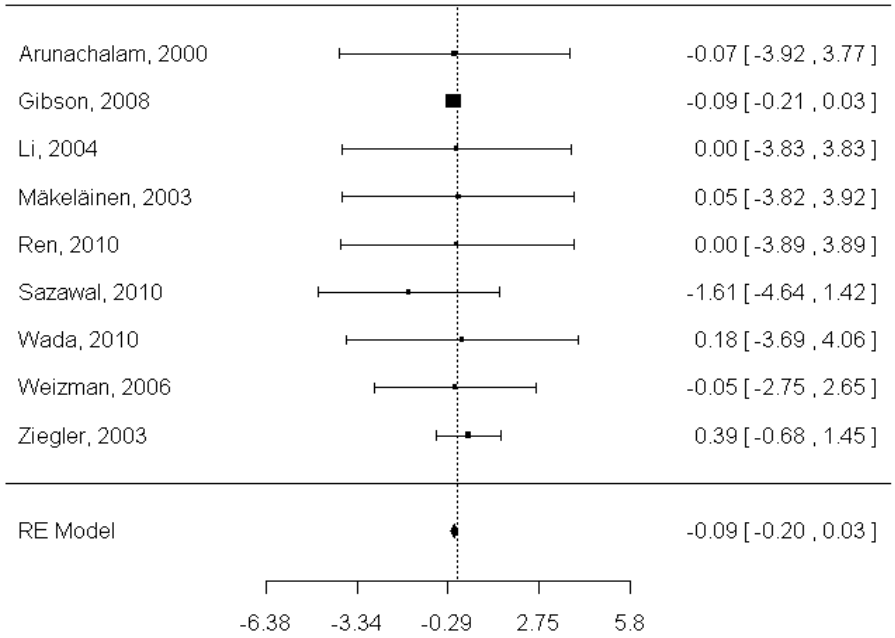
To explore the nature of adverse events experienced in *Lactobacillus* exclusive trials, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. There was no statistically significant difference between intervention and control group in their risk to experience any of the three different types of adverse events (gastrointestinal events: RR 1.05; 95% CI: 0.83, 1.24; p=0.885; RD 0.007; 95% CI: -0.004, 0.018; p=0.206; infections and infestations: RR 1.09; 95% CI: 0.90, 1.31; p=0.374; RD -0.001 (95% CI: -0.004, 0.003; p=0.762; or other reported adverse events: RR 0.91; 95% CI: 0.80, 1.04; p=0.182; RD -0.002; 95% CI: -0.008, 0.004; p=0.496).

We also investigated the genus *Lactobacillus* as a factor in a metaregression comparing studies that used *Lactobacillus* strains (alone or in combination) with interventions that did not. The relative risk ratio across studies did not indicate that the *Lactobacillus* genus was associated

with a statistically significantly increased risk of adverse events compared to other genera based on the number of participants with adverse events (relative risk ratio 1.08; 95% CI 0.95, 1.22; p=0.224). This result was confirmed by the alternative measure of adverse event incidences (relative risk ratio 1.08; 95% CI: 0.89, 1.31; p=0.794).

Bifidobacterium. Probiotic studies often used *Bifidobacterium* strains in combination with other genera, and we also identified a few studies using exclusively *Bifidobacterium* organisms. The identified case study describing harms potentially associated with this genus is described in Key Question 1. Selecting only parallel RCTs that used exclusively *Bifidobacterium* products, the relative risk based on the number of participants with adverse events was 0.92 (95% CI: 0.82, 1.03; p=0.141) between groups. Figure 15 shows the estimated relative risk reported in each included RCT.

Figure 15. RR number of participants with adverse events *Bifidobacterium* RCTs



Individual study results varied, and there was no indication that the number of participants with adverse events differed systematically between a group taking a *Bifidobacterium* strain and an equivalent control group not taking probiotics. The equivalent risk difference was -0.006 (95% CI: -0.017, 0.004; p=0.228) across all included trials. Using the alternative measure, the number of adverse event incidences, the relative risk was 0.90 (95% CI: -0.74, 1.10; p=0.302) for intervention participants compared to control, with a corresponding risk difference of -0.005 (95% CI:--0.0145, 0.004; p=0.289).

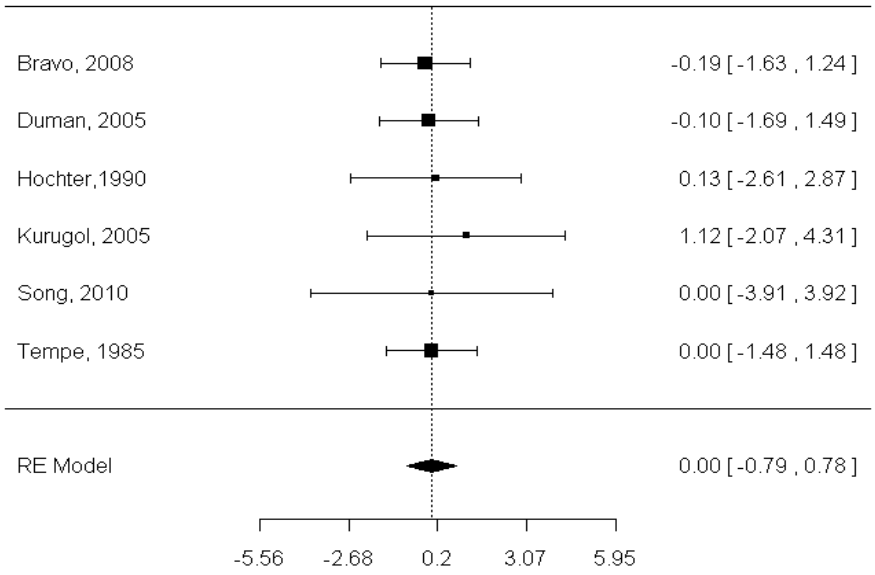
To explore the nature of adverse events experienced in exclusively *Bifidobacterium* trials, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. There was no statistically significant difference between intervention and control group in their risk to experience any of the three most common types of adverse events (gastrointestinal events: RR 1.02; 95% CI: 0.55, 1.90; p=0.941; RD 0.003; 95% CI: -0.017, 0.024; p=0.752; infections and infestations: RR 0.75; 95% CI: 0.55, 1.02; p=0.067; RD -0.018;

95% CI: -0.057, 0.021; p=0.366; or other reported adverse events: RR 1.22; 95% CI: 0.71, 2.09; p=0.468; RD -004; 95% CI: -0.013, 0.006; p=0.463).

We also investigated the genus *Bifidobacterium* as a factor in a metaregression comparing studies that used *Bifidobacterium* strains (alone or in combination) with interventions that did not. The relative risk ratio across studies did not indicate that the *Bifidobacterium* genus was associated with an increased or reduced risk of adverse events compared to other genera, based on the number of participants with adverse events (relative risk ratio 1.04; 95% CI 0.93, 1.17; p=0.700). This result was confirmed by the alternative measure of adverse event incidences (relative risk ratio 1.11; 95% CI: 0.96, 1.28; p=0.794).

Saccharomyces. We identified a number of case studies describing harms potentially associated with this genus; details are reported in the response to Key Question 1. Selecting only parallel RCTs investigating exclusively *Saccharomyces* interventions, the relative risk of adverse events in the intervention group was 1.00 (95% CI: 0.46, 2.18; p=0.993) compared to control and based on the number of participants with adverse events. The forest plot in Figure 16 shows the results of RCTs that were included in the analysis.

Figure 16. RR number of participants with adverse events *Saccharomyces* RCTs



Individual study results varied: Some studies reported no adverse events in either group or an equal number of events; there was no indication that the number of participants with adverse events differed systematically between a group taking a *Saccharomyces* strain and an equivalent control group not taking probiotics. The risk difference for intervention and control group participants was not detectable (RD 0.000; 95% CI: -0.005, 0.005; p=0.890) in the *Saccharomyces* trials. Using the alternative measure, the number of adverse event incidences per treatment group, the relative risk was 1.15 (95% CI: 0.38, 3.52; p=0.802), also not statistically significantly different from that of control group participants, and the corresponding risk difference was -0.001 (95% CI: -0.025, 0.024; p=0.956).

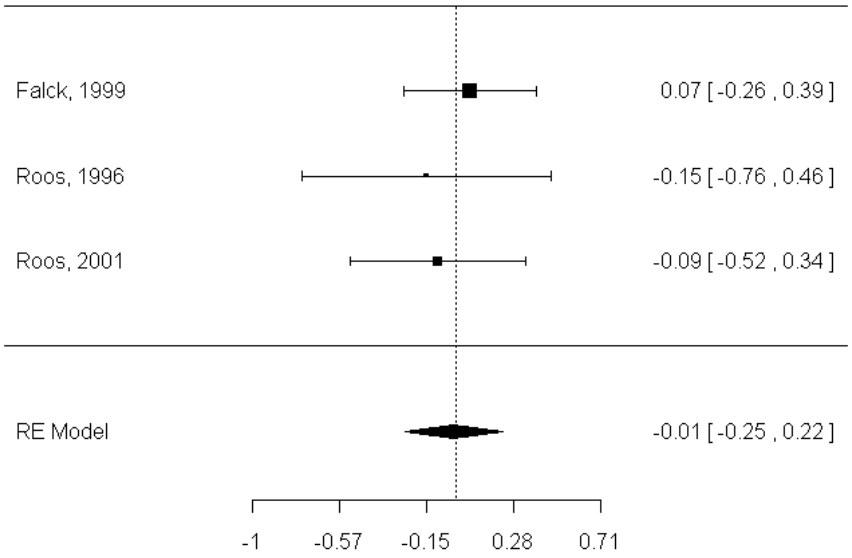
To explore the nature of adverse events experienced in RCTs using exclusively *Saccharomyces* organisms, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. There was no statistically significant

difference between intervention and control groups in their risk to experience gastrointestinal adverse events (RR 1.05; 95% CI: 0.25, 4.49; p=0.947; RD -0.002; 95% CI: -0.031, 0.027; p=0.892). There was a trend for more infections and infestations in intervention participants compared to control, but it was not statistically significant across the three studies that reported on infections and infestations (RR 1.69; 95% CI: 0.21, 13.53; p=0.622), and the risk difference was not detectable (RD 0.000; 95% CI -0.006, 0.006; p=0.919). There was also no statistically significant difference for all other adverse events (RR 1.19; 95% CI: 0.23, 6.05; p=0.832; RD 0.005; 95% CI: -0.047, 0.056; p=0.863)

We also investigated the genus *Saccharomyces* as a factor in a metaregression comparing studies that used *Saccharomyces* strains (alone or in combination) with interventions that did not. The relative risk ratio across studies did not indicate that the *Saccharomyces* genus was associated with a statistically significantly increased risk of adverse events compared to other genera, based on the number of participants with adverse events (relative risk ratio 1.08; 95% CI 0.51, 2.27; p=0.845). This result was confirmed by the alternative measure of adverse event incidences (relative risk ratio 1.57; 95% CI: 0.77, 3.20; p=0.215).

Streptococcus. Very few studies were identified that studied exclusively *Streptococcus* strains. Across the parallel RCTs using exclusively *Streptococcus* strains, the relative risk for adverse events was 0.99 (95% CI: 0.78, 1.25; p=0.907) in the intervention group, compared to an equivalent control group. The forest plot in Figure 17 shows results obtained in individual RCTs.

Figure 17. RR number of participants with adverse events *Streptococcus* RCTs



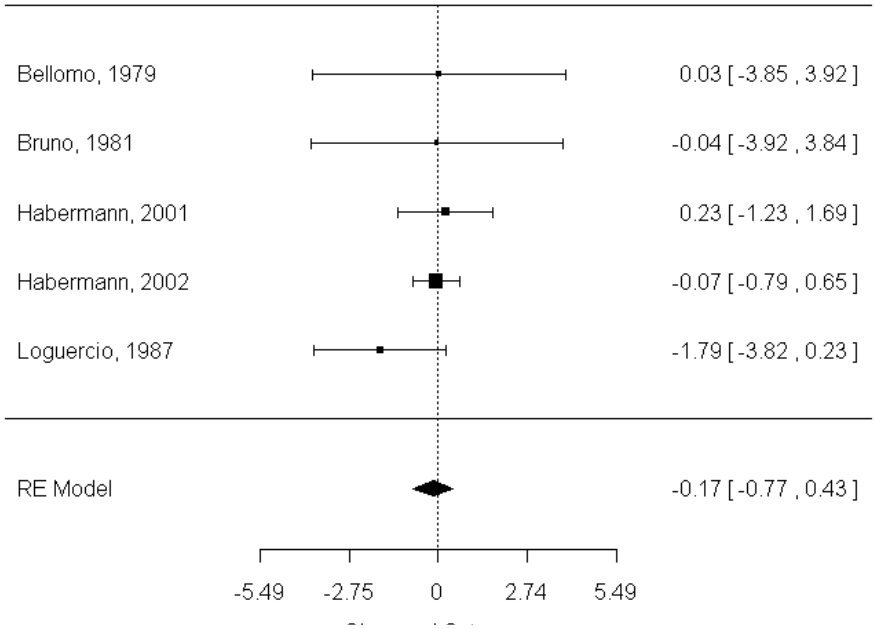
The analysis was based on only three RCTs, the individual study results varied, and there was no indication that the number of participants with adverse events differed systematically between groups taking *Streptococcus* and control group participants. The corresponding risk difference in *Streptococcus* RCTs was -0.004 (95% CI: -0.084, 0.076; p=0.528). Using the alternative measure, the number of adverse event incidences, there was also no statistically significant difference between intervention and control groups (RR 0.90 (95% CI: 0.45, 1.79;

p=0.768; RD -0.014; 95% CI: -0.056, 0.029, p=0.532), this analysis is also based on only three RCTs. The results of the individual studies are reported in the Evidence Table C4, Results.

We also investigated the genus *Streptococcus* as a factor in a metaregression comparing studies that used *Streptococcus* strains (alone or in combination) with interventions that did not. The relative risk ratio across studies did not indicate that the *Streptococcus* genus was associated with an increased or reduced risk of adverse events compared to other genera, based on the number of participants with adverse events (relative risk ratio 1.03; 95% CI 0.91, 1.17; p=0.624). However, the result using the alternative measure of adverse event incidences indicated that intervention participants were at a greater risk of adverse events compared to other genera (relative risk ratio 1.43; 95% CI: 1.09, 1.87; p=0.009).

Enterococcus. Few *Enterococcus* studies were identified. The relative risk seen in the *Enterococcus* arm compared to control was 0.85 (95% CI: 0.47, 1.54; p=0.588) across all studies that reported data. The forest plot in Figure 18 shows the individual results obtained in the included RCTs.

Figure 18. RR number of participants with adverse events *Enterococcus* RCTs



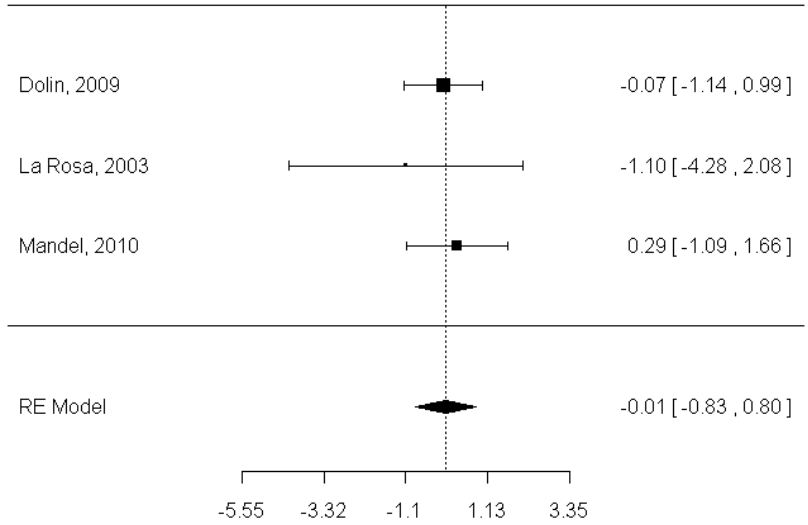
The analysis was based on only five RCTs, and most studies reported no adverse events or an equal number of adverse events for participants using an *Enterococcus* product and control group participants. The risk difference across *Enterococcus* treatment arms was -0.008 (95% CI: -0.051, 0.036, p=0.733) in *Enterococcus* trials. Using the alternative measure, the number of adverse event incidences, there was also no difference between intervention and control group (RR 1.33; 95% CI: 0.43, 4.16; p=0.624; RD 0.002; 95% CI: -0.019, 0.023, p=0.833); this analysis is based on six RCTs. The results of the individual studies are reported in the Evidence Table C4, Results.

We also investigated the genus *Enterococcus* as a factor in a metaregression comparing studies that used *Enterococcus* strains (alone or in combination) with interventions that did not. The relative risk ratio across studies did not indicate that the *Enterococcus* genus was associated

with a statistically significantly increased or reduced risk of adverse events compared to other genera, based on the number of participants with adverse events (relative risk ratio 0.88; 95% CI 0.52, 1.51; p=0.507). This finding was confirmed by the alternative measure of adverse event incidences (relative risk ratio 0.79; 95% CI 0.39, 1.60; p=0.507).

Bacillus. Few *Bacillus* studies were identified, as indicated in Figure 19. We included the study described by La Rosa (2003), although the study originally described the investigated organism as *Lactobacillus coagulans*. The relative risk for intervention participants exposed to *Bacillus* organisms to experience an adverse event was 0.99 (95% CI: 0.44, 2.22; p=0.973) compared to control and based on the number of participants with adverse events.

Figure 19. RR number of participants with adverse events *Bacillus* RCTs



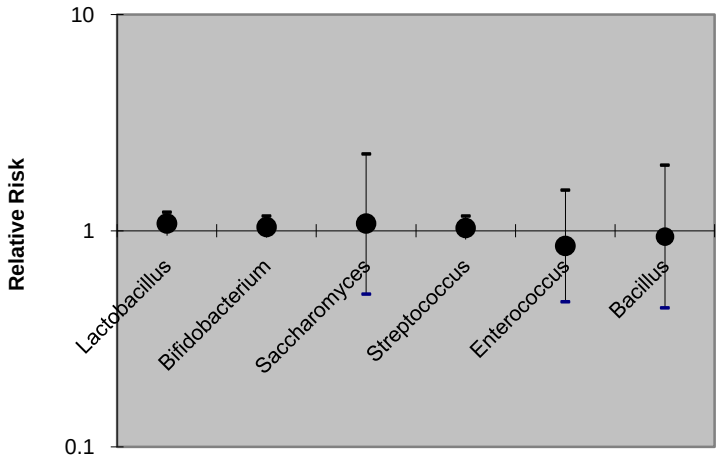
The analysis was based on only three RCTs with an exclusive *Bacillus* intervention, and individual study results varied. The corresponding risk difference in *Bacillus* RCTs was -0.014 (95% CI: -0.057, 0.029, p=0.529). The pooled number of adverse incidences could not be computed, as only two studies reported the number of individual adverse event incidences for both treatment groups. The only other study that investigated a *Bacillus* intervention (Cui, 2004) found no adverse reactions in either the *Bacillus coagulans* group or the control group receiving *Bifidobacterium longum*.

We also investigated the genus *Bacillus* as a factor in a metaregression comparing studies that used *Bacillus* strains (alone or in combination) with interventions that did not. The relative risk ratio across studies did not indicate that the *Bacillus* genus was associated with a statistically significantly different risk of adverse events compared to other genera, based on the number of participants with adverse events (relative risk ratio 0.94; 95% CI 0.44, 2.01; p=0.883). This result was confirmed by the alternative measure of adverse event incidences (relative risk ratio 0.88 95% CI 0.27, 2.92; p=0.841).

The indirect comparison of genera across studies did not indicate genera-specific safety results, with the exception of *Streptococcus* interventions: a metaregression based on the number of adverse incidences indicated a different risk ratio for participant and control group participants compared to other genera. However, this result was not confirmed based on the alternative measure, the number of participants with adverse events; the risk difference between intervention

and control groups was not statistically significantly different; and only few studies were identified overall that used other genera than *Lactobacillus* and *Bifidobacterium* alone or in combination. Finally, direct comparisons within studies are needed to answer this Key Question with confidence. Figure 20 shows the relative risk ratio and confidence intervals for studies using each genus, compared with all other RCTs using other genera in the probiotics interventions.

Figure 20. Comparison of adverse events across genera (RR log scale)



The absence of case reports of serious adverse events potentially caused by *Streptococcus* or *Enterococcus* (see Key Question 1c) can not be used as an indication that the risk of serious adverse events is absent: The overall identified body of literature reporting on the presence and absence of harms indicates absence of relevant literature. The strains have not been used in research studies, which may indicate less use in clinical practice.

Species

We identified one study comparing different species within genera. Rosenfeldt (2003) compared *Lactobacillus rhamnosus* plus *Lactobacillus reuteri* with another preparation containing *Lactobacillus casei alactus*, *Lactobacillus delbrueckii lactis*, and *Lactobacillus GG* ATCC 53103 and reported mild, transitory abdominal pain in two participants in the former group (one participant in the placebo group reported abdominal pain and loose stools).

The case studies that used genetic fingerprinting methods to match administered and recovered organisms identified species specified as *Lactobacillus rhamnosus* or LGG, *Bifidobacterium breve*, *Saccharomyces boulardii [cerevisiae]*, and *Bacillus subtilis* (see Key Question 1).

Given the potentially unreliable identification of species actually used in the intervention studies, the large number of blends, the differences in dosing, the absence of direct comparisons, and the unsystematic assessment of adverse events across studies, it appears infeasible to draw conclusions regarding species-specific safety in interventions studies.

Strains

We identified four studies comparing different probiotic strains. Chouraqui (2008) compared *Bifidobacterium longum* BL999 plus *Lactobacillus rhamnosus* LPR with BL999 plus *Lactobacillus paracasei* ST11 and found 7 incidences of noteworthy adverse events in the first

group (1 diarrhea, 1 surgery, 3 bronchiolitis, 2 inguinal hernia; n=70) and 4 in the second group (2 vomiting, 1 pyelonephritis, 1 bronchiolitis; n=74). Gracheva (1999) reported one incident of abdominal pain in a group given *Bifidobacterium bifidum* forte to treat acute intestinal infections, chronic diseases of the gastrointestinal tract, and viral hepatitis B (the participant withdrew) but no incidence in another *Bifidobacterium bifidum* treatment group. The exact strains were not reported. Higashikawa (2010) compared yogurt containing *Lactobacillus plantarum* SN35N with yogurt containing *Lactobacillus plantarum* SN13T and reported no abnormal changes in urinalysis or in serum biochemical parameters in either group. Krasse (2005) compared 2 *Lactobacillus reuteri* strains (both of human origin but not named) and reported that 1/20 participants in one of the groups experienced increased bowel movement.

Some included studies compared groups consuming a yogurt product enriched with probiotic organisms to a control group consuming ordinary yogurt, and the results are documented in the evidence tables, but other comparisons of *probiotic* species were not found.

No other studies made direct comparisons between probiotic products or compared mixtures of genera, species, or strains that would allow insight into the differential adverse event rates of individual species or individual strains. Based on the extremely limited number of studies that directly compared adverse events between probiotic organisms of different species or strains, it is not possible to draw any conclusions regarding the comparative safety of species or strains. Few studies employed a single species or strain; few studies characterized or verified the exact strain used; and given that microbial strains also mutate relatively quickly, the potential for attributing a particular event to a particular strain, let alone comparing events attributed to particular strains, is limited.

(3c) What is the scientific evidence that harms differ between active and lyophilized forms of probiotics?

In many studies, the form of the probiotic organism was not described, as can be seen in the Evidence Table C2, Intervention. We identified 10 studies that compared adverse events between forms of organisms, but these were comparisons of viable and heat-killed strains rather than comparisons between active and lyophilized forms.

The direct comparisons did not indicate that adverse events were restricted to or more common in viable preparations.

Alberda (2007) compared viable probiotic strains (*Lactobacillus, Bifidobacterium, Streptococcus* strains) with bacterial sonicates and reported one case of bowel obstruction and one congestive heart failure death in the viable treatment group. There was one death due to respiratory failure in the sonicates group and one myocardial infarction in the placebo groups. No cases of *Lactobacillus* induced sepsis occurred in this group of critically ill patients. Awad (2010) compared living and heat-killed *LGG* preparations to reduce sepsis and necrotizing enterocolitis in neonates and reported 14 deaths in the heat-killed arm compared to 5 deaths in the viable intervention arm. No cases of probiotic bacteria in blood samples were observed. Horvat (2010) reported one mild wound infection with secretion in the heat-killed group of a synbiotic intervention containing *Lactobacillus*, *Pediococcus*, and *Leuconostoc* strains. Isolauri (1991) compared a *Lactobacillus* casei GG fermented milk product with *Lactobacillus* GG as a freeze-dried powder (as described in section 3a, delivery vehicles) and reported no significant difference in vomiting across groups of children recovering from diarrhea. Kirjavainen (2003) randomized infants with atopic eczema and cow's milk allergy to placebo, viable *Lactobacillus* GG, or heat-killed *Lactobacillus* GG. The study was prematurely terminated due to complaints

of adverse gastrointestinal symptoms in the heat-killed group. In total, 5/13 children in the heat-killed LGG group reported diarrhea, while none in the viable group or the placebo group reported any adverse events (p=0.05). Merenstein (2009) reported one incidence of emesis in the active and one incidence of constipation in the heat-killed group. Rampengan (2010) compared a live and a heat-killed Lactobacillus preparation and reported four versus three adverse events (respiratory or bowel symptoms) in the respective groups. Rayes (2002) compared active and heat-killed *Lactobacillus plantarum* 299 strains and found 6/31 abdominal side effects in the active group, 11/31 in the heat-killed group and 8/32 in the not enriched enteral nutrition formula group in liver transplant recipients. In a study on patients with major abdominal surgery, Rayes (2002) reported three incidences of abdominal distention, four of abdominal cramps, and zero of diarrhea in the active *Lactobacillus plantarum* 299 group compared to six, five, and zero events in the heat-killed group; the corresponding control group incidences were four, six, and zero. Tsuchiya (2004) compared a synbiotic with (presumably) active *Lactobacillus* and *Bifidobacterium* strains with a similar heat-killed preparation and found no overt clinical or biochemical adverse side effects, but "a few" of the irritable bowel syndrome participants presented initially with transient diarrhea-like symptoms (group unclear). Xiao (2003) compared lyophilized and heat-killed *Lactobacillus acidophilus* to an active strain and found three cases of vomiting in the active group compared to one case in the heat-killed group. There was one case of constipation and one case of insomnia in the heat-killed group.

The authors' descriptions of the investigated organisms varied to such an extent in the included studies that the data do not seem suitable for an analysis across trials using metaregression or subgroup analyses. In particular, the description of "active" may have been used interchangeably with "viable" rather than explicitly differentiating active and lyophilized forms. Very few studies indicated that they independently tested the content of the preparation given to participants, either for contaminants or for the viability of the included organisms at the time of the intervention.

(3d) Does harm differ by products containing a single probiotic versus a mixture of probiotics?

The Evidence Table C4, Results lists the organisms that constituted the intervention for easy reference. Overall, 60 percent of the included studies investigated the effect of only one genus believed to have probiotic properties, while 40 percent investigated the effect of a mixture of organisms, for example using a product that contained *Lactobacillus* and *Bifidobacterium* strains.

Only two studies were identified that compared a single probiotic with a mixture of probiotic organisms directly. As described previously, De Simone (2001) compared a commercial product including several *Streptococcus, Bifidobacterium,* and *Lactobacillus* strains to treatment with *Enterococcus faecium* and found no significant changes in blood counts and chemistry across groups. Margreiter (2006) compared results of *Lactobacillus gasseri* plus *Bifidobacterium longum* treatment with the results of a group receiving *Enterococcus faecium* and reported no adverse events or clinically relevant abnormalities in laboratory characteristics. One other study (Metts, 2003) randomized participants to vaginal suppositories of *Lactobacillus acidophilus,* suppositories and oral capsules containing *Lactobacillus* and *Bifidobacterium* strains, and placebo; one participant in the oral and vaginal suppository group and one in the placebo group reported vaginal discharge. Kim (2006) compared interventions with 5, 6, and 12 probiotic species and reported that one participant with pre-existing hypertension had elevated blood pressure, loose stool, diarrhea, and dehydration in the 12-species treatment group, one participant

each in the 5- and the 6-species groups reported loose stool, diarrhea, and worsening of gastrointestinal symptoms.

In the absence of further direct comparisons, we compared the included trials indirectly in subgroup analyses and a metaregression.

Single Probiotic Strain Interventions

A stratified analysis for studies using only one probiotic strain indicated a somewhat reduced, although not statistically significant, relative risk of adverse events compared to control (0.94; 95% CI: 0.86, 1.03; p=0.171) based on the number of participants with adverse events. The corresponding risk difference between intervention and control group participants was -0.001 (95% CI: -0.006, 0.003; p=0.557). Using the alternative measure, the number of adverse event incidences showed a similar result, a relative risk of 0.98 for probiotic intervention participants (95% CI: 0.89, 1.07; p=0.600; RD -0.001; 95% CI: -0.005, 0.003; p=0.748).

We also explored the nature of the adverse events encountered in single-strain studies and found no statistically significant differences in the relative or absolute risk for any of the adverse event groups (gastrointestinal events: RR 1.00; 95% CI: 0.82, 1.22; p=0.988; RD 0.003; 95% CI: -0.004, 0.009; p=0.434; infections and infestations: RR 1.07; 95% CI: 0.80, 1.44; p=0.828; RD 0.000; 95% CI: -0.003, 0.003; p=0.790; all other events: RR 1.03; 95% CI: 0.89, 1.18; p=0.708; RD 0.002; 95% CI: -0.002, 0.006; p=0.335) when comparing intervention and control group participants.

Multiple Probiotic Strains Interventions

Across studies with multiple probiotic strains, the relative risk for the number of participants with adverse events was slightly higher compared to the result observed for single probiotic strains but it was not different from the risk for control group participants (RR 1.01; 95% CI: 0.94, 1.09; p=0.729), the corresponding risk difference was -0.001 (95% CI: -0.010, 0.008; p=0.79). Similar results were seen using the alternative measure, the number of adverse incidences (RR 1.06; 95% CI: 0.94, 1.20; p=0.317; RD 0.006; 95% CI: -0.001, 0.013; p=0.106). Both types of intervention showed no statistically significantly increased risk of adverse events compared to control; however, results appeared to favor single-strain interventions compared to interventions including multiple probiotic strains.

We also explored the nature of the adverse events encountered in multiple strain studies but found no statistically significant differences in the relative or absolute risk for any of the adverse event groups (gastrointestinal events: RR 1.06; 95% CI: 0.86, 1.30; p=0.571; RD 0.003; 95% CI: -0.-003, 0.009; p=0.317; infections and infestations: RR 0.98; 95% CI: 0.84, 1.15; p=0.828; RD -0.001; 95% CI: -0.005, 0.004; p=0.790; all other events: RR 0.97; 95% CI: 0.82, 1.15; p=0.746; RD -0.002 (95% CI: -0.007, 0.004; p=0.536) when comparing intervention and control group participants.

Meta-Regression: Single Versus Multiple Probiotics

To find out whether the risk for adverse events was significantly different between these two kinds of interventions, we conducted a meta-regression. The metaregression did not indicate a statistically significant difference for the risk of adverse events between single and multiple strain interventions (relative risk ratio 0.93; 95% CI: 0.82, 1.04; p=0.205).

(3e) Does harm differ by products containing only probiotics and those containing a mixture of probiotics and prebiotics?

A number of studies were identified that investigated a synbiotic product; that is containing a probiotic as well as a prebiotic, or explicitly gave probiotic organisms together with prebiotics.

Some studies were identified that compared the effects of probiotics and synbiotics directly. Satokari (2001) and also Alander (2001) reported one incident of gastrointestinal symptoms and one participant not completing the study in the prebiotic treatment group (galacto-oligosaccharide), and no adverse events in the probiotic group or the group consuming probiotics and prebiotics (as described in the response to Key Question 1f). Chouraqui (2008) reported 7/70 adverse event incidences in a group receiving *Bifidobacterium longum*, *Lactobacillus rhamnosus*, and galacto-oligosaccharide; 4/74 incidences in a second group receiving *Bifidobacterium longum*, *Lactobacillus paracasei*, and prebiotics; 11/70 incidences in the probiotics group; and 7/70 in a control group (for event details see Evidence Table C4, Results). De Preter (2006) compared *Saccharomyces boulardii* [*cerevisiae*], lactulose, and placebo in various sequences and reported that "some" participants experienced flatulence in the lactulose and placebo phases. Fujimori (2009) reported no adverse events related to blood counts, liver enzymes, total protein, albumin, total cholesterol, triacylglycerol, serum urea nitrogen, creatinine, and electrolytes across groups receiving probiotic organisms (*Bifidobacterium longum*), prebiotics (psylium), or synbiotics (both preparations). Ishikawa (2005) reported the deaths of two participants who died from colorectal cancer in a probiotic group during a 4-year study on prevention of colorectal tumors compared to one death from colorectal cancer in the group that consumed probiotics and wheat bran biscuits; in addition, one participant in this group died from cerebral hemorrhage, and one reported peritonitis, but no lung cancer death occurred in either group. Tomoda (1991) reported no changes in blood chemistry in treatment groups receiving a *Bifidobacterium* intervention with or without lactulose. Underwood (2009) reported four cases of necrotizing enterocolitis, six infections, and three cases of feeding intolerance in the probiotics group compared to one, two, and zero incidences of the same outcome in the synbiotic group. Worthley (2009) reported that 11/18 participants in the synbiotic group reported excessive flatus compared to 5/19 in the probiotic group.

In the absence of further direct comparisons we investigated differences between probiotics and synbiotics in subgroup analyses and a metaregression.

Probiotics Only

Probiotic studies showed a relative risk of 0.98 (95% CI: 0.92, 1.04; p=0.446) for the number of participants with adverse events, comparing probiotics and control groups, and a risk difference of -0.001 (95% CI: -0.05, 0.004; p=0.681). Using the number of incidences per group as an alternative measure, no significant difference between probiotics and control groups are shown either (RR 1.01; 95% CI: 0.93, 1.09; p=0.879; RD 0000; 95% CI: -0.003, 0.003; p=0.916).

We also explored the nature of the adverse events encountered in all studies that used a probiotic rather than a synbiotic and found no differences in the relative or absolute risk for any of the adverse event groups, comparing intervention and control group participants (gastrointestinal events: RR 1.04; 95% CI: 0.88, 1.22; p=0.678; RD 0.001; 95% CI: -0.003, 0.005; p=0.545; infections and infestations: RR 1.04; 95% CI: 0.89, 1.22; p=0.618; RD 0.000; 95% CI: -0.003, 0.003 p=0.810; all other events: RR 1.01; 95% CI: 0.89, 1.14; p=0.901; RD 0.001; 95% CI: -0.003, 0.004; p=0.774).

Synbiotics Only

Selecting only synbiotic studies, that is, studies that explicitly gave a product that contained prebiotics as well as probiotics, or studies that gave probiotics together with prebiotics, we found a slightly higher risk of adverse events than seen in the probiotics-only studies (RR 1.08; 95% CI: 0.83, 1.39; p=0.582; RD 0.001; 95% CI: -0.013, 0.015; p=0.880) but no statistical difference between intervention and control group participants, based on the number of participants with adverse events. This result was confirmed using the alternative measure, the number of adverse event incidences (RR 1.05; 95% CI: 0.84, 1.32; p=0.670; RD 0.017; 95% CI: -0.004, 0.037; p=0.108).

We also explored the nature of the adverse events encountered in studies using synbiotics and found no statistically significant differences in the relative or absolute risk for any of the adverse event groups (gastrointestinal events: RR 1.01; 95% CI: 0.76, 1.34; p=0.947; RD 0.008; 95% CI: -0.004, 0.019; p=0.202; infections and infestations: RR 0.85; 95% CI: 0.61, 1.17; p=0.324; RD 0.001; 95% CI: -0.004, 0.005; p=0.748); all other events: RR 1.00; 95% CI: 0.82, 1.21; p=0.972; RD 0.001; 95% CI: -0.005, 0.006; p=0.824) comparing intervention and control group participants.

Meta-Regression: Probiotics Versus Synbiotics

To establish whether the results seen in probiotics only and synbiotics studies differ statistically significantly, a metaregression was undertaken. This analysis indicated no statistically significant difference in the number of adverse events (RR ratio 1.10; 95% CI: 0.84, 1.44; p=0.480 for number of participants with adverse events and 1.01; 95% CI: 0.93, 1.09; p=0.879 for adverse event incidences).

Summary and Strength of Evidence Key Question 3

What is the evidence that harms of *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus* differ by product and delivery characteristics?

Volume: Varied across questions

Risk of bias: Medium

The evidence to answer this Key Question stem from a variety of study designs and quality.

Consistency: Inconsistent

Very few studies overall were identified that directly compared delivery characteristics. Indirect comparisons showed only trends in replications rather than confirming exact results.

Directness: Indirect

Very few direct comparisons were identified; the majority of comparisons were indirect, across different RCTs.

Precision: Imprecise

The majority of included studies used small or moderate sample sizes and although some large studies were included, these were not designed to monitor adverse events.

Overall, the identified evidence is insufficient to answer the Key Question with confidence.

The lack of detail in the description of administered probiotic organisms in most studies hindered evaluations of the safety. Many studies did not specify which probiotic strains were investigated, nor was there indication that intervention preparations were tested for identity of the included organisms, viability, or contaminants.

Stratified analyses by probiotic genus identified a large number of studies exclusively using *Lactobacillus* strains; about a dozen studies on *Bifidobacterium* entered stratified analyses; and there were a small number of exclusive *Saccharomyces* interventions. However, there were very few studies using *Streptococcus*, *Enterococcus*, and *Bacillus* strains exclusively, and only some studies using these genera in combination with other genera. Due to the absence of studies on the latter group, there is an insufficient evidence base to answer product-specific safety questions. However, even for *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* research, there is a lack of direct comparisons between genera; information on the genera-specific safety of probiotics is primarily based on indirect comparisons.

Stratified analyses indicated that adverse events were not statistically significantly increased in treatment participants compared to control group participants for any of the reviewed genera. In indirect comparisons, there was some indication that interventions including *Streptococcus* strains showed more adverse events compared to the other genera, but as outlined before, the risk for intervention participants relative to control group participants was also not increased in these interventions.

There is a lack of studies directly comparing product characteristics. There was some indication across studies that safety findings may differ by delivery vehicle. Intervention participants in yogurt or dairy product studies were more likely to experience adverse event incidences than control group participants in subgroup analyses (RR 1.37; 95% CI: 1.05, 1.79; p=0.022). However, studies directly comparing delivery vehicles are missing.

The only included studies that compared the form of probiotic organisms directly compared viable and heat-killed organisms. Heat-killed organisms are not included in prominent definitions of probiotics; hence, this comparison is of minor interest. There was no indication that active forms were associated with a higher number of adverse events. The reporting of the form of organisms was too poor in included studies to allow a systematic investigation of the influence of the form.

There was a trend of single probiotic studies to report fewer adverse events compared to studies using a mixture of organisms; however, this finding was based on an indirect comparison across studies, in the absence of direct comparisons, and the difference did not reach statistical significance.

We did not identify evidence showing that synbiotics differ from probiotics with respect to adverse events; however, there is a lack of direct comparisons.

Key Question 4. How do the harms of *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and *Bacillus* vary based on (a) dose (cfu); (b) timing; (c) mode of administration (e.g., catheter); (d) age (all ages, including infants), gender, ethnicity, disease or immunologic status of the patient; (e) relationship to efficacy?

Although a large number of probiotics studies are included in the review, the identified studies rarely addressed more complex questions such as associations of participant or study characteristics and adverse events, which should be investigated with appropriate multivariate

methods. The number of studies contributing to answer the Key Questions varied across subquestions.

(4a) Is there a threshold or dose-response relationship between probiotics and harm? Does the duration of intervention relate to harm?

Threshold/Dose Response

Few studies were identified that compared different doses of a probiotic product. We considered the daily dose, rather than the length of exposure, for this question.

Lactobacillus. In the controlled trials, most studies investigated effects of *Lactobacillus* dosing. Basu (2009) compared two doses of 10^{10} and 10^{12} cfu of LGG powder among children with acute watery diarrhea and recorded that five children in the higher dose group dropped out due to electrolyte imbalance (compared with three in the lower dose group); three developed septicemia (compared with one in the low-dose group); one death occurred in the control group (compared with none in the treatment groups). Gao (2010) compared doses using 1 or 2 capsules containing 50 billion cfu *Lactobacillus acidophilus* and *Lactobacillus casei* and reported 1 case of fever in the higher dose group that was not study-related according to the authors, and 1 incidence of hematochezia in the control group. Hemmerling (2009) randomized participants to $5 * 10^8$, 10^9, $2 * 10^9$ cfu of *Lactobacillus crispatus* CTV-05 organisms or placebo, and reported that all participants experienced at least 1 of 45 adverse events without any apparent pattern associated with treatment arms. Ishikawa (2003) compared a dose of $2 * 10^7$ versus 10^8 cfu of *Lactobacillus salivarius, Lactobacillus acidophilus* and *Lactobacillus rhamnosus GG* and reported that 2 participants withdrew due to soft stools and abdominal discomfort, but it was not reported to which group these participants had been allocated. Karvonen (2001) compared *Lactobacillus reuteri* in doses of 10^5, 10^7, and 10^9 cfu and concluded that abdominal symptoms (days with discomfort, pain, or cramps) were similar across groups of neonates. Lu (2004) compared what they characterized as a low ($1.5 * 10^8$ cfu), medium ($2.7 * 10^8$ cfu), and high ($4 * 10^8$ cfu) dose of *Lactobacillus rhamnosus* given to participants and reported no episodes of vomiting, diarrhea, constipation, abdominal pain, cough, or other allergic reaction. Nobuta (2009) randomized participants to $3 * 10^9$, $6 * 10^9$, 10^{10}, or $3 * 10^{10}$ cfu *Lactobacillus brevis* KB290 or placebo and reported that 1 participant in the first group reported abdominal pain, 1 participant in the second group reported a cold, and 1 participant in the group with the highest dose reported abdominal pain and diarrhea. Petschow (2005) compared a low (10^6 cfu), medium (10^7 cfu) and high (10^8 cfu) dose of *LGG* and found that stool consistency, flatulence, and fussiness were similar among groups. Tursi (2008) randomized participants to various doses of *Lactobacillus casei casei* DG and reported 2 incidences of epigastric pain, 1 nausea, 1 diarrhea, but the group allocation was unclear; 1 participant in the $1.6 * 10^7$ group developed acute bronchial pneumonia.

Bifidobacterium (alone or in combination). Gill (2001) compared *Bifidobacterium lactis* HN019 given in a dose of $5 * 10^{10}$ or $5 * 10^9$ cfu and 1 participant in the lower dose reported digestive discomfort. Guyonnet (2009) compared a group eating 1 pot of a commercially available probiotic yogurt versus 2 pots of yogurt (each containing $1.25 * 10^{10}$ cfu *Bifidobacterium lactis* DN-173010 and yogurt cultures ($1.2 * 10^9$ *Streptococcus thermophilus* and *Lactobacillus bulgaricus*) and reported no adverse effects on digestive comfort. Larsen (2006) compared doses of 10^8, 10^9, 10^{10}, and 10^{11} cfu of *Bifidobacterium animalis lactis* BB-12 and *Lactobacillus paracasei paracasei* CRL-431 and reported 1 case of diarrhea in the 10^{10} group and that across

all groups, 68 percent of participants reported flatulence, 37 percent of abdominal bloating, and 22 percent of headache. Ruiz-Palacios (1996) compared a low (10^6 cfu), medium (10^8 cfu), and high dose (10^{10} cfu) of a probiotic blend containing *Lactobacillus reuteri, Lactobacillus acidophilus,* and *Bifidobacterium infantis* and reported that intake, incidence of vomiting, abdominal discomfort, gas, and stool characteristics were not statistically significantly different across groups. Saavedra (2004) compared a dose of 10^6 and 10^7 cfu of *Bifidobacterium, lactis*, Bb 12 and *Streptococcus thermophilus* and reported that 3 infants in the higher dose treatment group withdrew due to a viral rash, loose stools, or vomiting.

Saccharomyces. De Preter (2006) randomized participants to various groups and treatment periods receiving 2 or 4 times 250mg of *Saccharomyces boulardii* [*cerevisiae*] and reported that some participants reported flatulence during prebiotic intake (but not during probiotic intake).

A case series (Elmer, 1995) described a group of participants that used a *Saccharomyces boulardii* [*cerevisiae*] product in increasing doses required to achieve a satisfactory response; the study reported that 1/7 participants reported intestinal gas (dose unknown).

Streptococcus and *Enterococcus.* Borgia (1982) compared treatment groups received one, two, or three capsules of *Streptococcus [Enterococcus] faecium* SF68 or control interventions in a trial to prevent side effects of antibiotic treatment and reported two cardiovascular deaths, but it was not clear to which treatment group these participants had been allocated. Other blends including these genera are described in the *Bifidobacterium* section.

Bacillus (alone or in combination)*:* No controlled trial was identified that compared different doses of *Bacillus*.

In a case series, Garrido (2005) administered 100mL of a product containing 10^8 cfu/ml of *Lactobacillus* and *Bacillus* strains daily for 1 week, increasing the dose to 200 mL during the second week, and 500mL during the third week. They reported mild increases of borborygmi during the last week.

Overall, no threshold effect or trend was identified indicating that a higher dose was associated with a larger number of reported adverse events. However, comparing the exposure across studies, it is apparent that there is no accepted standard of what is considered a low or high dose of exposure. The high dose in one comparative study is the low dose in another. Dosing depended in part on the publication year, with later publications using higher doses, and the dose characteristics are also likely to be genera or species dependent, precluding systematic analyses. In addition, many studies used a mixture of organisms, confounding potentially existing effects of dose-response relationships for specific genera, species, or strains.

Intervention Duration

Many of the included studies used intervention periods of short duration, often only 1 week. For analysis purposes, we characterized short-term use as 1 month or less and long-term use as 1 year or more. In total, 46 percent of studies reported intervention periods of 1 month or less. Only 5 percent of all identified studies reported on long-term use of probiotic products. In the remaining studies (49 percent), participants used probiotics for longer than 1 month but less than 1 year (medium-term use), or in rare cases, it could not be established how long the study product was used. The exact reported intervention duration is shown for each study in Evidence

Table C2, Intervention. We undertook stratified analyses and metaregression to explore whether the intervention duration is associated with encountered adverse events.

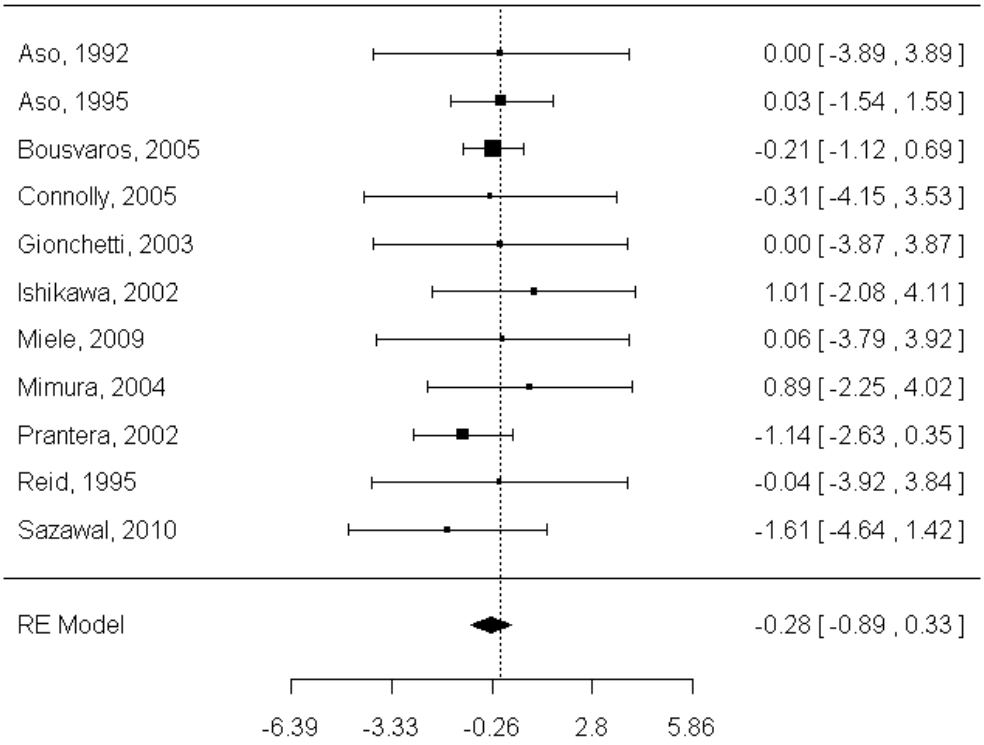
Short-term use. The relative risk of adverse events across all short-term studies was 1.02 (95% CI: 0.89, 1.17; p=0.780), with no detectable risk differences between treatment and control groups (RD 0.000; 95% CI: -0.005, 0.004; p=0.866) based on the number of participants with adverse events. Using the alternative measure, the number of adverse event incidences, results were very similar (RR 1.12; 95% CI: 0.96, 1.31; p=0.138; RD 0.008; 95% CI: -0.002, 0.017; p=0.132).

Medium-term use. Medium-term studies showed a relative risk of 0.98 (95% CI: 0.92, 1.04; p=0.470; RD -0.001; 95% CI -0.012, 0.010; p=0.889) based on the number of participants with adverse events. The total number of adverse event incidences showed very similar results (RR 0.95; 95% CI: 0.87, 1.04; p=0.283; RD 0.000; 95% CI -0.003, 0.003; p=0.914), also indicating no increased risk of adverse events for intervention participants compared to controls.

Long-term use. Adverse events associated with long-term use is of particular interest. The 18 identified studies that reported on long-term use (defined as one year or longer) included 1 case study (Jensen, 1976) that described a patient who used *Saccharomyces boulardii* [*cerevisiae*] for several years and was hospitalized for fever of unknown origin. We did not identify any other observational studies, such as case series, on long-term use.

The other long-term studies were controlled trials; adverse events results varied, sometimes favoring the intervention, sometimes the control group. To investigate whether the intervention duration was associated with an increased risk of adverse events, we undertook a subgroup analysis for long-term use in parallel RCTs. The individual RCTs investigated *Lactobacillus* interventions (Aso, 1995; Aso, 1992; Bousvaros, 2005; Connolly, 2005; Dekker, 2009; Prantera, 2002; Reid, 1995), a *Bifidobacterium* intervention (Sazawal, In press), a blend of *Lactobacillus* and *Bifidobacterium* strains (Gionchetti, 2003; Ishikawa, 2003), or a blend of *Lactobacillus, Bifidobacterium*, and *Streptococcus* (Miele, 2009; Mimura, 2004). First, considering the number of participants with adverse events, the relative risk was RR: 0.76; 95% CI: 0.41, 1.39; p=0.259) for intervention participants compared to control group participants, with a trend favoring intervention participants, although not statistically significantly. The forest plot in Figure 21 shows the individual studies that entered the analysis.

Figure 21. RR number of participants with adverse events in long-term use RCTs



Individual study results varied, sometimes favoring the probiotics group, sometimes the control group. The risk difference between treatment and control group participants was very small and not statistically significant (RD -0.006; 95% CI -0.016, 0.004; p=0.259). Using an alternative measure, the total reported incidences per group, the results also do not indicate a relative or absolute risk difference from control group participants (RR 0.86; 95% CI: 0.69, 1.08; p=0.209; RD -0.005; 95% CI: -0.014, 0.005; p=0.311).

Each individual encountered adverse event in the intervention and control groups is documented in the Evidence Table C4, Results. To explore the nature of the adverse events associated with long-term use, we differentiated gastrointestinal complaints, infections and infestations, and other adverse events and undertook separate analyses. None of the analyses indicated an increased risk of adverse events in any of the three categories, compared to control group participants (gastrointestinal events: RR 1.02; 95% CI: 0.57, 1.84; p=0.932; infections and infestations: RR 1.84; 95% CI: 0.59, 5.74; p=0.293; all other adverse events: RR 0.78; 95% CI: 0.59, 5.02; p=0.075).

Metaregression. None of the stratified analyses indicated a statistically significantly increased risk of adverse events for intervention participants compared to control group participants. However, the subgroup analyses indicated that long-term use may be associated with fewer adverse events compared to results found in short-term and medium-term use studies. In order to investigate whether the results differ statistically significantly between studies, we undertook a meta-regression. For this, two different analyses were available.

First, we used a categorical variable differentiating short-term, medium-term, and long-term use. For the number of participants with adverse events, no statistically significant difference was found (p=0.596); however, for the number of adverse event incidences, studies differed

significantly across short-, medium-, and long-term use (p=0.039). We then used the intervention duration as a continuous variable, extracting the exact duration of the intervention in months. This analysis did not confirm a statistically significant difference between studies associated with the length of the intervention; neither an analysis based on the number of participants with adverse events (p=0.115), nor one based on the number of adverse event incidences (p=0.162) showed a statistically significant difference. It has to be kept in mind that the proportion of identified long-term use studies was very small compared to the overwhelming proportion of short- and medium-term studies reported in the literature.

(4b) Is there a relationship between time of onset of harm and time of probiotic administration? How does time of exposure affect harm? Is harm sustained after the intervention or exposure stops?

For the purpose of this review, we recorded the time of onset of the harm whenever possible. The time of onset was then compared to the timing of the administration of the probiotic. We also recorded any information regarding the clinical course of adverse events and the length of time for which harms were sustained after the intervention was stopped and the participant was no longer exposed to the probiotic product. Few studies provided information on the onset of adverse events, but some of these studies, in particular the case studies, gave some insight into the development of harms.

Timing descriptions included information on gastrointestinal side effects such as constipation, which was reported in two studies. In one of these studies, constipation began 2 weeks after treatment while another did not pass stools beginning on the third day of the intervention period (Hirata, 2002; Rosenfeldt, 2002) and 10 days after treatment in one case (Loguercio, 1987). Loose stools and diarrhea were also reported on the first day of treatment, 3 days into treatment, on days 3 to 7 of treatment, and accompanied by abdominal discomfort after 1 week of taking probiotic (Black, 1991; Fukuda, 2008; Gotteland, 2003; Ishikawa, 2003); at 10 days (Mimura, 2004); in the third week of treatment after dose increase (Garrido, 2005); or after 1 month (Glintborg, 2007). Projectile vomiting after 2 hours was reported in one infant (Hwang, 2009). Vomiting occurred on the first day of treatment and incidences continued until the third day (Isolauri, 1991) in another study. One study reported one participant leaving the study on the second day due to nausea (Tasli, 2006); large amounts of gas on the third day (Beck, 1961); increased appetite was reported for the first 5 days of treatment (Anukam, 2006), another reported that four participants discontinued during the first week because of vomiting (Xiao, 2003); and bloating occurred primarily during the first week of treatment in three reports (Gionchetti, 2007; Parfenov, 2005; Ranganathan, 2009). One study reported that one participant dropped out on day 11, following 1 week of abdominal pain (Nobuta, 2009). General gastrointestinal side effects were reported in anotherone study at week 1 (Lee, 2010).

With regard to infections, a submandibular abscess was noted 2 weeks after study entry in one study (Vleggaar, 2008); one participant received antibiotics for bronchitis after 3 weeks (Reid, 2001); one infant developed a viral rash after 30 days (Saavedra, 2004); an abscess developed after 4 weeks (Conen, 2009); a coryza-like illness developed in the second month of treatment (Ishikawa, 2003); one case of liver abscess was reported in one case after 4 months of probiotic ingestion (Rautio, 1999); D-lactic acidosis was diagnosed after 3 months (Oh, 1979), and 4 months (Ku, 2006).

Reports of more serious infections included incidences of fungemia and bacteremia. Cases of fungemia began 4 days (Fredenucci, 1998; Lungarotti, 2003), 5 days (Lolis, 2008; Piechno,

2007; Richard, 1988; Viggiano, 1995; Zunic, 1991), 7 days in two cases (Cherifi, 2004; Munoz, 2005), 8 days (Hennequin, 2000; Munoz, 2005), 10 days (Ohishi, 2010), 13 days (Pletinex, 1995), 18 days (Bassetti, 1998), 20 days (Riquelme, 2003), 21 days (Niault, 1999), 32 days (Hennequin, 2000), 7 weeks (Hennequin, 2000; Trautmann, 2008) and 2 months (Hennequin, 2000) after starting treatment. Bacteremia was seen after a median of 9 days in four patients (Richard, 1988) and 1.5 weeks (De Groote, 2005), 20 days (Land, 2005), and 3 weeks (Ledoux, 2006) after starting probiotic treatment. Sepsis started after "several" days (Rijnders, 2000), 6 days (Lestin, 2003), 23 days (Kunz, 2004), and 179 days (Kunz, 2004) of treatment. These adverse events developed while using probiotics. Only Niault (1999) and Land (2005) reported on adverse events that developed after the treatment was stopped.

Other adverse events that occurred included local burning and irritation on the first 2 days of product application (Di Pierro, 2009); colposcopy findings of erythema, petechiae, edema, abrasion, and laceration on days 1, 7 and/or 14 (Hemmerling, 2009); anemia in 1 infant at 6 months and in 16 at 2 years (Kuitunen, 2009); one case of cervicobrachialgia that began 2 weeks after stopping active treatment (Ligaarden, 2010); increased days with eye symptoms early in treatment (Ouwehand, 2009); and a flare of rheumatoid arthritis at week 1 in one participant (Lee, 2010).

Few studies provided information on the clinical course of experienced adverse events. Gastrointestinal events appeared to resolve spontaneously, regardless of whether the intervention was continued or discontinued. The described cases of bacteremia and sepsis resolved within 24 to 72 hours (Bassetti, 1998; Land, 2005) or 8 days (Ledoux, 2006) in the studies that provided information on the clinical course. Blood cultures were negative after 10 days (Kunz, 2004) and 21 days (De Groote, 2005). Fungemia resolved within 58 hours (Hennequin, 2000), 6 days (Viggiano, 1995), 8 days (Piechno, 2007), 10 days (Pletinex, 1995), 11 days (Riquelme, 2003), 13 days (Trautmann, 2008), 15 days (Niault, 1999), 18 days (Riquelme, 2003), 60 days (Hennequin, 2000), 3 weeks (Hennequin, 2000), or 6 months (Conen, 2009). Sepsis cleared after 14 days (Zein, 2008). Burning and irritation lasted only a few hours (Di Pierro, 2009). Increased eye symptoms resolved within a month (Ouwehand, 2009). One participant experienced pseudomonas aeruginosa septicemia from leg cellulitis believed to be due to spending time in a public hot tub (Bajaj, 2008) and died on day 67 of the study.

(4c) Does the route of administration (e.g., orally, jejunostomy tube, central venous catheter) relate to harm?

We differentiated a number of routes of administration—oral, enteral feeding, intravenous catheter, intravaginal, and topical routes of administration—to investigate whether the route of administration of probiotics is linked to the risk of adverse events. As the route of administration depends primarily on clinical necessity, no study was identified that directly compared two routes of administration. To identify potentially different safety trends associated with the use of a particular route of administration, we undertook stratified analyses and a metaregression to compare across studies.

Oral Administration

In most of the included studies, the participants consumed the probiotic organisms orally (272/387); participants swallowed pills or capsules or ate probiotics-enriched food. This number included 17 case studies that reported the mode of administration.

To investigate whether adverse events are more frequent in probiotic interventions compared to control interventions, we undertook a stratified analysis. Across all parallel RCTs that reported oral administration, the relative risk of adverse events for intervention participants compared to controls was 0.98 (95% CI: 0.93, 1.04; p=0.581) based on the number of participants with adverse events. The corresponding risk difference between groups was -0.001 (95% CI: -0.005, 0.003; p=0.207). Based on the alternative measure, the number of adverse event incidences, no statistically significant difference between intervention and control group participants could be found either (RR 1.01; 95% CI: 0.93, 1.08; p=0.960; RD 0.003; 95% CI: -0.002, 0.009; p=0.207).

To explore the nature of encountered adverse events, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. In none of the categories did the probiotic intervention group show an increased risk compared to control (gastrointestinal: RR 1.06; 95% CI: 0.91, 1.25; p=0.453; RD 0.007; 95% CI: -0.001, 0.015; p=0.072; infections and infestations: RR 0.98; 95% CI: 0.85, 1.14; p=0.831; RD 0.000; 95% CI: -0.003, 0.003; p=0.886; other adverse events: RR 0.98; 95% CI: 0.88, 1.11; p=0.782; RD 0.000; 95% CI: -0.004, 0.003; p=0.867). Individual adverse events reported in each study are shown in Evidence Table C4, Results.

Enteral Administration

A number of studies (43/387) reported on interventions where probiotics were administered through enteral feeding tubes in hospitalized patients. We grouped all studies that described the use of a nasal tube or gastric feeding tubes, or indicated a jejunostomy in this category. This group included 11 of the 29 case studies that reported the mode of administration for described patients.

To investigate whether this group of studies reported more adverse events in a probiotics group than in a control group from the same patient population, we undertook a stratified analysis. Even if adverse events are more likely in patients needing enteral feeding overall, and events may have a greater clinical impact in these people (e.g., an infection), it is critical to evaluate whether patients on probiotics experience more adverse events relative to a control group with similar patient characteristics. A pooled analysis based on the number of participants with adverse events indicated no statistically significantly different risk or trend of an increased risk compared to control (RR 0.84; 95% CI: 0.55, 1.29; p=0.350; RD -0.002; 95% CI: -0.022, 0.017; p=0.828). Using the alternative measure, the number of adverse event incidences, no statistically significantly increased risk was identified either (RR 1.15; 95% CI: 0.86, 1.55; p=0.350; RD 0.001; 95% CI: -0.009, 0.011; p=0.777).

To explore the nature of encountered adverse events, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. In none of the categories did the probiotic intervention group show an increased risk compared to controls (gastrointestinal events: RR 0.85; 95% CI: 0.51, 1.42; p=0.527; RD 0.010; 95% CI: -0.019, 0.038; p=0.507; infections and infestations: RR 1.17; 95% CI: 0.69, 1.99; p=0.567; RD 0.000; 95% CI: -0.008, 0.008; p=0.969; other adverse events: RR 1.29; 95% CI: 0.82, 2.03; p=0.273; RD 0.004; 95% CI: -0.013, 0.020; p=0.637). Individual adverse events reported in each study are shown in Evidence Table C4, Results.

Other Routes of Administration

Fifteen studies included in this review investigated the intravaginal administration of probiotic organisms. Most of the adverse events related to the administration of probiotic organisms or placebo were mild to moderate (such as vaginal discharge). None of the case studies reported this mode of administration.

Based on the number of women with adverse events in each treatment group, the parallel RCTs reported no statistically increased risk of adverse events compared to controls (RR 1.06; 95% CI: 0.72, 1.57; p=0.761; RD -0.004; 95% CI: -0.054, 0.046; p=0.870). No statistically significant difference compared to control or even a trend for increased risk of events was identified in the alternative measure, the number of adverse event incidences either (RR: 0.84; 95% CI: 0.57, 1.23; p=0.363; RD -0.013; 95% CI: -0.039, 0.012; p=0.313).

To explore the nature of encountered adverse events in studies with an intravaginal administration of probiotics, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. In none of the adverse event categories did the probiotic intervention group show an increased risk compared to control (gastrointestinal events: RR 0.67; 95% CI: 0.16, 2.78; p=0.583; RD -0.005; 95% CI: -0.022, 0.013; p=0.612; infections and infestations: RR 1.51; 95% CI: 0.57, 1.99; p=0.408; RD 0.035; 95% CI: -0.069, 0.14; p=0.505; all other adverse events: RR 0.74; 95% CI: 0.43, 1.26; p=0.0.268; RD -0.016; 95% CI: -0.052, 0.020; p=0.389). Individual adverse events reported in each study are shown in Evidence Table C4, Results.

With regard to other routes of administration, four studies reported a topical application of probiotic organisms. Details of the intervention and the adverse events results are shown in the evidence tables. Across the three parallel RCTs, no statistically significant difference in adverse events between intervention and control group could be detected (RR 1.06; 95% CI: 0.65, 1.72; p=0.817; RD 0.048; 95% CI: -0.045, 0.0140; p=0.311).

The nature of the adverse events encountered with topical applications varied. Falck (1999) used alpha-streptococci to treat recurrence of streptococcal pharyngotonsillitis and reported that 16 percent of participants reported respiratory complaints related to the common cold compared to 13 percent in the control group. Klarin (2008) reported 5/23 deaths in the treatment group (*Lactobacillus plantarum* 299) compared to 6/21 in the control group of intubated patients. Peral (2009) reported that five patients with burns in the *Lactobacillus plantarum* group had (tolerable) pain, there were no local or systemic allergic symptoms, and the administered organism was not found in blood or wound samples. Roos (1996) reported 13 participants with throat pain, headache, coughing, runny nose, common cold, and fever compared to 18 control group participants reporting similar adverse events, among the 130 participants with streptococcal pharyngotonsillitis.

The case of *Saccharomyces boulardii* [*cerevisiae*] sepsis reported by Piechno (2007) described the use of an intravenous catheter for parenteral nutrition; no other study reported explicitly on this route of administration

Metaregression: Routes of Administration

To investigate whether study results different significantly based on the route of administration, we undertook a metaregression adding the route of administration as a moderator in the meta-analysis. Based on both alternative measures of adverse event risks, no statistically significant difference was found (number of participants with adverse events: p=0.840; number of adverse event incidences: p=0.633). In addition, enteral feeding is a route of administration as

well as intrinsically related to the participant characteristics. Differences associated with participant characteristics, such as the health status, are described in the next result section (4d).

(4d) How does harm relate to subpopulations, including different age groups (specifically including neonates and infants under age 24 months), men and women, ethnic/race subgroups, or health status (healthy to high risk) individuals?

Age

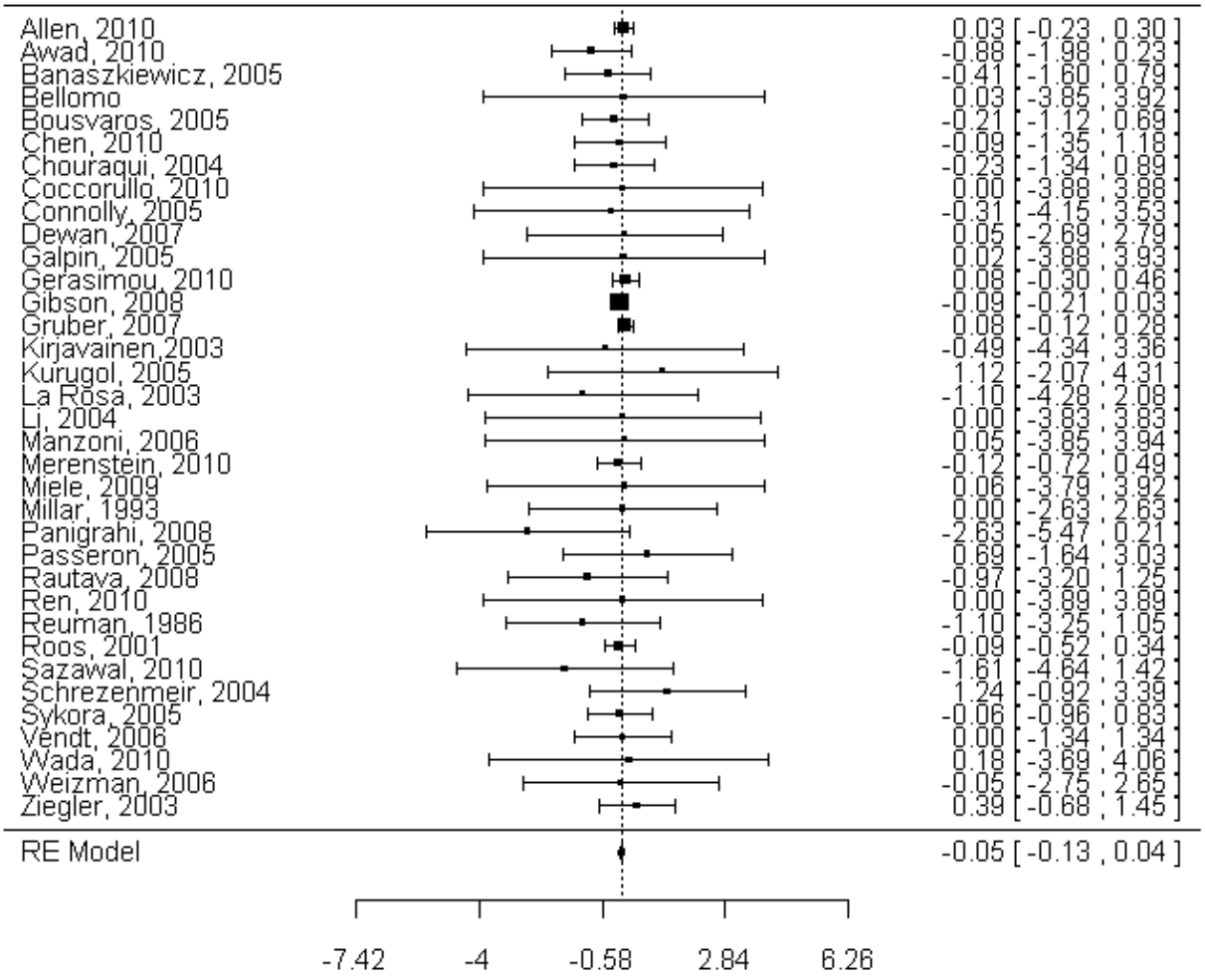
The majority of the identified studies included adult participants. We distinguished, where possible, studies in children (up to 18), adults, and elderly participants (using 65 as the age cut-off).

Children. We identified 123 studies that included children. Some of the studies in children exposed them to probiotic organisms prenatally with the mother consuming probiotic organisms as well as postnatally. Overall, studies in children tended to be better reported than studies in adults. This pertained to the reporting of the intervention (e.g., reporting the strain of the administered probiotics) and the reporting of the adverse events (e.g., reporting a list of adverse events that was determined a priori and monitored and then reporting on the results).

Seventeen of the included 43 case studies described children (Barton, 2001; Cesaro, 2000; De Groote, 2005; Hennequin, 2000; Hwang, 2009; Ku, 2006; Kunz, 2004; Land, 2005; Lungarotti, 2003; Munakata, 2010; Ohishi, 2010; Perapoch, 2000; Pletinex, 1995; Trautmann, 2008; Viggiano, 1995).

In total, we identified 35 parallel RCTs that reported the total number of participating children in a group receiving probiotics compared to a group of children not using probiotics, and the total number of children with adverse events per treatment group. Most studies in children investigated *Lactobacillus* interventions, alone or in combination with *Bifidobacterium*, some studies used only *Bifidobacterium* strains (in infant formulae), and there were some exceptions of studies using *Saccharomyces* (Kurugol, 2005), *Streptococcus* (Roos, 2001), *Enterococcus* (Bellomo, 1979), or *Bacillus* (La Rosa, 2003 [*Lactobacillus sporogenes*]) strain interventions. The relative risk of children in probiotics groups to experience an adverse event was not statistically significantly different from children receiving the control intervention (RR 0.96; 95% CI: 0.88, 1.04; p=0.296). The forest plot in Figure 22 shows the individual study results.

Figure 22. RR number of children with adverse events



The risk difference across intervention and control group participants was -0.004 (95% CI: -0.012, 0.004; p=0.302) based on the number of children with adverse events in each group. The alternative measure, the relative risk of adverse event incidences, was 0.95 (95% CI: 0.87, 1.04; p=0.296) comparing intervention and control groups was similar and the corresponding risk difference was -0.001 (95% CI: -0.004, 0.003; p=0.757); this analysis is based on a much larger number of trials (75 RCTs), as the number of individual adverse event incidences was reported more often than the number of children with adverse events per treatment group.

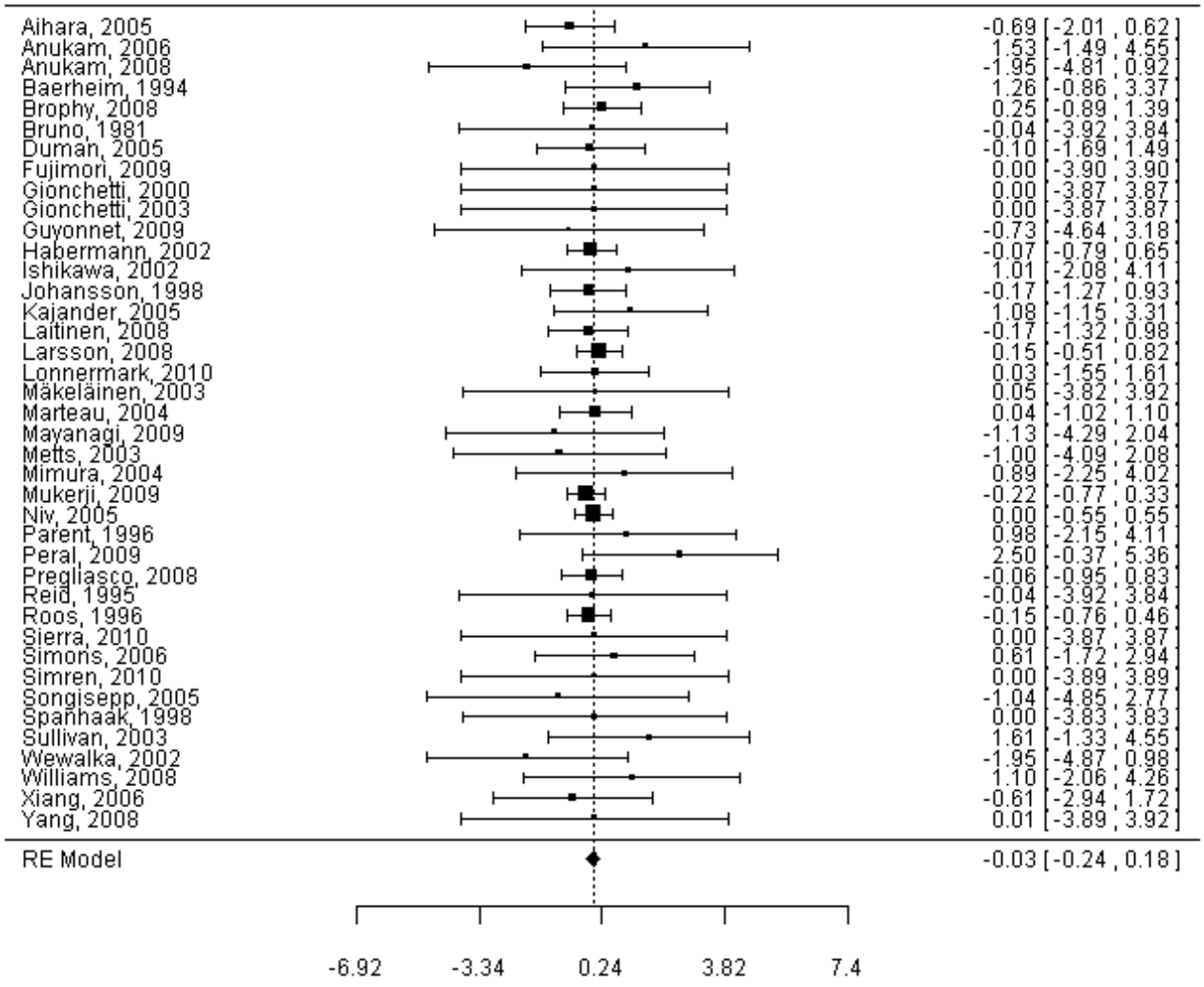
For very young children (under 24 months of age), the relative risk to experience an adverse event was 0.96 (95% CI: 0.88, 1.05; p=0.332; 27 trials) compared to the control group, and the risk difference was -0.005 (95% CI: -0.013, 0.004; p=0.289), indicating no trend for increased adverse events associated with the probiotics intervention. The alternative measure, the relative risk of adverse event incidences, was similar, with a relative risk of 0.94 (95% CI: 0.86, 1.03; p=0.202; 65 RCTs) comparing intervention and control groups, and the corresponding risk difference was -0.001 (CI: -0.005, 0.003; p=0.0505).

To explore the nature of encountered adverse events, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. In none of the categories did the probiotic intervention group show an increased risk compared to control

(gastrointestinal events: RR 0.99; 95% CI: 0.80, 1.22; p=0.895; RD 0.001; 95% CI: -0.005, 0.008; p=0.706; infections and infestations: RR 0.94; 95% CI: 0.77, 1.14; p=0.511; RD 0.000; 95% CI: -0.004, 0.004; p=0.999; all other adverse events: RR 0.98; 95% CI: 0.86, 1.12; p=0.748; RD -0.001; 95% CI: -0.005, 0.004; p=0.683). Individual adverse events reported in each study are shown in Evidence Table C4, Results.

Adults. The majority of identified studies included adult participants (233 studies). A separate meta-analysis for parallel RCTs with only adult participants indicated a relative risk of adults in probiotics group to experience an adverse event of 0.97 (95% CI: 0.79, 1.19; p=0.745) compared to control. The individual results are shown in the forest plot in Figure 23, and the corresponding risk difference was 0.001 (95% CI: -0.009, 0.011; p=0.865). Individual study results varied, sometimes favoring the probiotic intervention group, sometimes the control group. The pooled results indicated no trend that the intervention was associated with a higher risk of adverse events compared to control.

Figure 23.RR number of adults with adverse events



The alternative measure, the relative risk of adverse event incidences, was 1.02 (95% CI: 0.82, 1.27; p=0.851; 63 RCTs) comparing intervention and control groups and the corresponding risk difference was 0.005 (95% CI: -0.005, 0.015; p=0.319), both also not indicating a statistically significant risk of adverse events compared to control.

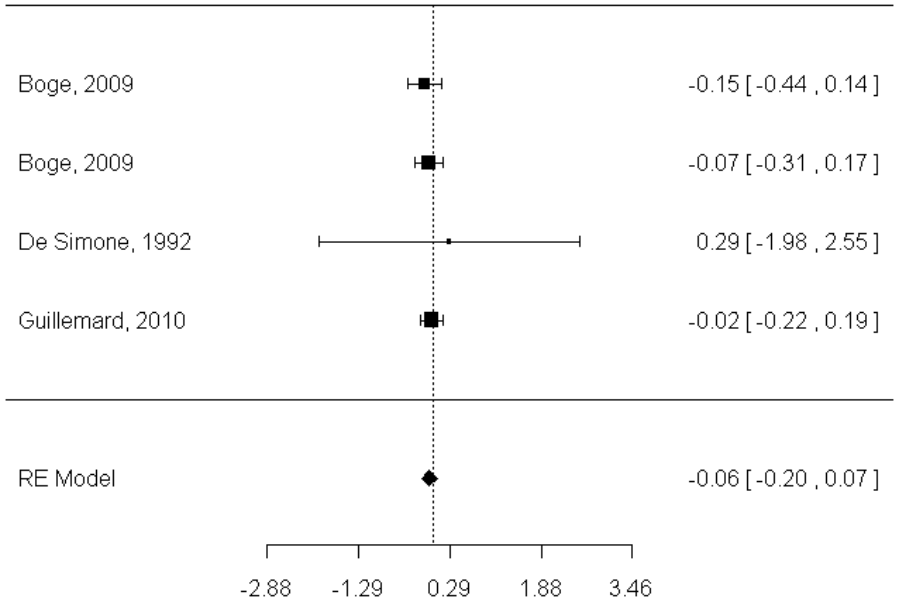
To explore the nature of encountered adverse events, we differentiated gastrointestinal complaints, infections and infestations, and all other reported adverse events. In none of the categories did the probiotic intervention group show an increased risk compared to controls (gastrointestinal events: RR 1.17; 95% CI: 0.82, 1.67; p=0.392; RD 0.006; 95% CI: -0.004, 0.015; p=0.225; infections and infestations: RR 1.39; 95% CI: 0.66, 2.93; p=0.386; RD 0.006; 95% CI: -0.017, 0.030; p=0.597; all other adverse events: RR 0.98; 95% CI: 0.72, 1.32; p=0.884; RD 0.004; 95% CI: -0.005, 0.012; p=0.430). Individual adverse events reported in each study are shown in Evidence Table C4, Results.

Elderly. Although one-third of the identified studies included participants 65 years of age or older, studies exclusively in the elderly account for only 5 percent of the review sample. In addition, elderly participants were explicitly excluded from 5 percent of the included studies (of those studies that were not in infants or other specified age samples). We identified 17 studies in total that reported exclusively on participants 65 years of age or older. Among these were several case studies of serious infections (Cherifi, 2004; Henry, 2004; Jensen, 1976; Mackay, 1999; Munoz, 2005; Oggioni, 1998; Rautio, 1999; Rijnders, 2000; Tommasi, 2008).

One of the two identified case series with elderly participants reported no adverse events (An, 2010); in the other one, two of the participants with dementia died during the followup, and one experienced diarrhea (Carlsson, 2009).

Only a small number of controlled trials targeted exclusively elderly participants (Boge, 2009; De Simone, 1992; Gill, 2001; Guillemard, 2010; Stotzer, 1996). Based on four parallel RCTs that reported on the number of participants with adverse events, as depicted in Figure 24, the relative risk of elderly participants in the probiotics group experiencing an adverse event was 0.94 (95% CI: 0.82, 1.08; p=0.367) compared to controls, and the risk difference was -0.013 (95% CI: -0.069, 0.033; p=0.545) indicating that the intervention was not associated with an increased relative risk of adverse events. The individual RCTs investigated *Lactobacillus* in combination with *Bifidobacterium* or *Streptococcus/Enterococcus* strains.

Figure 24. RR number of elderly participants with adverse events



The nature of the encountered adverse events varied across RCTs that studied participants 65 years of age and older.

The Boge (2009) trials reported common infectious diseases, and Guillemard (2010) reported muscular-bone adverse events, gastrointestinal adverse events, and infections other than common infectious diseases, but the exact number per treatment group was not reported. De Simone (1992) reported 2 participants with incidences of intestinal rumbling and flatulence compared to 1 participant with variation in stool consistency and diarrhea among 15 elderly participants taking *Bifidobacterium bifidum* and *Lactobacillus acidophilus* treatment and 10 elderly control participants. Gill (2001) reported only one case of digestive discomfort in the control group in a study using *Bifidobacterium lactis* HN019 to enhance immunity. Of the 17 elderly participants with small intestinal bacterial overgrowth described by Stotzer (1996), 1 was excluded from a crossover trial on *Lactobacillus fermentum* due to the deterioration of her general condition (presumably associated with radiation enteritis after treatment for ovarian cancer); 1 other participant was excluded due to side effects not further described.

Given the paucity of trials exclusively in the elderly, we also investigated the presence of participants 65 years of age or older in the study samples and its effects on adverse events. A metaregression showed no statistically significant effect based on the number of participants with adverse events (p=0.438) and based on the number of adverse event incidences (p=0.991).

Metaregression. Age: In order to investigate whether different safety results are reported for different age groups for treated participants relative to controls (relative risk ratio), we tested this assumption in a meta-regression. Based on the number of participants with adverse events, there was no indication that the risk of experiencing an adverse event in the treatment group relative to controls differs by age (p=0.559, joint significance test). For the outcome adverse event incidences, no analysis could be undertaken due to the small number of studies in the elderly.

Gender

Almost all samples in the included studies were of mixed gender. We identified 38 studies describing female participants only and 35 studies that included only male participants. The case studies described more male than female patients, where gender was reported (see Evidence Table C1, Study Details), and 24 of the exclusively male studies were case studies. Very few parallel RCTs with exclusively male participant samples were identified. Studies in female participants were primarily those using the vaginal route of administration, and the results have been described under Key Question 4c.

To investigate whether there was any indication that adverse events depended on the sex of the participants, we added gender as a moderator in a metaregression model. This question was investigated using two different approaches. First, we investigated exclusively male and exclusively female parallel RCTs (categorical variable analysis). Second, we used the number of female participants in each RCT as a moderator for safety results (continuous variable analysis). In both analyses, there was no indication that encountered adverse events due to probiotics compared to control was more common in female or in male participant groups based on the number of participants (categorical variable analysis: p=0.188; continuous variable analysis: p=0.210) and the number of adverse event incidences (categorical variable analysis: p=0.123; continuous variable analysis: p=0.447).

Ethnicity

With regard to race and ethnicity, almost none of the studies targeted a particular demographic group, and many studies provided no information regarding these participants' features, as recorded in the Evidence Table C1, Participant and Study Details.

Health Status

The clinical characteristics of participants included in the identified studies are reported in Evidence Table C1, Participant and Study Details. The included studies report on participants with widely varying health conditions. In addition to indicating the specific clinical condition (where applicable), we also differentiated participants on a continuum ranging from generally healthy to critically ill. A large number of included studies (229 studies) could not be classified as enrolling either critically ill or generally healthy persons but fell into the middle of this continuum. This group included the many studies in participants being treated for a health concern such as IBS, ulcerative colitis, Crohn's disease, diabetes, or other similar health concerns. Of all included studies, 83 were in participants that could be classified as generally healthy. In all, 76 studies described high-risk patients, that is, those hospitalized for serious health concerns and critically ill patients.

Of note, 13 percent of included studies reported explicitly that immunocompromised participants were excluded from identified studies.

Generally healthy. First, of all included case studies that reported cases of serious adverse events such as fungemia and bacteremia, only one reported case (see Jensen, 1974) was considered generally healthy before the onset of the observed adverse event.

To investigate whether healthy participants using probiotics were more likely to experience adverse events compared to control group participants not using probiotics we undertook a subgroup analysis for all studies enrolling generally healthy participants. There was no indication that healthy participants using probiotics were statistically significantly more likely to suffer

from adverse events than control group participants based on the number of participants with adverse events (RR 0.95; 95% CI: 0.88, 1.03; p=0.207; RD -0.004; 95% CI: -0.016, 0.008; p=0.491), and similar results were seen based on the number of adverse event incidences (RR 0.96; 95% CI: 0.83, 1.10; p=0.544; RD 0.008; 95% CI: -0.004, 0.020; p=0.213).

To explore the nature of encountered adverse events, we differentiated gastrointestinal complaints, infections and infestations, and other adverse events. There was no indication of a statistically significantly increased risk of gastrointestinal complaints (RR 1.10; 95% CI: 0.88, 1.39; p=0.401; RD 0.013; 95% CI: -0.003, 0.029; p=0.117) or infections and infestations (RR 0.86; 95% CI: 0.68, 1.08; p=0.198; RD 0.002; 95% CI: -0.005, 0.009; p=0.198). There was a trend for more other adverse events compared to control (RR 1.30; 95% CI: 0.96, 1.75; p=0.094; RD 0.002; 95% CI: -0.003, 0.007; p=0.476). However, this trend was not statistically significant across studies.

Medium health status. For 17 case studies, the preceding health status of the presented patients was categorized as medium on a scale ranging from generally healthy to critically ill, the described patients varied, or the health status before the probiotic associated adverse event was not reported.

To investigate whether the participants with medium health status studied in the included trials were more likely to experience adverse events compared to control group participants not using probiotics we undertook a subgroup analysis for all parallel RCTs studying this health status group. There was no indication that participants with medium health status were statistically significantly more likely to suffer from adverse events than control group participants, based on the number of participants with adverse events (RR 1.03; 95% CI: 0.94, 1.13; p=0.491; RD -0.001; 95% CI: -0.005, 0.003; p=0.475), and similar results were seen based on the number of adverse event incidences (RR 1.04; 95% CI: 0.95, 1.13; p=0.379; RD 0.002; 95% CI: -0.004, 0.008; p=0.560).

To explore the nature of encountered adverse events, we differentiated gastrointestinal complaints, infections and infestations, and other adverse events. There was no indication of a statistically significantly increased risk of gastrointestinal complaints (RR 1.00; 95% CI: 0.83, 1.22; p=0.975; RD 0.004; 95% CI: -0.003, 0.011; p=0.263.), infections and infestations (RR 1.09; 95% CI: 0.90, 1.32; p=0.384; RD -0.001; 95% CI: -0.005, 0.004; p=0.802), or other adverse events (RR 1.01; 95% CI: 0.88, 1.16; p=0.856; RD 0.000; 95% CI: -0.005, 0.005; p=0.925).

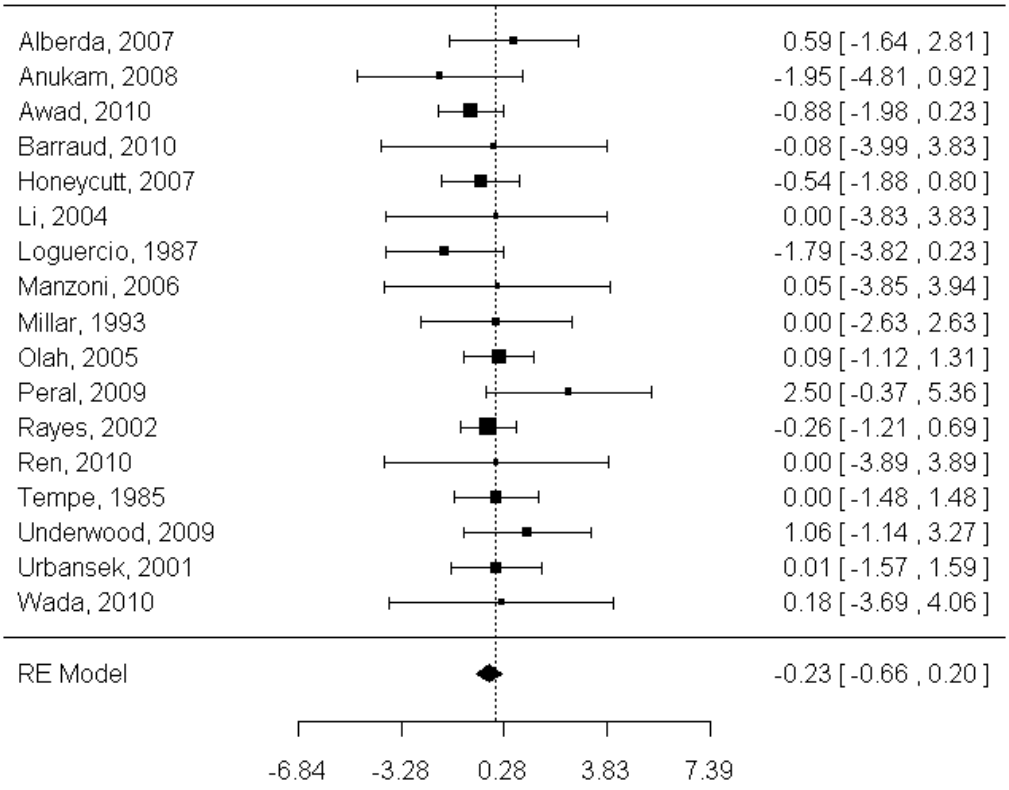
Critically ill. Twenty-five case studies reporting on 42 cases (Barton, 2001; Cesaro, 2000; De Groote, 2005; Force, 1995; Hennequin, 2000; Henry, 2004; Kniehl, 2003; Ku, 2006; Kunz, 2004; Land, 2005; Ledoux, 2006; Lestin, 2003; Lherm, 2002; Lolis, 2008; Oggioni, 1998; Ohishi, 2010; Perapoch, 2000; Piechno, 2007; Richard, 1988; Rijnders, 2000; Riquelme, 2003; Trautmann, 2008; Viggiano, 1995; Zein, 2008; Zunic, 1991) explicitly described a high-risk patient, an individual who was critically ill before consuming probiotic organisms and experienced any subsequent associated harms. Described cases were patients who were already hospitalized for other conditions, who suffered from multiple health concerns, or who had to be considered high risk due to a serious health condition.

Adverse events are more likely and potentially more harmful in critically ill and high-risk patients. To investigate whether any of the observed adverse events could be linked to probiotic

intake, we undertook a stratified analysis for all parallel RCTs studying critically ill or high-risk patients, such as patients currently being treated in an intensive care unit or babies with very low birth weight. This analysis can show whether participants using probiotics were more likely to experience adverse events compared to a control group with similar health status and similar co-interventions and risk factors apart from the probiotics intake.

Almost all interventions in critically ill patients included *Lactobacillus* strains. Some studies used *Bifidobacterium* strains alone or in combination with *Lactobacillus*. Across studies, there was no indication that critically ill and high risk participants taking probiotics were more likely to experience adverse events than control participants with the same health status (RR 0.79; 95% CI: 0.51, 1.22; p=0.286) when comparing the number of participants with adverse events per treatment arm. The forest plot in Figure 25 shows results obtained in individual studies.

Figure 25. RR number of critically ill or high-risk participants with adverse events



Results differed in individual studies, sometimes favoring the probiotics, sometimes the control group. The observed risk difference across treatment and control group participants was -0.001 (95% CI: -0.020, 0.019; p=0.955). Using the alternative measure, the number of incidences per treatment arm, the relative risk for treatment group participants was 0.91 (95% CI: 0.76, 1.09; p=0.297). The risk difference between treatment and control group participants was too small to be detected (RD 0.000; 95% CI: -0.005, 0.004; p=0.62).

To explore the nature of adverse events encountered in studies of critically ill or high risk participants, we differentiated gastrointestinal symptoms, infections and infestations, and other adverse events. No statistically significant differences between control and intervention

participants could be observed for gastrointestinal adverse events (RR 0.91; 95% CI: 0.56, 1.50; p=0.718; RD 0.000; 95% CI: -0.008, 0.008; p=0.956), for infections and infestations (RR 1.15; 95% CI: 0.70, 1.88; p=0.576; RD 0.000; 95% CI: -0.003, 0.003; p=0.997), or other adverse events (RR 0.88; 95% CI: 0.72, 1.08; p=0.214; RD -0.001; 95% CI: -0.007, 0.006; p=0.787).

We explored in a sensitivity analysis whether the difference in adverse events is still non-significant when the deaths reported in the PROPATRIA trial (Besselink, 2008) are added. In our categorization system, the patients and their baseline disease were not seen as critically ill, but the patients were predicted to have a severe disease course; hence, it is possible to classify them as critically ill/high risk. The sensitivity analysis showed similar results, also not indicating a statistically significantly increased risk of adverse events (RR 0.98; 95% CI: 0.83, 1.17; p=0.871; RD 0.000; 95% CI: -0.004, 0.005; p=0.856).

Metaregression. Health status: To investigate whether the reported adverse events differed across the three types of studies, we undertook a metaregression. There was no indication that adverse events differed statistically significantly depending on the health status of the participants, based on the number of participants with adverse events (p=0.329) as well as the number of adverse event incidences (p=0.352) observed in treatment and control groups.

(4e) Do randomized controlled studies that report harm show efficacy or no efficacy?

In total, 59 percent of included studies that monitored the presence or absence of harms described the intervention as effective; 23 percent described the intervention as not effective, and for the remaining studies, it was not clearly stated or the authors reported mixed results. We used the abstract of the publication as the author's summary statement. The efficacy of the included interventions was not the target of the review; hence, we did not extract data that would allow an independent analysis of the efficacy or effectiveness of the intervention. Whether interventions were considered effective by the authors is indicated for each study in the Evidence Table C4, Results.

To investigate whether reported adverse events are associated with the efficacy of the intervention, we differentiated studies where the intervention was described as effective and studies where it was described as not effective and added this variable as a moderator to a meta-analysis. Unclear publications were excluded from this analysis. There was no statistically significant indication that adverse event results differed across studies based on the efficacy of the intervention using the number of participants with adverse events (relative risk ratio 0.99; 95% CI: 0.88, 1.12; p=0.909) or the number of adverse event incidences (relative risk ratio 0.93; 95% CI: 0.80, 1.08; p=0.352).

Summary and Strength of Evidence Key Question 4

How do the harms of *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and *Bacillus* vary based on (a) dose (cfu); (b) timing; (c) mode of administration (e.g., catheter); (d) age (all ages, including infants), gender, ethnicity, disease or immunologic status of the patient; (e) relationship to efficacy?

Volume: Varied across questions

Risk of bias: Medium

The evidence to answer this Key Question stem from a variety of study designs and quality.

Consistency: Inconsistent

The high level of evidence studies show different results from case studies.

Directness: Indirect

Few direct comparisons; the majority of comparisons are indirect across different studies.

Precision: Imprecise

The majority of included studies use moderate sample sizes, but studies were pooled in a meta-analysis.

The identified evidence is insufficient or has to be characterized as low with regard to being able to answer the Key Question with confidence.

Only a few studies in the literature explore the effect of intervention and participant characteristics on safety.

Very few studies explored the effect of different treatment doses on the experienced adverse events. Definitions of high and low dose varied across the small number of studies that attempted to conduct dose comparisons. This issue, together with other confounders, hindered systematic evaluation of a dose-response relationship.

Very few published studies were identified that investigated the effects of long-term use of probiotics; information on the safety of long-term consumption is lacking.

There were few descriptions of the time of onset of harms and the further clinical course of adverse events. In the few studies that reported on the time of onset of gastrointestinal effects, most effects were observed in the first three days of treatment. The onset of infections tended to occur one or several weeks later, however this information is primarily based on case studies. The described bacteremia cases cleared within 8 days; several fungemia cases took up to 3 weeks to clear.

The route of administration is as much an intervention as it is a patient characteristic, and direct comparisons across routes of administrations are unlikely. In indirect comparisons, we found no evidence that the form of administration (oral, enteral, or other) of probiotic organisms pointed to an increased risk of participants in the probiotics group to experience an adverse event relative to a comparable control group from the same participant population.

Stratified analyses and metaregressions showed no increased risk for adverse events for children, adults, or elderly participants who took probiotics compared to adverse events observed in equivalent control groups; however it has to be noted that only very few studies were identified that reported on elderly participants.

The identified case studies described more male than female patients. In indirect comparisons across RCTs, we found no indication that encountered adverse events relative to control group incidences depend on the sex of the participants.

The included studies did not provide enough information to investigate whether safety results are associated with ethnic characteristics.

With regard to the health status of participants, there was some indication that health status is associated with the experience of an adverse event when using probiotics. Case studies reporting serious adverse events described health-compromised patients, not generally healthy participants, contracting (most commonly) a serious infection potentially caused by probiotic organisms. However, a subgroup analysis of RCTs in critically ill patients did not show a statistically

significantly increased risk of experiencing adverse events for participants using probiotics compared to control group participants with similar patient characteristics.

There was no indication that the efficacy of the intervention was associated with encountered adverse events across all included parallel RCTs.

Key Question 5. How often does harm associated with *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and *Bacillus* lead to hospital admission or lengthened hospitalization?

The following describes the evidence related to hospitalizations as well as serious adverse events.

Hospitalizations

None of the case series, controlled trials, crossover RCTs, or parallel RCTs indicated that the use of a product including *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, or *Bacillus* led to a hospital admission. Evidence for hospital admissions due to probiotics use came only from case studies. However, we also recorded all hospitalizations in included studies, regardless of perceived associations with the study products in question.

Lactobacillus intervention. Conen (2009) described a patient with ulcerative colitis who was hospitalized with a neck abscess that the authors associated with the intake of a product containing *Lactobacillus rhamnosus* (DNA-based identification). LeDoux (2006) described a patient with AIDS and Hodgkin's disease who presented to the emergency department with fever, intermittent chills, and left neck pain with swelling; the diagnosis of bacteremia due to *Lactobacillus acidophilus* was associated with the intake of a probiotic medication. Mackay et al. (1999) reported on a patient with *Lactobacillus rhamnosus*-associated endocarditis who was admitted to the hospital; the patient was taking a probiotic preparation that included *Lactobacillus rhamnosus, Lactobacillus acidophilus,* and *Streptococcus faecalis*. Munakata (2010) described a child with short bowel syndrome admitted to a hospital for evaluation of ataxia; the authors associated the diagnosis of D-lactic acidosis with a probiotic product containing *Lactobacillus acidophilus, Lactobacillus bulgaricus, Streptococcus faecalis,* and *Streptococcus faecium*. Oh (1979) described a patient brought to the emergency room because of sudden disorientation, blurred vision, nausea, and vomiting. D-lactic acidosis was associated with *Lactobacillus acidophilus* intake. Rautio (1999) described a diabetic patient who was admitted to a hospital because of a 2-week history of mild abdominal discomfort and then fever. The diagnosis of liver abscess was associated with a dairy drink containing *Lactobacillus rhamnosus* GG (DNA-based identification). Tommasi (2008) described a patient admitted to a hospital for persistent fever and night sweating who was later diagnosed with bacteremia, associated with consumption of *Lactobacillus casei*- containing products. The case report by Zein (2008) described a hospital admission due to fever, headaches, nausea, and vomiting. The publication linked the *Lactobacillus rhamnosus*-associated septicemia to a probiotic product containing *Lactobacillus rhamnosus, Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Bifidobacterium longum,* and *Streptococcus thermophilus*.

Bifidobacterium intervention. No study was identified that reported a new hospitalization other than the potentially *Lactobacillus*-associated case reported by Zein (2008), which involved use of a probiotics blend that included *Bifidobacterium* organisms.

Saccharomyces intervention. Hwang (2009) reported on an infant who was treated for presumed bacterial colitis and in addition was taking a *Saccharomyces boulardii* [*cerevisiae*] product and who presented to the emergency department with repetitive vomiting and cyanosis, requiring intravenous fluid resuscitation. The condition was assumed to be food protein-induced enterocolitis syndrome caused by the probiotic intervention, according to the authors. Jensen (1974) reported on a patient admitted to a hospital with fever, diaphoresis, and nausea, which the authors associated with the patient's use of a *Saccharomyces cerevisiae* product.

Streptococcus intervention. No study was identified that reported a new hospitalization other than the potentially *Lactobacillus*-associated case studies described above that used blends.

Enterococcus intervention. No study was identified that reported a new hospitalization other than the potentially *Lactobacillus*-associated case studies described above that used blends.

Bacillus intervention. Oggioni et al. (1998) reported on an immunocompromised patient admitted to a hospital with high fever who subsequently developed septicemia that was associated with previous treatment with *Bacillus subtilis* (DNA-based identification).

All other case reports were in patients who were already hospitalized, or an in-hospital treatment was not reported.

All hospitalizations. Given that the specific diagnostic reason for hospitalization may be difficult to determine and hospitalizations may not have been associated with probiotic product use at all by other study investigators, we recorded all hospitalizations mentioned in included studies during or after receiving the study intervention. The outcome, hospitalization, was not an inclusion criterion per se for this review. Only hospitalizations recorded in publications addressing adverse events were considered, and studies using the number of hospitalizations as an efficacy or effectiveness measure were not sought. Only new hospitalizations were considered for this question; participants already hospitalized when a probiotic intervention was initiated were not counted. As shown in the Evidence Table C4, Results, a number of studies reported SAEs of which several must have led to hospitalizations. However, the studies did not report this outcome explicitly, and in order to provide a systematic evidence overview, only the exact reported outcome was considered for all treatment groups.

A case series described by Huynh (2009) reported that one child with acute ulcerative colitis taking a product containing various *Lactobacillus, Bifidobacterium* and *Streptococcus* strains was hospitalized for vomiting and diarrhea, diagnosed as viral gastroenteritis. No virus or bacterial pathogens were isolated from the stool.

In 12 parallel RCTs that reported the number of new hospitalizations, the relative risk was 1.14 (95% CI: 0.79, 1.65; p=0.470; 11 RCTs), and the risk difference was 0.007 (95% CI: -0.006, 0.020; p=0.276) indicating that the probiotics intervention was not associated with a statistically significantly higher risk of hospitalization across all parallel RCTs. Study authors did not report that the intervention caused the hospitalizations in the included trials, but Gibson (2008) reported 18/72 serious adverse events that required hospitalizations in the treatment group

compared to 11/70 in the control group. The authors reported further that three events in total were judged to be possibly related to the formula intervention (one gastrointestinal problem in each group and one respiratory problem in the control group).

None of the identified studies indicated that the evaluated intervention led to a lengthened hospitalization. Only five studies (Kerac, 2009; Mackay, 1999; Munakata, 2010; Oggioni, 1998; Tommasi, 2008) included in the review reported the number of newly hospitalized patients and the length of hospitalization (this number excludes in-hospital samples, and studies that used the length of hospitalization as an efficacy or effectiveness measure were also not sought). In the included controlled studies, Kerac (2009) reported 27/399 readmissions to hospital in a group of malnourished Malawian children receiving synbiotics compared to 16/396 children in the control group. The other data on the length of hospitalization stem from case studies. The participant described by Oggioni (1998) remained in the hospital 25 days; in the case described by Mackay (1999), 14 days; the child with D-lactic acidosis described by Munakata (2010) was hospitalized for 25 days; and the case described by Tommasi (2008) appears to have spent a total of about 90 days in the hospital but not necessarily without interruption when symptoms were under control.

Serious Adverse Events

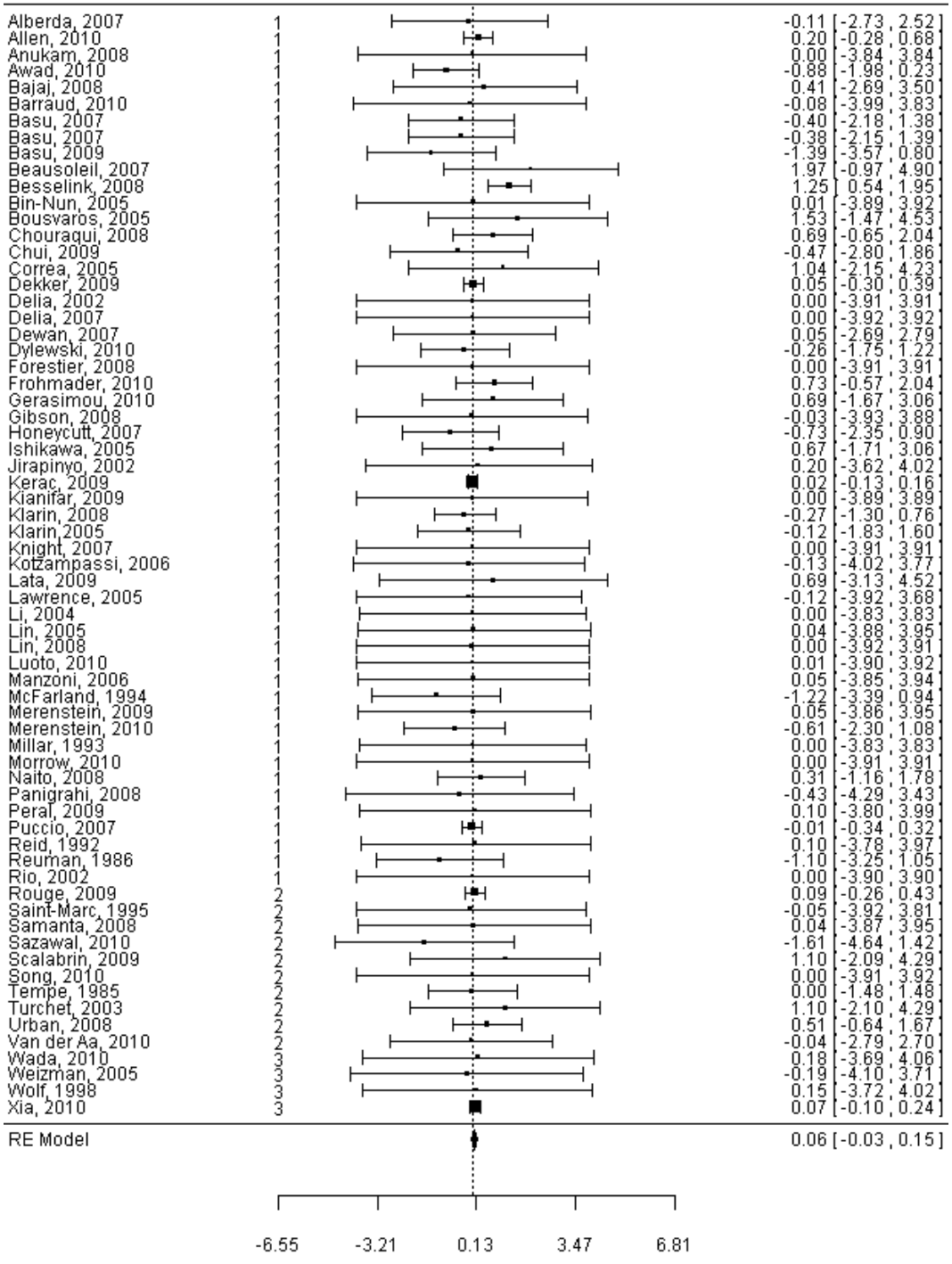
We also investigated the quality of the adverse events, apart from exploring the quantity (Key Question 1) and the nature of the adverse events (Key Question 2). For all recorded adverse events reported in the individual studies, we assessed whether the experienced harm was a serious adverse event such as a hospitalization or recorded incidences of death. For a conservative analysis, we also included any sign of probiotics bacteria in blood samples as a serious adverse event.

Several included studies reported on the presence or absence of serious adverse events, in particular the case studies. The results of case studies have been summarized in Key Question 1c. However, some controlled studies also reported on the presence or absence of serious adverse events and these studies allow a comparison of the risk experienced in a probiotic group compared to that of participants not using probiotics but from a similar population and with comparable underlying diseases, cointerventions, and other factors that may contribute to serious adverse events. Some of the included studies enrolled critically ill patients; the occurrence of serious adverse events and health concerns regardless of any association with probiotics is more likely in this clinical population than in other participant groups.

In total, 67 parallel RCTs reported on the presence or the absence of at least one serious adverse event, recorded the number of serious adverse event incidences in the treatment and the control group arms, and also reported the total number of participants in each treatment arm. Only the main treatment group was compared with the control group most similar to the treatment group minus the probiotics.

The relative risk of a serious adverse event was 1.06 (95% CI: 0.97, 1.16; p=0.201), indicating that probiotics interventions were not associated with a statistically significantly higher risk of serious adverse events. The forest plot for the relative risk is shown in Figure 26. The graph is ordered by the included probiotic genera, starting with *Lactobacillus*, used alone or in combination with other genera, followed by *Bifidobacterium* (#2) interventions that did not include a *Lactobacillus* strain, and finally *Saccharomyces* (#3) interventions without *Lactobacillus* or *Bifidobacterium* strains In total, 39 percent of studies investigated blends, and most often the blend included a *Lactobacillus* strain. The lack of *Streptococcus*, *Enterococcus,* and *Bacillus* interventions is highlighted in the following text.

Figure 26. RR number of participants with serious adverse events



Results in most included trials were accompanied by wide confidence intervals, and the obtained relative risks within the individual RCTs varied greatly, sometimes favoring the probiotics group, sometimes the control group. A large effect indicating problems with probiotics was seen only in the PROPATRIA trial (Besselink, 2008), a failed effectiveness study in patients with acute pancreatitis. The pooled risk difference for a serious adverse event was not detectable (RD 0.000; 95% CI: -0.003, 0.003; p=0.866) across the treatment groups. The risk of a serious

adverse event was low in both groups, and the difference between the probiotic and control groups was not detectable. The Evidence Table C4, Results shows all serious adverse events reported in all included studies.

Lactobacillus intervention. As documented in the Key Question 1 section, the serious adverse events associated with a *Lactobacillus* intervention where administered species or strains were matched with genetic fingerprinting approaches included two cases of an abscess, two cases of bacteremia, and one case of sepsis.

To quantify the risk of serious adverse events associated with *Lactobacillus* strains, we stratified parallel RCTs by genus. Interventions exclusively using *Lactobacillus* strains indicated no increased risk of serious adverse events compared to controls (RR 1.03; 95% CI: 0.93, 1.14; p=0.614; RD 0.000; 95% CI: -0.006, 0.006; p=0.981). In order to explore further whether the genus of the organism could be associated with reported serious adverse events, we undertook a metaregression adding the genus as a moderator to a meta-analysis of serious adverse events. This analysis compared studies that used *Lactobacillus* strains, alone or in combinations with other microorganisms, with interventions that did not. The relative risk ratio across studies did not indicate that the *Lactobacillus* genus was associated with a statistically significantly different risk of serious adverse events compared to other genera (relative risk ratio 1.07; 95% CI: 0.78, 1.46; p=0.423).

Bifidobacterium intervention. As documented in the Key Question 1 section, the serious adverse events associated with a *Bifidobacterium* interventions where administered species or strains were matched with genetic fingerprinting approaches included one documented case of septicemia. No stratified analysis of parallel RCTs to quantify the risk of serious adverse events could be undertaken, as no study was identified that used exclusively *Bifidobacterium* strains and reported on the presence or the absence of a serious adverse event. A metaregression adding the presence of the genus *Bifidobacterium* in the intervention as a moderator to a meta-analysis of serious adverse events did not indicate that the *Bifidobacterium* genus was associated with a statistically significantly increased risk of serious adverse events (relative risk ratio 1.18; 95% CI: 0.96, 1.47; p=0.814).

Saccharomyces intervention. As documented in the Key Question 1 section, the serious adverse events associated with a *Saccharomyces* interventions where administered species were matched with genetic fingerprinting approaches included 20 cases of fungemia. No stratified analysis could be undertaken for parallel RCTs to quantify the risk, as no study was identified that used exclusively *Saccharomyces* strains and reported on the presence or the absence of a serious adverse event. A metaregression adding the presence of the genus *Saccharomyces* in the intervention as a moderator to a meta-analysis of serious adverse events did not indicate that the *Saccharomyces* genus was associated with a statistically significantly increased risk of serious adverse events (relative risk ratio 0.68; 95% CI: 0.22, 2.07; p=0.494).

Streptococcus intervention. No *Streptococcus* intervention where administered species were matched with genetic fingerprinting approaches was identified, and a stratified analysis for parallel RCTs also could not be undertaken, as no study was identified that used exclusively *Streptococcus* strains and reported on the presence or the absence of a serious adverse event. A metaregression adding the presence of the genus *Streptococcus* in the intervention as a moderator

to a meta-analysis of serious adverse events did not indicate that the *Streptococcus* genus was associated with a statistically significantly increased risk of serious adverse events (relative risk ratio 1.17; 95% CI: 0.54, 2.54; p=0.695).

Enterococcus intervention. No *Enterococcus* intervention where administered species were matched with genetic fingerprinting approaches was identified and a stratified analysis for parallel RCTs could also not be undertaken, as no study was identified that used exclusively *Enterococcus* strains and reported on the presence or the absence of a serious adverse event. A metaregression adding the presence of the genus *Enterococcus* in the intervention as a moderator to a meta-analysis of serious adverse events did not indicate that the *Enterococcus* genus was associated with a statistically significantly increased risk of serious adverse events (relative risk ratio 0.59; 95% CI: 0.06, 6.05; p=0.656).

Bacillus intervention. As documented in the Key Question 1 section, the serious adverse events associated with a *Bacillus* intervention where administered species were matched with genetic fingerprinting approaches included 1 case of sepsis. No stratified analysis and metaregression could be undertaken for parallel RCTs to quantify the risk of serious adverse events due to the lack of *Bacillus* studies reporting on serious adverse events.

We also explored pertinent subgroups that were identified in the review with regard to serious adverse events. The quality of adverse events can be very different, ranging from mild complaints to critical events, and analyses in prior chapters have shown that some investigated participants and some intervention characteristics warrant more exploration.

Serious adverse events by health status. We also explored whether critically ill participants taking probiotics were more likely to experience serious adverse events compared to control group participants. In these patients, serious adverse events are of critical importance. There was no indication that critically ill patients were more likely to experience serious adverse events when we stratified results for this subgroup. The relative risk in studies with participants of this health status to experience a serious adverse event was 1.01 (95% CI: 0.89, 1.14; p=0.898; RD 0.002; 95% CI: -0.004, 0.004; p=0.973) relative to control group participants with similar clinical symptomatology. In addition, we added health status as a variable to a meta-analysis in order to see if health status moderates reported serious adverse events seen in participants relative to control group participants, but there was also no empirical evidence for an increased or reduced risk of serious adverse events that depended on the participants' health status (p=0.481).

Serious adverse events by participant age. Children in probiotics groups were not more likely to experience serious adverse events than control group participants (RR 1.02; 95% CI: 0.92, 1.14, p=0.685; RD 0.002; 95% CI: -0.006, 0.003, p=0.458). The few published studies in the elderly did not report on the presence or absence of serious adverse events. Comparing the relative risk ratio of children and adults for serious adverse events, there was a significant difference (p=0.019) indicating that adults in probiotics groups were more likely to experience serious adverse events; however this result was driven entirely by the PROPATRIA trial (Besselink, 2008) in acute pancreatitis, which reported statistically significantly more incidences of death in the probiotics group compared to control. Excluding this study, there was no evidence of serious adverse event results being moderated by participants' ages (p=0.728).

Serious adverse events by delivery vehicle. Stratified analyses indicated that yogurt and dairy delivery vehicles may influence the ratio of risks for adverse events seen in intervention and control groups. There was no evidence that intervention participants in yogurt and dairy studies were statistically more likely to experience adverse events compared to control group participants (RR 1.16; 95% CI: 0.38, 3.56, p=0.793); RD 0.001; 95% CI: -0.009, 0.012, p=0.219). In addition, we added delivery vehicles as a variable to a meta-analysis in order to see if this factor moderated reported serious adverse events seen in participants relative to control group participants, but there was also no empirical evidence for an increased or reduced risk of serious adverse events depending on the vehicle the probiotic organisms were delivered in (p=0.998).

Serious adverse events by route of administration. There was a trend but no evidence for a statistically significantly different risk for patients receiving probiotics through enteral feeding tubes to experience a serious adverse event compared to control group participants (RR 1.21; 95% CI: 0.92, 1.58, p=0.168; RD 0.002; 95% CI: -0.008, 0.011, p=0.694), based on the existing literature. We also added routes of administration as a variable to a meta-analysis in order to see if these factors moderated the serious adverse events seen in participants relative to control group participants, but there was no evidence for an increased or reduced risk of serious adverse events that depended on the route of administration (p=0.714).

Summary and Strength of Evidence Key Question 5

How often does harm associated with *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus* lead to hospital admission or lengthened hospitalization?

Volume: 26 studies for hospitalization, 66 controlled trials for serious adverse events

Risk of bias: Medium

Evidence to answer this Key Question stems from RCTs and case studies, but the RCTs may not have reported on the outcome of hospitalization consistently

Consistency: Inconsistent

Directness: Direct

Several comparative studies if the Key Question is widened to include serious adverse events

Precision: Precise

The identified evidence has to be characterized as medium to low with regard to being able to answer the Key Question with confidence.

While several case studies reported a new hospitalization associated with the consumption of a product, including *Saccharomyces, Lactobacillus,* or *Bacillus* strains, none of the case series, CCTs, or parallel and crossover RCTs reported that a probiotics intervention led to a hospitalization in the intervention participants.

A comparison of all reported hospitalizations regardless of the perceived association with the intervention treatment indicated no statistically significantly increased risk in probiotics interventions compared to the number of hospitalizations in control group participants. However,

the number of hospitalizations due to adverse events was explicitly reported on in only a few of the included studies, older publications may not have associated a hospitalization with probiotics intake, and several studies reported on participants who were already hospitalized.

Only a few studies overall reported on the presence or absence of serious adverse events following the FDA definition, as outlined in the method section. Results for serious adverse events varied across RCTs, sometimes favoring the probiotics group and sometimes the control group, and differences across probiotic and control groups were not statistically significant. The same result was obtained for *Lactobacillus* and *Saccharomyces* interventions, but there were too few studies (*Bifidobacterium*) or no studies (*Streptococcus*, *Enterococcus*, *Bacillus*) to analyze serious adverse events as studies did not report on the presence or absence of serious adverse events.

We also investigated pertinent subgroups that were highlighted in previous chapters of the report. There was no evidence to document an increased risk of critically ill patients in probiotics groups experiencing more serious adverse events than critically ill patients in a control group; the health status of participants was not associated with an increased risk of serious adverse events relative to control group participants. Children in intervention groups were not more likely to experience serious adverse events compared to control group children, but a formal systematic analysis of age as a moderator could not be undertaken due to the absence of reporting on the presence or absence of serious adverse events in the few identified studies in the elderly. The ratio of adverse events between intervention and control group participants also was not affected by the delivery vehicle or the route of administration. However, this finding is again based on an indirect comparison across studies; direct evidence is missing.

Key Question 6. How does harm associated with *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus* relate to use of concomitant antibiotics, confounding diet therapies, corticosteroid use, immune suppressants, or other potential confounders?

None of the studies included in this review reported a statistical interaction analysis investigating whether confounders such as concomitant antibiotics, diet therapies, corticosteroid use, use of other immune suppressants, or other variables affects adverse events associated with probiotics. An interaction effect might indicate that participants on probiotics and antibiotics are more likely to experience adverse events, beyond the adverse events that can be expected in a control group of patients with similar characteristics.

A potential interaction effect between probiotics and medications has been explored in the Key Question 2a and indicated a trend but no statistically significant indication that intervention participants in studies with pertinent cointerventions report more adverse events than control group participants with corresponding cotreatments.

Antibiotics

A substantial number of identified studies described concomitant antibiotic use (110/387). In these studies, probiotics were often given to counterbalance adverse events caused by antibiotics, for example, to prevent or treat antibiotic-associated diarrhea. We included only those studies that did report on adverse events associated with probiotics, that is, studies addressing the safety of probiotics in addition to efficacy or effectiveness outcomes. Studies reporting only on the efficacy or effectiveness of probiotics in the prevention or reduction of antibiotics-associated adverse events were outside the scope of this review.

In order to answer the question of whether participants using probiotics and antibiotics simultaneously makes them more at risk to experience adverse events associated with probiotics, we undertook a stratified analysis for all RCTs with concomitant antibiotic treatment. There was a trend but no statistically significant indication that participants in the probiotics group were more likely to experience adverse events compared to control group participants also taking antibiotics, based on the number of participants with adverse events (RR 1.07; 95% CI: 0.94, 1.23; p=0.271; RD 0.001; 95% CI: -0.005, 0.006; p=0.855) as well as according to the number of adverse incidences across groups (RR 1.13; 95% CI: 0.91, 1.41; p=0.272; RD 0.005; 95% CI: -0.004, 0.014; p=0.259).

Exploring the nature of the adverse events further, there was also no indication that participants experience statistically significantly more gastrointestinal adverse events compared to control group participants (RR 1.10; 95% CI: 0.82, 1.48; p=0.530; RD 0.006; 95% CI: -0.004, 0.016; p=0.253), more infections and infestations (RR 1.07; 95% CI: 0.56, 2.06; p=0.835; RD 0.000; 95% CI: -0.003, 0.003; p=0.945), or more other adverse events (RR 1.13; 95% CI: 0.91, 1.41; p=0.270; RD 0.005; 95% CI: -0.005, 0.015; p=0.365).

Participants were also not more likely to experience serious adverse events compared to control group participants also on antibiotic cotreatment (RR 1.04; 95% CI: 0.91, 1.19; p=0.534; RD 0.000; 95% CI: -0.005, 0.005; p=0.972).

Diet Therapies

Seven studies (five parallel and one crossover RCT) were identified that described participants on a particular diet regime (e.g., a diet based on the American Heart Association guidelines) in addition to probiotics intake. The relative risk for the number of participants with adverse events in this subgroup of studies was 1.08 (95% CI: 0.74, 1.58; p=0.683; RD 0.003; 95% CI: -0.043, 0.048; p=0.898), and the relative risk for the number of adverse event incidences in the treatment arms was 0.97 (95% CI: 0.79, 1.18; p=0.724; RD -0.001; 95% CI: -0.020, 0.018; p=0.948).

There was also no indication of differences in gastrointestinal complaints (1.10; 95% CI: 0.82, 1.48; p=0.530; RD 0.006; 95% CI: -0.004, 0.016; p=0.253), infections and infestations (1.09; 95% CI: 0.53, 2.24; p=0.808; RD 0.000; 95% CI: -0.003, 0.003; p=0.945), other adverse events (RR 0.94; 95% CI: 0.75, 1.16; p=0.538; RD 0.004; 95% CI: -0.023, 0.031; p=0.784) or serious adverse events (RR 1.02; 95% CI: 0.89, 1.18; p=0.749; RD 0.010; 95% CI: -0.016, 0.036; p=0.449) compared to control group. However, it should be noted that the stratified analyses were based on between three and seven RCTs only, due to the small number of studies reporting concomitant diet therapies. Most individual trials reported either no adverse events or similar incidences across groups.

Corticosteroid Use

There were 26 studies that reported using corticosteroids in conjunction with an intervention of probiotic organisms. None of these studies reported an interaction analysis or related the adverse events experienced to the use of confounding corticosteroids with probiotics.

In order to answer the question of whether participants using probiotics and corticosteroids simultaneously makes them more at risk to experience adverse events associated with probiotics, we undertook a stratified analysis for all RCTs with concomitant corticosteroid treatment. There was no indication that participants in the probiotics group were more likely to experience adverse events compared to control group participants also taking corticosteroids, based on the number of

participants with adverse events (RR 1.04; 95% CI: 0.88, 1.22; p=0.650; RD 0.002; 95% CI: -0.032, 0.035; p=0.920) as well as according to the number of adverse incidences across groups (RR 1.06; 95% CI: 0.77, 1.46; p=0.719; RD 0.000; 95% CI: -0.021, 0.021; p=0.986).

Exploring the nature of the adverse events further, there was a trend but no statistically significant indication that participants experience statistically significantly more gastrointestinal adverse events compared to control group participants (RR 1.11; 95% CI: 0.73, 1.68; p=0.615; RD 0.000; 95% CI: -0.030, 0.030; p=0.992), more infections and infestations (1.15; 95% CI: 0.79, 4.68; p=0.466; RD 0.008; 95% CI: -0.039, 0.054; p=0.750), or more other adverse events (RR 1.29; 95% CI: 0.83, 2.01; p=0.257; RD 0.007; 95% CI: -0.010, 0.232; p=0.448).

Participants were also not more likely to experience serious adverse events compared to control group participants also on corticosteroid cotreatment (RR 1.01; 95% CI: 0.33, 3.10; p=0.980; RD 0.012; 95% CI: -0.027, 0.051; p=0.545).

Immune Suppressants

Eight studies, including three case studies, were identified that reported on patients using probiotics while taking immune suppressant medications several studies described patients with ulcerative colitis.

Two case reports in patients using immune suppressants to control an underlying condition described fungemia infections (Bassetti, 1998; Zunic, 1991), and one case report reported an abscess potentially associated with *Lactobacillus rhamnosus*.

One of the case series in patients on immune suppressant medications noted a patient with an erythema around the anus (Benchimol, 2004), and two other case series reported several gastrointestinal incidences in patients with ulcerative colitis (Huynh, 2009; Karimi, 2005).

One RCT in patients with atopic dermatitis listed abdominal pain as an adverse event with 2/24 in the treatment group compared to 1/24 in the prebiotics control group (Passeron, 2006). An RCT in transplant patients noted diarrhea, abdominal pain, and abdominal cramps similarly distributed across treatment arms (Rayes, 2005). Tursi (2010) reported 8/65 adverse events such as abdominal bloating with or without discomfort compared to 9/66 patients with adverse events in the control group in an RCT in patients with ulcerative colitis

No other pertinent confounder was identified in this review that clearly warranted further investigation.

Summary and Strength of Evidence Key Question 6

How does harm associated with *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus* relate to use of concomitant antibiotics, confounding diet therapies, corticosteroid use, immune suppressants, or other potential confounders?

Volume: Indirect comparisons are based on 387 studies, no evidence from individual interaction studies

Risk of bias: Medium

Evidence to answer this Key Question stems from RCTs and case studies

Consistency: Inconsistent

Directness: Indirect

Question can be analyzed only through cross-study comparisons or subgroup analyses

Precision: Precise

There is insufficient evidence to answer this Key Question with confidence.

We did not identify studies meeting the review inclusion criteria that reported statistical interactions between concomitant antibiotics, diet therapies, corticosteroid use, or immune suppressants.

Although the risk of adverse events in general might be higher in participants on multiple medications, in subgroup analyses of studies in which the intervention participants as well as the control group participants received antibiotics or corticosteroids, no statistically significantly increased risk of adverse events was identified among intervention participants. Across RCTs, there was no evidence for a statistically significant interaction between these medications and the risk for adverse events being increased in the treatment group relative to the control group.

We identified only a few studies with concomitant diet therapies, and studies in participants using immune suppressants were also largely absent in the existing literature. The few studies identified did not indicate an increased risk of adverse events, but rare events are difficult to assess, and the existing evidence base is not sufficient to draw conclusive conclusions.

Discussion

Results Summary

The review demonstrates that there is a large volume of literature on probiotics. However, the literature provided only limited evidence to address the questions the review set out to answer. The search of 10 databases combined with reference screening of included studies and pertinent reviews identified 11,201 publications, and 622 studies were included in the review. Of these 622 studies, 235 studies made only nonspecific safety statements ("well tolerated"), and the remaining 387 studies reported the presence or absence of one or more specific adverse events.

The review includes a large number of randomized controlled trial (RCTs); however, the majority of these were not designed to monitored adverse events but primarily tested the efficacy of probiotics in managing, treating, or preventing clinical symptoms. The quality of included studies varied within study design categories; only a minority of trials reported adequate randomization methods, concealment of treatment group allocation, and blinding of outcome assessors to the treatment group; and studies were not powered to assess adverse events. Adverse events were poorly documented and publications seldom stated what parameters were monitored. Further, in the majority of included studies, interventions were poorly documented, lacking detail, for example, on the specific probiotic strain that was administered as well as the dose and viability.

Identified case studies indicated that fungemia, bacteremia, and sepsis may be associated with administered probiotic organisms. None of the identified case series, controlled clinical trials (CCTs), parallel and crossover RCTs reported an infections caused by the administered probiotic strains. However, these studies did not monitor routinely for such infections; reported adverse events were primarily gastrointestinal in nature. In parallel RCTs, no statistically increased risk for adverse events in the quantity of adverse events was observed, analyzing the number of participants with adverse events and reported adverse event incidences per treatment group. Exploring the nature of reported events in the literature, we found that adverse events were gastrointestinal in nature, addressed infections and infestations, or addressed other adverse events. In none of the different types of adverse events did parallel RCT show a statistically significantly increased risk for adverse events in intervention participants compared to control. Across studies, there was also no statistically significantly increased risk of serious adverse events associated with probiotic product use. Long-term effects are largely unknown as very few existing studies report on followup periods of one year or more.

Stratifying studies by probiotic genus, it was apparent that the existing literature covers primarily the genus *Lactobacillus*, alone or in combination with other genera, most frequently *Bifidobacterium*. There was some evidence from a metaregression that indicated *Streptococcus* interventions may be associated with a larger number of adverse events compared to other genera, but evidence from direct, head-to-head comparisons is lacking. Stratifying RCTs that used each genus exclusively, no statistically significant difference between intervention and control group participants was observed for any of the six genera. However, published reports on the genera *Enterococcus*, *Bacillus*, *Streptococcus* are largely absent from the literature. *Saccharomyces* interventions and *Bifidobacterium* interventions were also rare, and a substantial proportion of studies used blends of probiotic organisms.

The review aimed to address a large number of participant and intervention variables and their effect on safety. Direct evidence comparing intervention factors is largely absent from the existing literature. Few studies directly compared the safety of different product or participant characteristics. Indirect comparisons indicated that effects of delivery vehicles should be investigated further. Analyzing participant factors such as health status showed that case studies described adverse events in patients with existing health concerns, often already hospitalized when potentially probiotics associated infections occurred. However, RCTs did not indicate a statistically significantly increased risk of adverse events in healthy, medium-risk, or critically ill participant groups compared to control.

Scope and Limitations

This evidence report considers a large number of studies and addresses a large number of research questions. Unlike the majority of existing reviews, this evidence report considers only adverse events reported in studies of probiotics, and does not cover efficacy or effectiveness questions for the management, prevention, or treatment of clinical symptoms or other indications for using probiotic products. For a risk–benefit analysis, both aspects would need to be considered.

A substantial number of reviews summarizing individual studies of effects of probiotics have been published. However, existing reviews focus on selected interventions, selected probiotic genera, selected patient groups, or selected outcomes (Abad, 2009; Alfaleh, 2008; Allen, 2003; Barclay, 2007; Boyle, 2009; Boyle, 2008; Brenner, 2009; Butterworth, 2008; Chande, 2009; Chande, 2008; Chmielewska, 2010; Chou, 2008; Dendukuri, 2005; Deshpande, 2007; Deshpande, 2010; Doherty, 2009; Doron, 2008; Dugoua, 2009; Fuccio, 2009; Gawronska, 2005; Gurusamy, 2008; Holubar, 2010; Hoveyda, 2009; Johnston, 2007; Kahn Ch, 2009; Kale-Pradhan, 2010; Lirussi, 2007; Mallon, 2007; McFarland, 2005; McFarland, 2010; Miller, 2009; Moayyedi, 2008; Osborn, 2007; Petrov, 2009; Pillai, 2008; Rolfe, 2006; Sachdeva, 2009; Szajewska, 2010; Szajewska, 2005; Szajewska, 2001; Szajewska, 2004; Tung, 2009; Vouloumanou, 2009; Wang, 2009; Watkinson, 2007; Whelan, 2010; Wu, 2008; Zigra, 2007). This evidence report has a broader scope, and due to the large number of included studies, allows unique statistical analyses. Adverse events reported in intervention studies of probiotic organisms are largely rare events encountered by only a small number of participants. Thus, large sample sizes are necessary to be able to detect any statistically significant incidence rates of such adverse events.

Search

This review aimed to capture the safety of probiotics, in particular the safety of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* used as probiotic agents. The search strategy was primarily designed to capture all explicitly identified probiotic studies, and steps were taken to ensure the completeness of the body of evidence of probiotic literature. We identified a large number of publications on probiotics and carefully screened full paper copies of all publications that might contain information on the safety of probiotics. Other studies that investigated the same genera in ways that resembled their use as probiotic agents but did not label their interventions as probiotic studies were not excluded but were also not sought systematically as outlined in the search strategy justification, and no claim

of completeness is made. These studies were primarily identified through reference mining, that is, scanning the bibliographies of included studies and pertinent review articles. This review was not restricted to particular species, strains, patient group, clinical fields, settings, or study design, and the sought interventions included genera such as *Bacillus* with known pathogenic properties, hence the decision to restrict the search to probiotic studies rather than expanding it to the wider literature on the individual bacteria and yeast strains. Judging from our experience, future reviews targeted towards more specific research questions should use a combination of search terms covering both the term "probiotic" and the genus to identify those studies that used a particular strain as a probiotic agent.

This review adopted a thorough process of identifying information on the safety of probiotics by screening full paper copies of empirical studies on probiotics, regardless of whether the safety of probiotics was mentioned in the summary of the article, that is, the title or abstract of the publication. Initial experiments with search filters have shown that screening studies at the title or abstract level would have resulted in missing a large proportion of the pertinent literature. The majority of included studies were not tagged by databases as including safety information, the title and the abstract gave no indication that adverse events would be addressed in the publication, and in the overwhelming majority of studies other than case reports, safety was not the main aim of the publication.

The review focuses on published literature, and a substantial number of studies of probiotics have been published in scientific journals. However, there may also be a substantial number of unpublished studies, most likely from manufacturers of probiotics. This factor, combined with the fact that we could not be certain studies that failed to mention adverse events indeed had no adverse events, limits the utility of the review as a basis for true risk–benefit analysis of probiotics.

Probiotics

This exploratory review on the safety of probiotics lists the reported presence and absence of adverse events for interventions that used *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* organisms as probiotic agents. The imbalance of genera in the included studies (favoring *Lactobacillus* alone and in combination with *Bifidobacterium*) presumably reflects the research conducted to date.

We adopted a very inclusive definition of probiotics. However, there is an ongoing debate about whether yogurt should be considered a probiotic product, since yogurt contains live bacteria (e.g., Guarner, Perdigon, Corthier, et al., 2005) of genera that are associated with probiotic properties, and the debate also extends to whether there is any reason to think adverse events need to be monitored for yogurt and lactic acid bacteria products (e.g., MacGregor, Smith, Thakker and Kinsella, 2002). For this review, yogurt studies that did not explicitly report the addition of a probiotic agent, that is, a strain in addition to the yogurt starter culture, were excluded.

A distinct limitation of this review is that most of the identified studies provided insufficient information on the intervention, that is, a clear description of the microbes that were included in the investigated probiotic product. The lack of identification or proper classification of the administered probiotic organisms is a safety concern in itself. A large number of published studies did not report the strain of the probiotic agent included in the preparation. Given that the efficacy of probiotics is often considered strain specific, the informational value of these studies

has to be questioned. Lack of documentation is hindering efficacy as well as safety evaluations (EFSA, 2009; Shane, 2010) and limits overviews necessary for consumers and policymakers.

A further limitation is the uncertain reliability of the reported product details. For this literature review, we rely on the information reported by the study authors. Very few studies reported using accepted methods (or any methods) to test the content of preparations given to participants. The exact organisms as well as any contaminants present in the preparations are pertinent information. For example, included studies indicated that the species used was *Lactobacillus sporogenes* however; the species designation *Lactobacillus sporogenes* is now considered an invalid name for *Bacillus coagulans* (Becker, 1950; De Clerck, 2004; Jung, 2009). Similarly, some studies reported on *Streptococcus faecium* and *Streptococcus faecalis*, which have been transferred to the genus *Enterococcus* (Schleifer, 1984). A study published in 2006 conducted a survey of commercial probiotic strains and found that 28 percent of the strains intended for use in humans as probiotics were misidentified at the genus or species level (Huys, 2006). Other reports show that products can contain more species than noted on the product labels (Marcobal, 2008; Underwood, 2009).

Also, over the time span covered by our literature search, many of the employed organisms may have undergone mutations (spontaneous or otherwise), identification techniques have improved (e.g., revealing them to be less similar to a more familiar strain or to belong to a different genus than previously thought), and taxonomic name changes were introduced (see, e.g., Masco, 2004; Mattarelli, 2008; No Author, 2008; Li, 2006; Posteraro, 2005; Morita, 2009).

Finally, we identified a large number of studies that gave a blend of different probiotic organisms to participants. These studies individually do not permit to attribute reported harms to a particular genus, species, or strain. Metaregressions can to some extent trace effects across studies, but this process cannot replace adequate study designs to investigate the safety of probiotic strains.

Intervention Studies

This report was explicitly limited to assessing the outcomes of interventions (as opposed to merely passive or accidental exposure). We identified a large number of intervention studies in the international literature assessing the effects of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus* used as probiotic agents. A number of publications exists that systematically collated example cases of fungemia associated with *Saccharomyces cerevisiae* (e.g., Munoz, 2005), or infections associated with *Lactobacillus* (e.g., Aguirre, 1993; Husni, 1997), or *Bifidobacterium* (e.g., Bourne, 1978). However, we considered only those case descriptions that reported a preceding intervention, that is, the purposeful use of probiotics. This limitation also pertains to reports from hospitals describing outbreaks of fungemia such as reports on an intensive care unit (ICU) where patients did not purposefully consume probiotics, but the yeast was reported to linger in the ICU (Cassone, 2003). One of the included case studies (Perapoch, 2000) also reported on an infant who appeared to have contracted an infection from an infant treated with *Saccharomyces cerevisiae* who later developed fungemia; hence, spread of infections should also be monitored in research studies.

The review considered studies without study design restrictions and it includes a large number of different study designs such as parallel and crossover RCTs, CCTs, case series, and case studies. However, the literature search did not identify any observational cohort studies comparing two cohorts or retrospective case-control studies on the safety (or even the efficacy)

of organisms used for their probiotic properties; all observational data came from case series following only one intervention group and case studies. The reason for this lack of large-scale observational studies of probiotic safety is unclear but may be the result of a general presumption of probiotic safety on the part of epidemiologists (and the failure to implicate them as the cause of any particular conditions). A 2002 epidemiological study addressing a similar question assessed changes in the incidence of *Lactobacillus*-associated bacteremia in Finland after a rapid increase in the use of *Lactobacillus rhamnosus* GG as a probiotic agent. The study found no increase in the incidence of *Lactobacillus*-associated bacteremia in the population, although a small proportion of isolates matched the strain of the probiotic agent, using the typing technology available at that time (Salminen, 2002).

Safety

The review identified a large number of relevant publications addressing the safety of probiotic products. For RCTs, we identified a similar volume of publications that addressed the potential efficacy of probiotic preparations but not their safety. It is not possible to extrapolate from the lack of mention of adverse events that no adverse events occurred in interventions (e.g., the adverse events associated with a particular trial might be reported in an accompanying or subsequent, not-yet-published, article). Even fewer RCTs reported on the presence and the absence of specific adverse events.

The review identified a large number of publications that made vague safety statements such as “the intervention was well tolerated” and “there were no adverse events.” We compiled these vague references to safety to allow a complete overview of the existing literature, but these studies were analyzed separately from studies with more specific statements. This group of studies reported no information on what was monitored or how “well tolerated” was defined. For an evidence report such as this whose purpose is to synthesize the evidence, these studies are of little informational value.

When publications reported that there were no adverse events, we did not make inferences from this statement to specific outcomes. Although it may appear plausible to assume that this means no death or hospitalizations occurred, this assumption is very problematic and should not replace actual empirical evidence on the safety of probiotics. The safety of probiotics has only recently been considered as an issue warranting further investigation (Liong, 2008). Older publications may not have thought to associate such harms with an intervention considered completely harmless. In order to advance the empirical evidence on the safety of probiotics, studies should monitor and report the presence and also the absence of specific harms.

For this review we extracted all reported adverse events, regardless of whether the authors of the publication considered these in their summary statement regarding the safety of probiotics. We also included outcomes regardless of the author’s assurance that the event was unrelated to the intervention. Such judgments are difficult to make and may change with increasing knowledge of the safety of probiotics. Very few publications appear to have addressed the assessment of the strength of association between adverse event and intervention systematically, as reported for example in Gibson (2009).

Safety reviews on probiotics have focused on various aspects of safety such as toxicity, the potential for translocation, and antibiotic resistance or other virulence factors (Ishibashi, 2001; Sanders, 2010; Yazdankhah, 2009). This report operationalized safety as the presence or absence of unintended adverse health events in probiotics interventions for human participants. We

document the quantity, quality, and nature of adverse events reported in research studies using probiotics to reduce risk of and prevent or treat disease in vivo.

Efficacy studies for which the efficacy outcome was the mitigation of an adverse event (e.g., efficacy of probiotics in preventing or treating antibiotic-induced diarrhea or other negative health outcomes) were excluded unless (1) the outcome was actually exacerbated in the probiotic treatment group compared to baseline or to a control group and this outcome was one of the main safety findings of the paper (stated in the abstract of the publication, so-called treatment failures); or (2) the safety of the probiotics, themselves, was also explicitly addressed in the publication. This operationalization is not without problems but it is a pragmatic solution adopted in other recent overviews of the safety literature (e.g., Pitrou, Boutron, Ahmad & Ravand, 2009).

Particular outcomes addressed in this review warrant further investigation as a risk-benefit analysis in a review that includes all studies reporting on a particular outcome such as all-cause mortality. Such a review would need to include all studies addressing the outcome, regardless of whether the outcome was considered a measure of efficacy or an unintended effect.

Key Questions

Key Question 1. What is the evidence that the active and lyophilized forms of probiotics (*Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and *Bacillus*) as single ingredients or in combination with other probiotics or prebiotics in all delivery vehicles (and formulations) when used to cure, treat, mitigate or prevent a disease or reduce disease risk are safe in the short term? Long term?

The question of whether probiotic interventions are safe cannot be answered with sufficient confidence based on the existing literature. The existing literature includes primarily the genera *Lactobacillus*, alone and in combination with other genera, often *Bifidobacterium*; adverse events associated with other genera are not well documented.

Case studies indicated that primarily fungemia, but also bacteremia, and incidences of sepsis have been linked to administered probiotic organisms. Although the confidence of matching strains has only recently been improved through DNA-based matching methods, the existing reports indicate that an association between administered probiotic strains and observed infections must be considered (Liong, 2008).

RCTs, CCTs, and case series did not report that they routinely monitor for the kinds of infections identified in case reports. This is particularly distressing as the identified case studies span a long period; the infectious potential of probiotic organisms is not a recent observation (Jensen, 1976; Richard, 1988). Most controlled trials did not state what harms were monitored, and the safety of the probiotic products was not addressed systematically. Poor reporting of adverse events is not specific to studies on probiotic products but a general concern of intervention studies (Ioannidis, 2004).

None of the identified case series, CCTs, or parallel and crossover RCTs reported an infections caused by the administered probiotic strains. However, these studies did not monitor routinely for such infections. The absence of reliable evidence on adverse events should not be mistaken for evidence of the absence of adverse events. The adverse events reported in RCTs in

the current literature do not suggest a widespread risk, but future studies that explicitly monitor for the safety issues of concern are needed to quantify the actual risk of specific adverse events in intervention studies.

Frequently reported individual adverse events were deaths that occurred during the study followup period; many gastrointestinal incidences such as diarrhea, constipation, or nausea; and respiratory infections. These types of outcomes were reported for both study arms, participants using probiotics as well as participants in control groups. Across studies most incidences were distributed evenly across treatment groups; nonetheless, there were individual studies such as the PROPATRIA trial reported by Besselink et al. (2008), a study of failed effectiveness reported a higher mortality rate in the probiotic treatment group than in the control group in patients with acute pancreatitis, which indicates that individual outcomes such as mortality should be monitored. In particular, as the mechanism of action must be investigated further, the study reported no incidences of infections caused by the administered probiotics organisms (*Lactobacillus* and *Bifidobacterium* strains). In a further publication, this mortality rate was determined to be increased in those taking probiotics who had organ failure, as compared to those who did not (Besselink, 2009). The analysis of individual outcomes also suggests that treatment failures should be highlighted in current research. Although treatment failures were not considered per se for this review, failed efficacy was sometimes considered a safety concern (Besselink, 2008; Boyle, 2008) and a central outcome of the study. Individual outcomes such as mortality should be assessed in a risk–benefit analysis that includes the outcome regardless of whether it was investigated as a safety concern or efficacy measure (i.e., where probiotics were given to reduce mortality).

To approach the question of safety of probiotics, we also systematically investigated the quantity of adverse events reported in probiotics studies. This information is meaningful only in comparison to a control group, a comparable group with similar patient characteristics, co-interventions, and other similar circumstances that permit investigation of whether adverse events are increased with probiotics use. We investigated two alternative measures, the number of patients with adverse events in each treatment group and the number of adverse-event incidences per treatment group. Each measure has inherent advantages and disadvantages, and the measures are not identical, as a single participant can experience multiple adverse events. Across all individual studies and identified adverse events, parallel RCTs did not indicate a statistically significantly increased risk of adverse events in either of the complementary measures. However, it has to be considered, though, that the existing literature is dominated by *Lactobacillus*-based interventions, both in combination with several other genera or alone.

Finally, the current literature also does not permit statements on the long-term safety of probiotics. With few exceptions, the existing literature reports on short- and medium-term use of probiotics assessed for a short or medium-term followup period. Research on probiotics has increased dramatically in recent years and studies in the near future may report more information on long-term effects of probiotics.

Key Question 2. What are characteristics and associations of the reported harms in Question 1?

The reported adverse events were primarily gastrointestinal in nature, others concerned infections and infestations, and a large group of studies did not fit any particular category in the published system used to classify adverse events (DHHS, 2009). While the case studies primarily

reported infections suspected or confirmed to be caused by an administered probiotic organism, the majority of other studies reported gastrointestinal incidences. In the included RCTs, there was no indication that participants using probiotic organisms have a higher risk of experiencing gastrointestinal adverse events than those not using them and this was also the case for infections and infestations and all other reported adverse events across studies. Studies rarely reported efforts to monitor harms specific to probiotic product interventions, including infections due to the administered strains. Hence, evaluations of the safety might change with future, more targeted, assessment of adverse events (Liong, 2008).

There is a lack of studies investigating potential interactions between probiotics and other, concomitantly administered, medications. The descriptions of cases experiencing serious adverse events suggest that either multiple medications or the underlying condition may have contributed to the severe adverse events reported but studies systematically addressing interaction effects are lacking.

We identified only a very small number of studies addressing acquired antibiotic resistance as a patient outcome with clinical relevance. Evidence for potential harms came from case studies in patients with multiple morbidities. Reported resistance pertained only to selected antibiotics. However, it has to be noted that we restricted the current review to patient outcomes, only where antibiotic resistance and translocation were described as clinical adverse events were these eligible for inclusion in the review. This excluded, for example, in vitro and animal research on the potential, or lack of potential, for antibiotic resistance and translocation that has been published for the investigated genera (Abe, 2010; Corthesy, 2007; Ishibashi, 2001).

Key Question 3. What is the evidence that harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* differ by product and delivery characteristics?

We set out to answer a large number of research questions related to the interventions and delivery characteristics. However, identified studies lacked detail in their description of administered probiotic organisms. Many studies did not specify which probiotic strains were investigated, nor was there indication that intervention preparations were tested for identity of the included organisms, viability, or contaminants.

The question of genus-specific safety profiles is not easy to answer with the existing literature. The review included probiotic organisms that were very different in nature (bacterial as well as yeast strains) with different histories and research experiences of using the genera as probiotic products (e.g., *Lactobacillus* versus *Enterococcus*). The number of identified fungemia case reports associated with of *Saccharomyces boulardii [cerevisiae]* outnumbered case reports of infections reported for the bacterial strains. However, RCTs, CCTs, and case series investigated primarily *Lactobacillus*, alone or in combination with *Bifidobacterium* strain interventions; the available evidence, including reports of the absence and the presence of adverse events as well as effectiveness studies, is very unbalanced across genera.

The kind of postmarket reports of adverse events that participants might encounter when using probiotic products had to be elicited from studies that often investigated products that included different genera or gave different probiotic genera for very different purposes, to different participant groups, in different doses and potencies. Very few studies provided head-to-head comparisons of different genera. For the included RCTs, we undertook stratified analyses for each genus in studies that used organisms from one genus only, for example, all studies using

exclusively *Lactobacillus* organisms. Stratified analyses by probiotic genus showed no increased risk of adverse events for any of the genera in studies using the genus in question exclusively. In addition, we undertook a metaregression and investigated each genus as a moderator in studies that used a particular genus alone or in combination with other genera (e.g., all studies including a *Lactobacillus* strain). There was some indication that interventions including *Streptococcus* strains showed a higher risk of adverse events compared to the other genera. However, this result was based on a small number of studies given the paucity of studies using genera other than *Lactobacillus* and direct evidence is missing.

Included studies used unique interventions that comprised a large number of different species and strains to investigate the efficacy, and in some cases the safety, for use as probiotic agents. Typically, there were too few comparable studies to enable individual safety statements for species or strains: many studies used interventions that included more than one probiotic organism so that it was not possible to link encountered adverse events to specific species or strains, and as outlined before, the documentation and validation of the interventions as well as the monitored adverse events were lacking. Other factors, such as a history of safe use of species in the food production, data on the prevalence of opportunistic infections, or reports of resistance to antibiotic or antifungal medications, may be considered to determine the potential for safe use. (see e.g., EFSA opinion, 2007; [Cote, 2006.]). However, these factors do not preclude the occurrence of rare adverse events, and such known properties of genera or species are only useful if there is evidence to suggest that all strains within the genus or within a species can be expected to behave similarly. Assuming that because a genus or individual species has low toxicity, no strain of the genus or species and no intervention including organisms of that genus or species can cause adverse events in intervention studies appears to be an overgeneralization.

There is also a lack of studies directly comparing product characteristics such as the mode of delivery. Indirect comparisons across the RCTs identified in this review indicated that the potential effect of different delivery vehicles should be investigated further. Subgroups indicated more adverse event incidences in the treatment group when probiotics were taken in a yogurt or other dairy product than when taken in any other vehicle. It must be kept in mind that no study actually compared adverse events between a yogurt/other dairy vehicle and any other vehicle within the same study; nevertheless, there are alternative explanations for such an observation. Probiotic organisms might maintain greater viability in dairy than nondairy vehicles, or the adverse events are actually attributable to lactose intolerance. Given that many consumers consume probiotics as part of dairy or yogurt products, this effect should be further investigated in direct comparisons. The possibility that the use of a particular food as a vehicle for probiotic organisms might alter their viability (and therefore the potential efficacy and toxicity) has been explored in a number of studies (Champagne, 2005), and some have reported that *Lactobacillus rhamnosus* GG isolated from 15 different manufactured food products (carriers) showed strain differences that could affect both efficacy and safety (Grzeskowiak, 2010).

The only included studies that compared the form of probiotic organisms directly compared viable and heat-killed organisms. Heat-killed organisms are not included in prominent definitions of probiotics; hence, this comparison is of minor interest. There was no indication that active forms were associated with a higher number of adverse events. The characterization of organisms was too poor in included studies to allow a systematic investigation of the influence of the form. Also seldom tested or reported was the viability of the administered organisms: Considering that probiotics are live organisms and that they presumably need to remain live to be

fully functional, it is concerning that few studies demonstrated that they were indeed able to maintain the evaluated organisms in a live and robust state. Related to this concern, *Bacillus* species are capable of forming spores, which would affect the count of viable organisms in a preparation. Furthermore, because several of the genera of interest are primarily anaerobic, exposure to oxygen during storage could easily affect viability. Another factor that might lower the potency of probiotic products is the failure to consider the potential for cryogenic damage during lyophilization and/or storage and to compensate by adding a cryoprotectant (see e.g., Savini, 2010).

We did not identify conclusive evidence in the existing literature showing that interventions with a mixture of different organisms reported more adverse events than studies using one probiotic strain only or that synbiotics (mixtures of prebiotics and probiotics) differ from probiotics; however, there is a lack of direct comparisons. Although the risk of adverse events (as well as the efficacy) is not necessarily comparable across species and strains, direct head-to-head comparisons are largely absent in the literature and in practice, probiotic interventions often included several different probiotics genera, species, and strains.

Key Question 4. How do the harms of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* vary based on (a) dose (cfu); (b) timing; (c) mode of administration (e.g., catheter); (d) age (all ages, including infants), gender, ethnicity, disease or immunologic status of the patient; (e) relationship to efficacy?

Only a few primary studies explored the effect of intervention and participant characteristics on safety. Both the variation in definitions of high and low dose across published studies and other factors such as the inherent differences in the compared organisms as outlined previously precluded a systematic evaluation of a dose-response relationship.

Very few published studies were identified that investigated the effects of long-term use of probiotics, that is, intervention durations of 1 year or longer; information on the safety of long-term use is lacking. Given the current research interest (Shane, 2010) studies will hopefully provide needed evidence on long-term interventions.

There were few descriptions of the time of onset of harms relative to treatment and the further clinical course of adverse events. In the few studies that reported on the time of onset of gastrointestinal effects, most effects were observed within in the first 3 days of treatment. The onset of infections tended to occur 1 to several weeks after initiation of probiotics use; however, this information is primarily based on case studies and was not systematically reported. A further pertinent question may be the optimal time for administering probiotics, that is, early to prevent, rather than aiming to treat or improve particular conditions, which may be associated with the risk–benefit ratio of interventions (Arciero, 2010; Sanders, 2010).

In indirect comparisons across all identified RCTs in this review, we found no evidence that a particular mechanism or route of administration of probiotic organisms (e.g., through enteral feeding) was associated with an increased risk of an adverse event relative to a control group. In the literature, serious adverse events associated with probiotic use have been linked to catheter use (e.g., Sanders, 2010). However, the route of administration is closely linked to the health status of participants.

With regard to the health status of participants, there was some indication that health status is associated with the risk for an adverse event when using probiotics. The majority of case studies reporting serious adverse events described a critically ill patient or someone suffering from multiple morbidities when they contracted a serious infection potentially caused by probiotic organisms. There was some indication in the metaregressions that health status may predict an increased risk of adverse events associated with probiotic organisms. However, a subgroup analysis of all controlled trials enrolling critically ill participants did not show a statistically significantly increased risk of experiencing adverse events for participants using probiotic organisms compared to control group participants with similar patient characteristics. Critically ill patients may be more prone to experience adverse events; however, these were not associated with the use of probiotics; adverse events were equally distributed across treatment groups. Further large controlled studies are needed to identify any increased risk for rare but pertinent adverse events, and the risk–benefit ratio should be considered (also Whelan, 2010).

For studies enrolling patients with compromised health, it would appear appropriate to use a data monitoring committee. A study by the Society for Clinical Trials' DAMOCLES Study Group found that only about 25 percent of articles presenting the main results of clinical trials mentioned having used a data monitoring committee to ensure the appropriate collection of data throughout the trial (Sydes, 2004). Such committees would also be helpful in standardizing the collection of adverse event data in large, well-powered trials as well as in some smaller trials in populations of interest; a data monitoring working group has provided a set of guidelines (STC, 2006).

To assess the role of the age in the safety of probiotics, we stratified studies according to the age of participants and undertook separate analyses for studies in children, adults, or elderly participants. The stratified analyses did not indicate an increased risk of adverse events in any of the subgroups associated with the use of probiotics compared to corresponding control group participants. However it has to be noted that very few studies were identified that reported on elderly participants.

The identified case studies described more male than female patients. In the RCTs, we investigated the results of subgroups in female only and male only studies as well as analyzing the percent of female participants as a factor in a meta-analysis. In these indirect comparisons across RCTs, we found no indication that encountered adverse events relative to control group incidences depend on the gender of the participants.

The included studies did not provide enough information to investigate whether probiotic safety is associated with racial/ethnic characteristics. It should be kept in mind that the majority of included studies were conducted in European countries where ethnic characteristics are rarely assessed in research studies. The research field needs to advance much further in order to be able to answer such specific questions regarding the safety of probiotics; such evidence is not available for other more established interventions (such as antibiotics use) either.

In total, 59 percent of included studies were explicitly described as effective by the study authors for the various applications of probiotic use under investigation. We found no indication that the efficacy of an intervention was related to the number of encountered adverse events across all included RCTs.

Key Question 5. How often does harm associated with *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* lead to hospital admission or lengthened hospitalization?

While several case studies reported a new hospitalization potentially associated with the consumption of a product including *Saccharomyces, Lactobacillus,* or *Bacillus* strains, none of the case series, CCTs, and parallel and crossover RCTs reported that a probiotics intervention led to a hospitalization in the intervention participants. A comparison of all reported hospitalizations regardless of the perceived association with the intervention treatment indicated no statistically significant risk in probiotics interventions compared to the number of hospitalizations in control group participants. However, the number of hospitalizations due to adverse events was only explicitly reported on in a few of the included studies. Older publications may not have associated a hospitalization with probiotics intake, and several studies were in participants already hospitalized. As outlined previously, the safety of probiotic products has only recently been considered as an issue warranting further investigation (Liong, 2008).

A proportion of included studies reported on the presence or absence of serious adverse events following the Food and Drug Administration definition. Results for serious adverse event varied across RCTs, sometimes favoring the probiotics group and sometimes the control group, and differences across probiotic and control group were not statistically significant. The same result was obtained for *Lactobacillus* and *Saccharomyces* interventions, but there were too few studies (*Bifidobacterium*) or no studies (*Streptococcus, Enterococcus, Bacillus*) in order to analyze serious adverse events for other genera, as studies did not report on the presence or absence of serious adverse events. The reporting of adverse events appears to have improved in recent years, presumably due to stricter guidelines and higher standards imposed by journals, for example, making it mandatory to report on adverse events when reporting the results of RCTs (e.g., Item 19 of the CONSORT statement, "All important harms or unintended effects in each group"). Relevant to this review is that the reporting of the presence and absence of infections has increased in particular, possibly a reaction in part to the PROPATRIA trial reported by Besselink et al. (2008).

We also investigated pertinent subgroups that were of particular interest to this evidence report. Most notably, we did not find evidence that health-compromised patients were at increased risk of experiencing more serious adverse events than health-compromised control group participants. However, it has to be taken into account that the monitoring and reporting of adverse events is lacking, existing interventions were again primarily *Lactobacillus* interventions, and future assessments may come to different conclusions as the evidence base improves.

Key Question 6. How does harm associated with *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus* relate to use of concomitant antibiotics, confounding diet therapies, corticosteroid use, immune suppressants, or other potential confounders?

Multivariate analyses in primary research studies are suitable to systematically trace interactions between cointerventions and probiotic use. In studies where some of the participants use these cointerventions while others do not, this factor and its effect on the study outcome can be investigated. We did not identify studies meeting the review inclusion criteria that reported

statistical interactions between concomitant antibiotics, diet therapies, corticosteroid use, or immune suppressants and probiotics.

Although the risk of adverse events in general might be higher in participants on multiple medications, the crucial issue for this Key Question is whether participants in probiotics interventions are more likely to experience adverse events compared to corresponding control group participants. Interactions between comorbidities and cotreatments are complex research questions (Fitzgerald, 2010). For example, we might assume an interaction between corticosteroids and probiotics when studies in participant samples using corticosteroids report a higher risk ratio of adverse events than other studies. In subgroup analyses of identified studies in which the intervention participants as well as the control group participants received corticosteroids, we found no statistically significantly increased risk of adverse events for intervention participants compared to control.

Probiotic interventions have been the focus of much research interest for the prevention of side effects associated with antibiotics (Abernethy, 2008; Cots, 2008; D'Souza, 2002; Doron, 2008; Elmer, 1998; Jack, 2010; Johnston, 2005; Johnston, 2006; Kale-Pradhan, 2010; Katz, 2006; Marshall, 2008; McFarland, 2005; McFarland, 2009; McFarland, 2006; Oldfield, 2008; Rohde, 2009; Ruszczynski, 2008; Szajewska, 2005; Szajewska, 2006; Wilcox, 2009; Young, 1998; Zou, 2009). While efficacy studies for the prevention of side effects were not eligible for inclusion in the review, we included those studies that addressed side effects of probiotics in addition to side effects of antibiotics where feasible, through the design and the adverse event monitoring of the study. Across RCTs, there was no evidence for a statistically significantly increased risk of adverse events for intervention participants compared to controls or an interaction between antibiotics and probiotics.

We identified only a few studies with concomitant diet therapies. Studies in participants using immune suppressants were also largely absent in the existing literature and patients on immune suppressants were systematically excluded from a number of RCTs. The existing evidence base is not sufficient to draw any meaningful conclusions from adverse events observed in the few studies that addressed these patients.

Future Research

Our search of the published literature on probiotics failed to uncover answers to several of the questions posed by the sponsors and identified little information on several of the organisms of interest. Performing a formal gap analysis was beyond the scope of the review; however a major aim of these recommendations for future research must be to fill in the research gaps we identified.

Monitoring and reporting. Future studies should describe the intervention and the results of interventions in more detail. This improved description would entail, first of all, documenting the investigated product with regard to the genus, species, and strain. As technology and methods develop, this should also entail a more reliable, DNA-based validation of the characteristics of the included microorganisms, that is, the valid identification of the studied organism and the purity or the identification of all included microorganism in the study product. There is a need for more reliable information on the identity, potency, and viability of the included microorganisms given to participants at the time of the intervention as this may depend on the storage and delivery vehicles chosen for interventions.

Future studies should describe which adverse events were monitored to allow a clearer overview of the presence and absence of adverse events in probiotics studies, in order to quantify the risk of adverse events for future intervention participants. The reporting of adverse events should follow reporting guidelines such as the extension of the CONSORT statement for harms (Ioannidis, 2004). In addition, there are comprehensive systems for cataloging adverse events such as the CTCAE system. The mention of adverse events almost in passing, as is typical for the existing literature, is hindering knowledge accumulation.

Generally, it should be standard to monitor and report on adverse events in interventions; general research into microbial behavior and early toxicity investigations cannot replace empirical evidence for the presence and absence of adverse events in studies aiming to reduce risk for, prevent, or treat diseases in human participants.

Study designs. Long-term effects of probiotics interventions are largely unknown and should be considered in future studies; despite the large number of publications on probiotics, there is a lack of long-term assessment studies. There is also a need to evaluate the long-term use of probiotics, that is, intervention durations of more than a few weeks, as are currently typical. In addition, the current literature is dominated by clinical research studies; large cohort studies following populations who have self-selected to use probiotics as dietary supplements or food components are needed to fully understand the effectiveness and safety of probiotics. Population surveillance studies and case-control studies are largely absent from the literature.

Research questions. Studies are needed to explore potential adverse events associated with interventions that include the genera *Enterococcus* and *Bacillus*, and possibly the use of some *Streptococcus* species, as well as the use of *Saccharomyces* in some patient groups; the majority of existing studies report on *Lactobacillus,* alone or in combination with other genera, most commonly *Bifidobacterium* strains. In addition, it is possible that safety results differ not only by genus but also by species or strains; hence, all probiotics research studies should report adverse events and not rely on results obtained with other species or strains.

The current literature rarely reports assessment efforts to monitor harms specific to probiotics, and more targeted assessments may change our understanding of the safety of probiotics from what is presented in this evidence report. The harms assessment should consider safety issues warranting further investigation as documented in this review. This process would include systematically monitoring for infections associated with probiotic organisms. Critical patient outcomes such as all-cause mortality or hospitalizations as well as treatment failures as suggested by reports of failed efficacy and effectiveness studies (for example, allergy sensitization) should be assessed in future primary research using controlled trials. Reviews should consider all studies measuring the outcome regardless of whether that outcome was utilized to evaluate the efficacy of the intervention or observed as an adverse event.

There is also a lack of studies addressing complex research questions such as interactions with participant, product, or intervention factors associated with the use of probiotic products. These effects should be addressed with appropriate multivariate analyses, or where possible, in head-to-head comparisons. With regard to participant characteristics studies evaluating effects on elderly participants are largely absent from the current literature. There is indication that participants with compromised health should be monitored closely for potential adverse events associated with probiotics, such as through the use of data monitoring boards. Controlled trials are needed to determine whether these patients are more likely to experience adverse events compared to control groups with similar participant characteristics, in order to address risk-benefit questions. Interactions with delivery vehicles, in particular yogurt and dairy products, should be investigated further in direct, head-to-head comparisons in order to fully understand the effect of these vehicles.

Conclusions

Despite a substantial number of publications on probiotics little evidence is available to answer specific questions regarding their safety in research studies. RCTs and case studies diverge in the outcomes they report, there is a lack of assessment and structured reporting of adverse events, and interventions are poorly documented. The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess and the current literature is not well equipped to answer specific questions on the safety of probiotics in intervention studies with confidence. To quantify potential health risks the presence and absence of adverse events should be reported, adverse events should be monitored (particularly in health-compromised participants), infections due to the administered organisms and treatment failures should be documented; and the effect of delivery vehicles should be assessed systematically. In addition, few studies currently exist that report on effects in the elderly, the long-term effects of probiotics use, or on interventions based on genera other than *Lactobacillus*. These limitations hinder conclusions regarding the safety of probiotics used to reduce risk and prevent or treat disease.

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Acronyms and Abbreviations

AHRQ – Agency for Healthcare Research and Quality
ATCC – American Type Culture Collection
CAERS – CFSAN Adverse Event Reporting System
CBER – Center for Biologics Evaluation and Research
CCTs – controlled clinical trials
CFSAN – Center for Food Safety and Applied Nutrition
cfu – colony forming units
CI – confidence interval
CTCAE – Common Terminology Criteria for Adverse Events classification system
DARE – Database of Abstracts of Reviews of Effects
EFSA – European Food Safety Authority
EPC – Evidence-based Practice Center
FAO/WHO – Food and Agriculture Organization of the United Nations and the World Health Organization
FDA – Food and Drug Administration
GRAS – generally recognized as safe
IND – investigational new drug
ITT – intention-to-treat
MANTIS – Manual, Alternative and Natural Therapy Index System
NCCAM – National Center for Complementary and Alternative Medicine
NCI-CTC – National Cancer Institute Common Toxicity Criteria
NTIS – National Technical Information Service
ODS – National Institutes of Health Office of Dietary Supplements
RCT – randomized controlled trial
RD – risk difference
RR – risk ratio
SAE – serious adverse event
TEP – Technical Expert Panel

Appendix A. Exact Search Strings and List of Manufacturers

Exact Search Strings

Probiotics—Search Methodologies

SEARCH #1:
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1966-8/2010

SEARCH STRATEGY:
probiotic* OR prebiotic* OR pre-biotic* OR synbiotic*
NOT
animals NOT humans

NUMBER OF ITEMS RETRIEVED: 6491
==========
SEARCH #2:
DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Database of Systematic Reviews via OVID Online Service – All dates

SEARCH STRATEGY:
probiotic* OR prebiotic* OR synbiotic* {No Related Terms}

NUMBER OF ITEMS RETRIEVED: 27
==========
SEARCH #3:
DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Database of Abstracts of Reviews of Effects (DARE) – All dates

SEARCH STRATEGY:
probiotic* OR prebiotic* OR synbiotic* {No Related Terms}

NUMBER OF ITEMS RETRIEVED: 17
==========
SEARCH #4:
DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Central (Controlled Clinical Trials Register) – All dates

SEARCH STRATEGY:
probiotic* OR prebiotic* OR synbiotic* {No Related Terms}

NUMBER OF ITEMS RETRIEVED: 151
==========
SEARCH #5:
DATABASE SEARCHED & TIME PERIOD COVERED:
CINAHL with Full Text – 1981-8/2010

SEARCH STRATEGY:
TI (probiotic* OR prebiotic* OR synbiotic*) OR AB (probiotic* OR prebiotic* OR synbiotic*) OR SU (probiotic* OR prebiotic* OR synbiotic*)
Search modes - Boolean/Phrase

NUMBER OF ITEMS RETRIEVED: 1633
==========
SEARCH #6:
DATABASE SEARCHED & TIME PERIOD COVERED:
NTRL – National Technical Reports Library (NTIS database) – ~1800-8/2010

SEARCH STRATEGY:
probiotic OR probiotics OR prebiotic OR prebiotics OR synbiotic OR synbiotics

NUMBER OF ITEMS RETRIEVED: 99
NUMBER OF RELEVANT ITEMS RETRIEVED AFTER INITIAL SCREENING: 12
==========
SEARCH #7:
DATABASE SEARCHED & TIME PERIOD COVERED:
Toxline/Toxfile – 1964 – 8/2010

SEARCH STRATEGY:
probiotic* OR prebiotic* OR synbiotic*

NUMBER OF ITEMS RETRIEVED: 371
==========
SEARCH #8:
DATABASE SEARCHED & TIME PERIOD COVERED:
Allied & Complementary Medicine via DIALOG Online Service File 164– 1984-8/2010

SEARCH STRATEGY:
probiotic? OR prebiotic? OR synbiotic?

NUMBER OF ITEMS RETRIEVED: 134
==========
SEARCH #9:
DATABASE SEARCHED & TIME PERIOD COVERED:
MANTIS (Manual, Alternative, and Natural Therapy) via DIALOG Online Service File 91 – 1880-5/2009

SEARCH STRATEGY:
probiotic? OR prebiotic? OR synbiotic?

NUMBER OF ITEMS RETRIEVED: 238
==========
SEARCH #10:
DATABASE SEARCHED & TIME PERIOD COVERED:
Academic Universe Company Profiles

SEARCH STRATEGY:
(probiotic! OR prebiotic! OR synbiotic!) AND (sic(mfg OR manufact! OR preparation) OR naics(mfg OR manufact! OR preparation))
AND
U.S. OR intenational companies

NUMBER OF ITEMS RETRIEVED: 355
==========
SEARCH #11:
DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1974-8/2010

SEARCH STRATEGY:
probiotic? OR prebiotic? OR synbiotic?
AND
Human

NUMBER OF ITEMS RETRIEVED: 6536
==========
SEARCH #12:
Agricola - 1970 – 8/2010

SEARCH STRATEGY:
probiotic? or prebiotic? or synbiotic?
AND
safe? or harm? or adverse or death or complication? or toxic?

NUMBER OF ITEMS RETRIEVED: 506

List of Manufacturers

The table lists manufacturers of probiotic, prebiotic or synbiotic products. The companies were identified searching the web pages of the IPA and ISAPP, www.usprobiotics.org, the database Nexis, the NLM Dietary Supplements Labels Database, a Google product search, examples listed in published papers and guidelines (e.g., World Gastroenterology Organisation Practice Guideline; Douglas & Sanders, 2008), and personal files (all searched May 2009).

Identified Manufacturers

	Manufacturer
1.	21st Century HealthCare, Inc.
2.	4Life Research
3.	Abbott Laboratories
4.	ADM Alliance Nutrition, Inc.
5.	Advanced Muscle Science
6.	Agropur
7.	Agtech Probiotic Fertilizers
8.	Alacer Corporation
9.	Albertsons
10.	Alcon Laboratories, Inc
11.	Allergy Research Group
12.	ALVA-AMCO Pharmacal Cos, Inc.
13.	American Health, Inc.
14.	American Ingredients Inc.
15.	American Nutrition
16.	Amerifit Brands, Inc.
17.	AmVac
18.	Anthony Robbins Companies
19.	Applied Nutriceuticals
20.	Applied Nutrition
21.	Ardeypharm
22.	Aria Foods
23.	Arthritis Research Corporation
24.	Asahi Kasei Corporation
25.	AST Sports Science
26.	Atkins Nutritionals, Inc.
27.	Attune Foods
28.	Bally Total Fitness Corporation
29.	Barlean's Organic Oil
30.	Barry Callebaut AG
31.	Bausch & Lomb
32.	Bayer Corporation/Consumer Care Division
33.	Bayer Health Care (Phillips')
34.	Belvedere Jay Brands
35.	Beneo-Orafti
36.	Berkeley Premium Nutraceuticals, Inc.
37.	Bio Human Netics, Inc.
38.	Biobank Co
39.	Biocodex
40.	BioGaia AB
41.	BioImmersion
42.	Bio-k Plus
43.	BioNatures
44.	Biotech Corporation
45.	Biotech Research
46.	Biotest Brands
47.	Biotics Reaearch Corporation
48.	Blairex Laboratories, Inc.
49.	Block Drug
50.	Bradley Pharmaceuticals
51.	Bradley Pharmaceuticals Inc
52.	Brewster Foods
53.	Bristol-Meyers Squibb Company
54.	Bronson Laboratories
55.	BSN
56.	California Academy of Health, Inc.

57.	Calpis USA Inc.
58.	Carb Wise
59.	Cargill Texturizing Solutions
60.	CCA Industries, Inc.
61.	Cerbios-Pharma
62.	Champion Nutrition, Inc.
63.	Chattem, Inc.
64.	China Meihua Biological Technology
65.	China-Biotics
66.	Choongang Biotech Co Ltd
67.	Chr. Hansen
68.	Clinicians Choice Inc.
69.	ConAgra Foods
70.	Contract Pharmacal Corp.
71.	Coromega Corp.
72.	Costco Wholesale Corporation (CWC), Inc. (Distributor)
73.	Country Life
74.	CSA Nutraceuticals, LLC
75.	Culturelle/Amerifit Brands
76.	Custom Probiotics
77.	CytoSport, Inc.
78.	Danisco
79.	Danone/Dannon
80.	Desert Health Products Inc
81.	Designs For Health
82.	Doctorâ€™s Best, Inc.
83.	Douglas Laboratories
84.	Dow
85.	DrNatura
86.	DSM Food Specialties France SAS
87.	EAS (Experimental and Applied Sciences)
88.	Eclectic Institute
89.	Ecological Formulas/Cardiovascular Research Ltd.
90.	Emerald Laboratories
91.	EnCoate
92.	Encysive Pharmaceuticals Inc
93.	Eniva Corporation
94.	Enzymatic Therapy, Inc.
95.	Epic Nutrition
96.	Ergopharm
97.	Essential Formulas Inc
98.	Fenchem
99.	Flora
100.	Fonterra Co-operative Group Ltd.
101.	Futurebiotics, LLC
102.	Futureceuticals
103.	Gaia Herbs
104.	Ganeden Biotech
105.	Garden of Life
106.	Gatorade Company, The
107.	General Mills
108.	GeneThera, Inc.
109.	GenMont Biotech
110.	GlaxoSmithKline (GSK)
111.	Global Health Trax Inc
112.	GNC (General Nutrition Companies), Inc.
113.	Great Ocean Ingredients

114.	GTC Nutrition, LLC
115.	GumRunners, LLC
116.	Harmonium International
117.	Health & Nutrition Systems International Inc
118.	Health Asure, Inc.
119.	Health Plus, Inc.
120.	Healthy N Fit Nutritionals
121.	Healthy Origins Products
122.	Hello Imports, LLC
123.	Hunan Taizinai Group Co Ltd
124.	HVL, Inc./Douglas Laboratories
125.	IDS Sports
126.	Imagenetix, Inc.
127.	Inkine Pharmaceuticals
128.	Institut Rosell Lallemand Inc
129.	Inverness Medical Innovations, Inc.
130.	Iovate Health Sciences U.S.A. Inc.
131.	IR Biosciences Holdings Inc
132.	Irwin Naturals
133.	iSatori Technologies
134.	ISS Research
135.	J.R. Carlson Laboratories
136.	Jarrow Formulas
137.	Jay Robb
138.	Kellogg (Canada and USA)
139.	Kendy USA
140.	Kibow Biotech
141.	Klaire Labs
142.	Klein-Becker USA
143.	Kmart
144.	Koninklijke Friesland Foods
145.	Kraft
146.	Labrada Nutrition
147.	LacPro
148.	Larkspur Wren Industries
149.	Leiner Health Products Inc. (LHP, Inc.) (Dist.)
150.	Lichtwer Pharma
151.	Life Enhancements Products, Inc.
152.	Life Extension Foundation
153.	Life Plus International
154.	Lifeway Foods
155.	LifeWise Naturals
156.	Longs Drug Stores Corporation
157.	Mayor Pharmaceuticals Laboratory, Inc.
158.	McNeil Nutritionals
159.	Mead Johnson & Company
160.	Meiji Dairies Corporation
161.	Merck
162.	Merz Pharmaceuticals, LLC
163.	Metabolife International, Inc.
164.	MET-Rx Engineered Nutrition
165.	MGI GP Inc
166.	Michael's Naturopathic Programs
167.	Mission Pharmacal Company
168.	Molecular Nutrition, LLC
169.	Montana Naturals, Inc.
170.	Morinaga Milk Industry
171.	MRM-USA
172.	Muscle Marketing USA, Inc.

173.	MuscleTech Research and Development Inc.
174.	Naked Juice Company
175.	Nancy's Yogurt
176.	Natrol, Inc.
177.	Naturade
178.	Natural Balance, Inc.
179.	Natural Bridges Products, Inc.
180.	Natural Factors
181.	Natural Factors Nutritional Products Inc.
182.	Natural Organics Inc.
183.	Natural Products, Inc.
184.	Naturally Vitamins
185.	Nature Made Nutritional Products
186.	Nature's Sunshine Products Inc
187.	Nature's Way Holding Company
188.	Natures Answer
189.	Natures Benefit
190.	Natures Best Inc
191.	Natures Bounty, Inc.
192.	Natures Resource Products
193.	Natures Secret
194.	Natures Sunshine
195.	Natures Way Products, Inc.
196.	Nebraska Cultures
197.	
198.	Nestlé Nutrition USA
199.	Nestlé Purina
200.	New Chapter
201.	New York Health Care, Inc.
202.	NewMark
203.	Newmark (NMK)
204.	Newmark / New Chapte...
205.	Next Foods
206.	Next Proteins International
207.	NFI Consumer Products
208.	NIZO Food Research B.V.
209.	Norrmejerier
210.	North Star Nutritionals
211.	Northwest Natural Products
212.	Novartis Consumer Health, Inc.
213.	Novato Swan Research
214.	Novogen Ltd
215.	Now
216.	Now Foods
217.	Nutracea
218.	Nutraceutical Corporation
219.	Nutraceutical Science Institute (NSI)
220.	Nutraceutix
221.	Nutramax Laboratories, Inc.
222.	NutraSanus
223.	NutriCology, Inc.
224.	Nutri-Health
225.	Nutrition Now, Inc.
226.	Nuvim, Inc.
227.	NxLabs
228.	Olympian Labs Inc.
229.	On The Rock Nutrition
230.	Optimal Therapeutics, Inc.
231.	Optimum Nutrition

232.	Oragenics Inc
233.	Organobalance GmbH
234.	P.L. Thomas & Company
235.	Passion 4 Life, LLC
236.	PatentHealth, LLC
237.	Performance Labs, Inc.
238.	Pharmanex
239.	Pharmaton
240.	Pharmavite, LLC
241.	Physician Formulas
242.	PhysioLogics
243.	Planetary Formulas
244.	Premier Nutrition
245.	Probi
246.	Probi AB
247.	Probiomics Ltd
248.	Probiotical
249.	Procter and Gamble
250.	Prolab Nutrition
251.	Pulmuone – Wildwood
252.	Pure Encapsulations, Inc.
253.	Pure Prescriptions, Inc.
254.	Pure Research Products
255.	PureTek Corporation
256.	Puritans Pride
257.	Qingdao Eastsea Pharmaceutical Co
258.	Quantum Health
259.	Questcor Pharmaceuticals Inc
260.	Radiance Vitamins
261.	Rainbow Light
262.	Rainbow Light Nutritional Systems
263.	Real Health Laboratories, Inc.
264.	Remington Health Products
265.	Renaissance Herbs, Inc.
266.	Renew Life
267.	ReNew Life Formulas, Inc.
268.	Renutra/Pivotal Health Solutions
269.	Rexall Sundown, Inc.
270.	Richardson Labs, Inc.
271.	RidgeCrest Herbals, Inc.
272.	Rite Aid Company (Distributor)
273.	Sanofi-Aventis
274.	Sausalito Lark Systems
275.	Schiff
276.	Schiff Products, Inc. (Distributor)
277.	Sedona Labs
278.	Sensus
279.	Shaklee Corporation
280.	Sigma-Tau Pharmaceuticals, Inc.
281.	Slimfast Foods Co.
282.	Solgar
283.	Solvay
284.	Somaxon Pharmaceuticals
285.	Spectrum Essentials
286.	Spectrum Organic Pro...
287.	Spectrum Organic Products, Inc.
288.	Super Nutrition Inc.
289.	Synbiotics
290.	Synbiotics Corporati...

291.	Ta'am-Teva Altman
292.	Target Corporation (Distributor)
293.	Tensall Bio-Tech Company, Limited
294.	The WholeSoy Co.
295.	Tiburon Cardinal Laboratories
296.	Trace Minerals Research
297.	Trader Joes (Distributor)
298.	Transitions For Health, Inc.
299.	TrimSpa
300.	Tropical Oasis Inc.
301.	Twinlab Corporation
302.	Twinwealth Biotech
303.	U.S. Nutrition
304.	UAS Laboratories
305.	Udos choice
306.	Ultimate Nutrition
307.	Unilever
308.	Universal Nutrition
309.	Upsher-Smith Laboratories, Inc.
310.	Urex Biotech
311.	Valio Worldwide
312.	Vincent Foods, LLC
313.	Vitabase
314.	Vitamin Shoppe, The
315.	Vitamin World, Inc.
316.	Vitarich
317.	VPX (Vital Pharmaceuticals)
318.	VSL Pharmaceuticals
319.	Wakunaga of America
320.	Weider Nutrition Group
321.	Weil Nutritional Supplements
322.	Wellements
323.	Western Research Laboratories
324.	Whole Health Products, LLC
325.	Winclove
326.	Windmill Health Products
327.	Wonder Laboratories
328.	World Nutrition, Inc.
329.	World Organics Corporation
330.	WorldWide SportNutrition
331.	Wyeth
332.	Wyeth Consumer Healthcare
333.	Yakult
334.	Yerba Prima
335.	Zoller Laboratories

Appendix B. Sample Data Extraction Forms

ID: _____ Reviewer:

First Author, Year: _____
LAST NAME ONLY, PUBLICATION YEAR

Number of publications: _____ ENTER '1OF 1' IF ONLY ONE

Description and IDs of related papers (if more than one publication):

Study Details & Participant Information

Country _____

Country category CHECK ALL THAT APPLY
- US ..... ☐
- Europe ..... ☐
- Asia (Japan, China, Taiwan, Korea, Singapore) . ☐
- Other or n/a ..... ☐

Study design CIRCLE ONE
- Case study [1c] 0
- Case series (uncontrolled) [1a,b] 1
- Case-Control (probiotics as risk factor) [1d,e] 2
- Cohort study (comparing 2 cohorts) [1d,e] 3
- Controlled clinical trial (controlled by investigator) [1a,b] 4
- Parallel RCT [1a,b] 5
- Other: _____ ☐
- n/a ..... ☐

Mechanistic study – could the study be described as a mechanistic study (e.g. investigating how, why probiotics may work)? [1f] CIRCLE ONE
- No 0
- Unclear - Somewhat unclear 1
- Yes 2

Source: CIRCLE ONE
- Conference abstract, letter 0
- Unclear - Somewhat unclear 1
- Journal article 2

Was the safety of probiotics the main aim of the paper?

No 0
Unclear - Somewhat unclear 1
Yes 2

Sample size category [4]

1-10 0
11-100 1
100+ 2
n/a - unclear..... ☐

Age at exposure to probiotics[4]

Young (prenatal to teens).....0
Adult 1
Elderly (> 65 yrs).....2
n/a, multiple – no info or mix ..... ☐

Age at data collection category (majority groups) [4]

CHECK ALL THAT APPLY

Prenatal ..... ☐
Newborns (≤1 mos)..... ☐
Infants (>1 - 12 mos)..... ☐
Toddlers (>12 - 24 mos)..... ☐
Children (> 2 to 11yrs)..... ☐
Teens (12 - 17yrs) ..... ☐
Adults (18 - 65 yrs) ..... ☐
Elderly (> 65 yrs) ..... ☐
Mix..... ☐
Other: _____.... ☐
n/a – no info ..... ☐

Gender [4d]: % Female: ____

Other info (if no % is given):

☐ "Mostly female" ☐ "Mostly male"
☐ n/a - no info, not reported

Race and ethnicity [4d]: Did the study target a particular demographic group or reported subgroup analyses for particular groups?

☐ n/a - no particular group; no info

Disease or immunologic status [4d]: Does the study focus on patients with any of the following health conditions?

CHECK ALL THAT APPLY . CONSIDER ONLY SUBSTANTIAL NUMBER OF PATIENTS, NOT 1 PATIENT WITH IBS WITHIN HEALTHY SAMPLE

- ☐ Healthy participants
- ☐ Cancer
- ☐ Obesity
- ☐ Gastrointestinal (unspecified)
- ☐ IBS
- ☐ IBD
- ☐ Dermatologic (unspecified)
- ☐ Eczema
- ☐ Atopic dermatitis
- ☐ Immunologic (unspecified)
- ☐ Vaginal yeast infection
- ☐ H. pylori
- ☐ Exposure to toxins
- ☐ Intestinal detox therapy
- ☐ Short gut syndrome
- ☐ Diarrhea
- ☐ Colitis
- ☐ Crohn's disease
- ☐ Invasive devise
- ☐ Immuno-compromised, HIV
- ☐ Chronic infection
- ☐ Lactose intolerance
- ☐ Allergies (not lactose)
- ☐ Other health condition: SPECIFY _____
- ☐ Other health condition: SPECIFY _____
- ☐ Other health condition: SPECIFY _____
- ☐ Other health condition: SPECIFY _____
- ☐ n/a – not specified, none of the above

Overall, assuming a continuum ranging from healthy to clinically high risk what describes the participants best [4d] CIRCLE ONE

Generally healthy 0
n/a - medium, neither, unclear.....1
High risk 2

Exclusion criteria: does the study explicitly exclude the following groups? CHECK ALL THAT APPLY

- Newborn or infants, under 2 years ☐
- Older participants (>65) ☐
- Immune compromised, critically ill, high risk ☐
- Pregnant women ☐
- Other (recurrent) group: SPECIFY _____ ☐
- n/a – not specified, none of the above ☐

Probiotic function CIRCLE ONE

- None specifically / nutrition (e.g. contained in yoghurt) 1
- Prevention 2
- Treatment (e.g. to counterbalance adverse effects of antibiotics 3
- Varies - Varies by participant 4
- n/a 5

Does the study include any of the following co-treatments (confounders) [6]?
CHECK ALL THAT APPLY

- Concomitant antibiotics ☐
- Diet therapies ☐
- Corticosteroid use ☐
- Immune suppressants ☐
- Other, specify: _____ ☐
- n/a - none of the above ☐

Did the authors file an Investigation of New Drug (IND) form prior to the research? [1a] CIRCLE ONE

- No 0
- Unclear - Somewhat unclear 1
- Yes 2

Describe the Main Probiotics Intervention and Control Group, if any, here

Intervention Group ARM 1 IN CONTROLLED TRIALS WITH MULTIPLE ACTIVE ARMS

ADD MORE INTERVENTION PAGES AND STAPLE TO THE BACK OF THIS FORM IF THERE ARE MORE THAN 2 TREATMENT ARMS WHERE PROBIOTICS WERE GIVEN.

Product name _____

Further product description (IF NECESSARY)

Delivery vehicle [3a] CHECK ALL THAT APPLY

- Infant formula ☐
- Yogurt ☐
- Dairy drink (e.g.Yakult) ☐
- Pill, capsule, gelcap ☐
- Mixed in with food (e.g. drops in porridge) ☐
- Other (SPECIFY, POTENTIALLY NEW CATEGORY?): _____) ☐
- Varies by participants ☐
- n/a, unclear ☐

Target of intervention CHECK ALL THAT APPLY

- Patient ☐
- Mother, patient in utero ☐
- n/a, unclear ☐

Single - Single or probiotic mixture CIRCLE ONE

- Mix of probiotics 0
- Varies by participant or unclear 1
- 1 probiotic strain only 2

Control Group: DESCRIBE CONTROL GROUP HERE, NOT ANY ADDITIONAL ACTIVE ARMS FIRST

Control category (control group or other non-probiotic control)

- None (uncontrolled study, no pre-test) 1
- Pre-test (no other control group) 2
- Placebo 3
- Non-probiotic Tx 4
- Other probiotic 5
- Synbiotics 6
- Prebiotics 7
- Other - specify: _____ 8
- N/A - unclear 9

If "Other probiotic", extract the following:

Product name _____

Product description (E.G. VSL CONTAINS…)

Delivery vehicle [3a] CHECK ALL THAT APPLY

- Infant formula ☐
- Yogurt ☐
- Dairy drink (e.g.Yakult) ☐
- Pill, capsule, gelcap ☐
- Mixed in with food (e.g. drops in porridge) ☐
- Other (SPECIFY, POTENTIALLY NEW CATEGORY?): _____) ☐
- Varies by participants ☐
- n/a, unclear ☐

Target of intervention CHECK ALL THAT APPLY

- Patient ☐
- Mother, patient in utero ☐
- n/a, unclear ☐

Single - Single or probiotic mixture CIRCLE ONE

- Mix of probiotics (genus, species, strain) 0
- Varies by participant or unclear 1
- 1 probiotic strain only 2

Intervention Group

Synbiotic - Single or mixed probiotics and prebiotics? [3e] CIRCLE ONE

Probiotic only.....0
Varies by participant, unclear.....1
Synbiotic (probiotic and prebiotics).....2

Genus investigated in the study [3b] CHECK ALL THAT APPLY

Lactobacillus ..... ☐
Bifidobacterium..... ☐
Saccharomyces ..... ☐
Streptococcus ..... ☐
Enterococcus ..... ☐
Bacillus..... ☐
Varies by participant ..... ☐
n/a ..... ☐

Notes (E.G. STREPT. USED FOR FERMENTION)_____

Details of all contained Probiotics STATE N/A WHERE NOT AVAILABLE

Genus	Species	Strain	Form (ACTIVE, LYOPHILIZED, HEAT-KILLED / TYNDALLIZED)	Potency (DOSE OF ACTIVE MICROORGANISM ACCORDING TO **PRODUCT LABEL**)
A				
B				
C				
D				
E				
F				
G				
H				

Control Group

Synbiotic - Single or mixed probiotics and prebiotics? [3e] CIRCLE ONE

Probiotic only.....0
Varies by participant, unclear 1
Synbiotic (probiotic and prebiotics).....2

Genus investigated in the study [3b] CHECK ALL THAT APPLY

Lactobacillus ..... ☐
Bifidobacterium ..... ☐
Saccharomyces ..... ☐
Streptococcus ..... ☐
Enterococcus ..... ☐
Bacillus ..... ☐
Varies by participant ..... ☐
n/a ..... ☐

Notes (E.G. STREPT. USED FOR FERMENTION)_____

Details of all contained Probiotics STATE N/A WHERE NOT AVAILABLE

Genus	Species	Strain	Form (ACTIVE, LYOPHILIZED, HEAT-KILLED / TYNDALLIZED)	Potency (DOSE OF ACTIVE MICROORGANISM ACCORDING TO **PRODUCT LABEL**)
A				
B				
C				
D				
E				
F				
G				
H				

Intervention Group

Characterize the consumption of above probiotics CHECK ALL THAT APPLY

- Mix - Each participant consumes a mixture of the above probiotic genera / only 1 strain ☐
- Varies – Genera/strain/species and mixture/single genera varies by participants ☐
- n/a ☐

Dose and frequency of above probiotics [4a]:

Dose		Frequency	
Number	Unit	Number	Per
_____	_____	_____	_____
Varies by participant ☐		Varies by participant ☐	
Varies over time ☐		Varies over time ☐	
n/a ☐		n/a ☐	

Route of administration [4c] CHECK ALL THAT APPLY

- Oral ☐
- Enteral, feeding / nasal /G tube, jenunostomy. ☐
- Intravenous catheter ☐
- Intravaginal ☐
- Topical ☐
- Other, specify:_____. ☐
- Varies by participant and or genus ☐
- n/a ☐

Duration of probiotic use during study in months [4a]

|_____|_____|_____|

- Varies – Duration varies by participant ☐
- n/a – no exact information on duration of use. ☐

Long term use – which category does the group fall into [4a]

- Short term (≤ 1 month) 0
- Medium, varies, or unclear 1
- Long term (≥1 year) 2

Control Group

Characterize the consumption of probiotics CHECK ALL THAT APPLY

- Mix - Each participant consumes a mixture of the above probiotic genera / only 1 strain ..... ☐
- Varies – Genera/strain/species and mixture/single genera varies by participants ..... ☐
- n/a ..... ☐

Dose and frequency of above probiotics [4a]:

Dose		Frequency	
Number	Unit	Number	Per
_____	_____	_____	_____
Varies by participant ..... ☐		Varies by participant ..... ☐	
Varies over time ..... ☐		Varies over time ..... ☐	
n/a ..... ☐		n/a ..... ☐	

Route of administration [4c] CHECK ALL THAT APPLY

- Oral..... ☐
- Enteral, feeding / nasal /G tube, jenunostomy. ☐
- Intravenous catheter ..... ☐
- Intravaginal ..... ☐
- Topical..... ☐
- Other, specify:_____ . ☐
- Varies by participant and or genus ..... ☐
- n/a ..... ☐

Duration of probiotic use during study in months [4a]

|_____|_____|_____|

- Varies – Duration varies by participant..... ☐
- n/a – no exact information on duration of use . ☐

Long term use – which category does the study fall into [4a]

- Short term (≤4 weeks) 0
- Medium, varies, or unclear.....1
- Long term (≥1 year) 2

Verification

Was the dose of active microorganism verified?

No, not described, none of the below apply 0
Somewhat unclear 1
Yes, verified 2
n/a, varied by participant, e.g. in observational study ..... ☐

Treatment Group (arm 1)

	Potency (dose of active microorganism) according to study test Number of viable bacteria per dose	Test used to check the amount of organisms	Culture (patent or repository / culture collection designation)
A			
B			
C			
D			
E			
F			
G			
H			

Contaminants mentioned? CIRCLE ONE

No 0
Somewhat unclear 1
Yes (specify _____) 2
n/a – no test ..... ☐

Arm 2 if applicable

	Potency (dose of active microorganism) according to study test Number of viable bacteria per dose	Test used to check the amount of organisms	Culture (patent or repository / culture collection designation)
A			
B			
C			
D			
E			
F			
G			
H			

Contaminants mentioned? CIRCLE ONE

No 0
Somewhat unclear 1
Yes (specify _____) 2
n/a – no test ..... ☐

Assessment

Assessed safety parameters - what did the study monitor (explicit description of what they looked out for) [1a, 1d]

CHECK ALL EXAMPLES THAT APPLY IF EXACT WORDING WAS USED, OTHERWISE WRITE OUT OR MARK CLEARLY IN TEXT COPY WHAT SHOULD BE ENTERED IN ACCESS

- Death ☐
- Stroke ☐
- MI ☐
- Infections (not restricted to sepsis) ☐
- Sepsis ☐
- Fungemia ☐
- Endocarditis ☐
- Deleterious physiologic/metabolic activity ☐
- Allergy ☐
- Hematocytometric values ☐
- Liver and renal function ☐
- Diarrhea ☐
- Bloating ☐
- Abdominal pain ☐
- Adverse / unexpected events, side effects (not further specified but named outcome in method section) ☐

ENTER EXACT TEXT OR INDICATE WHICH TEXT SECTION SHOULD BE ENTERED

n/a (unclear, not specified) ☐

Hospital admission or lengthened hospitalization explicitly assessed? [5]

CIRCLE ONE

- No 0
- Possible – somewhat unclear 1
- Yes 2

Was a published tool used to assess harms? [1a, d] CHECK ALL THAT APPLY

- No, unlikely 0
- Possible 1
- Yes SPECIFY_____ 2

Data collection - What method was used to record harms?

CHECK ALL THAT APPLY

- Participant diary ☐
- Participant questionnaire ☐
- Telephone interview ☐
- Healthcare provider assessment, face to face ☐
- Other SPECIFY_____ ☐
- n/a – no info provided ☐

Duration of follow-up category

CIRCLE ONE

- Short-term (<6 months) 0
- Unclear - Somewhat unclear 1
- Long-term (≥ 1 year) 2

Follow-up after consumption stopped

CIRCLE ONE

- No, consumption ongoing 0
- Consumption has stopped (recently); unclear 1
- Consumption has stopped long ago (≥ 1 year) 2

Results

Does the study describe an analysis to accomplish any of the following? CHECK ALL THAT APPLY

- Differentiate probiotics and medication effects ☐
- Differentiate effects of probiotics and confounders ☐
- Trace interactions between harms ☐
- Trace interactions between probiotics and medications (statistical interaction effect or subgroup analysis [2a] ☐
- Unclear ☐
- No, none of the above ☐

Effectiveness – according to the abstract (check conclusion) of the publication is the probiotic intervention described as effective (with regard to health outcomes other than harms) [4e] CIRCLE ONE

- No 0
- Partially, unclear 1
- Yes 2

Does the study provide a direct comparison (= within study comparison, e.g. there are 2 groups in the study or the study reports subgroup analyses) of any of the following: [4e]

- Genera [3b] ☐
- Species [3b] ☐
- Strains [3b] ☐
- Forms (e.g. active vs lyophilized) [3c] ☐
- Delivery vehicles (e.g. milk drink) [3a] ☐
- Genera mix – single vs mixture of prob.genera [3d] ☐
- Genera mix – single vs mixture of prob.genera [3d] ☐
- Synbiotic mix – probiotics only vs probiotics and prebiotics mix [3e] ☐
- Dose [4a] ☐
- Timing [4b] ☐
- Mode of administration (e.g. catheter) ☐
- n/a – none of the above ☐

Does the study provide subgroup analysis for any of the following:

- Gender [4d] ☐
- Age [4d] ☐
- Ethnicity [4d] ☐
- Disease or immunologic status (healthy vs high risk) [4d] ☐
- n/a – none of the above [4d] ☐

Assessed and Reported Harms for the Probiotics (Intervention) and Control Group

1. Blood and lymphatic system
2. Cardiac
3. Congenital, familial and genetic
4. Ear and labyrinth
5. Endocrine
6. Eye
7. Gastrointestinal
8. General and administration site conditions
9. Hepatobiliary
10. Immune system
11. Infections and infestations
12. Injury, poisoning and procedural complications
13. Investigations
14. Metabolism and nutrition
15. Musculoskeletal/connective tissue
16. Neoplasms benign, malignant and unspecified (incl. cysts, polyps)
17. Nervous system
18. Pregnancy, puerperium and perinatal conditions
19. Psychiatric
20. Renal and urinary
21. Reproductive system, breast
22. Respiratory, thoracic, mediastinal
23. Skin and subcutaneous tissue
24. Social circumstances
25. Surgical and medical procedures
26. Vascular
27. Other/Unclear, does not apply

If paper doesn't distinguish between intervention and control group, check here ☐

Probiotics Intervention Group ARM 1 IN CONTROLLED TRIALS WITH MULTIPLE ACTIVE ARMS

ENTER CODE, WRITE IN CATEGORY, AND COLLECT HARMS DATA

Code	Harm	SAE	# of patients n/a if unknown	Notes

Patients with AEs (if clearly stated) [1]: _____ NUMBER **or** _____ PERCENT

Other information, above system does not apply

Control Group ONLY DESCRIBE CONTROL GROUP HERE, NOT ANY ADDITIONAL ACTIVE ARMS

ENTER CODE, WRITE IN CATEGORY, AND COLLECT HARMS DATA

Code	Harm	SAE	# of patients n/a if unknown	Notes

Patients with AEs (if clearly stated) [1]: _____ **or** _____

NUMBER PERCENT

Other information, above system does not apply

Probiotics treatment Group

Timing and Duration: Is there information 1. on the time of onset of harm and probiotic use (e.g., when did symptoms start in relation to probiotics use) and 2. how long the harm was sustained after the intervention or exposure stopped? [4b]

n/a - unknown, not mentioned ☐

Yes (describe)..... ☐

DESCRIBE TIMING AND DURATION FOR EACH HARM SEPARATELY IF STATED

Hospitalizations: Number of (new) hospital admissions [5]

ONLY STATE 0 IF IT WAS EXPLICITLY ASSESSED

|_____|_____|

n/a - unknown, not mentioned..... ☐

Length of hospitalization [5]

|_____|_____|_____| days

n/a - unknown, not mentioned..... ☐

Did the study describe an antibiotic therapy designed to treat unintended pathology caused by the probiotics? [1g]

CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes..... 2

Was acquired antibiotic resistance and/or transferability reported? [2b]

CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes..... 2

Control Group

Timing and Duration: Is there information 1. on the time of onset of harm and probiotic use (e.g., when did symptoms start in relation to probiotics use) and 2. how long the harm was sustained after the intervention or exposure stopped? [4b]

n/a - unknown, not mentioned ☐

Yes (describe)..... ☐

DESCRIBE TIMING AND DURATION FOR EACH HARM SEPARATELY IF STATED

Hospitalizations: Number of (new) hospital admissions [5]

ONLY STATE 0 IF IT WAS EXPLICITLY ASSESSED

|_____|_____|

n/a, unknown, not mentioned ..... ☐

Length of hospitalization [5]

|_____|_____|_____| days

n/a - unknown, not mentioned..... ☐

Did the study describe an antibiotic therapy designed to treat unintended pathology caused by the probiotics? [1g]

CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes..... 2
n/a - no probiotics..... ☐

Was acquired antibiotic resistance and/or transferability reported? [2b]

CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes..... 2
n/a - no probiotics..... ☐

Probiotics treatment Group

Was any other treatment (not antibiotics) for administered organism reported? CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes, _____

Did the study describe methods for recovery of the administered organism from the gastrointestinal tract, serum, mouth, vagina? [1h] CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes 2

Control Group

Was any other treatment (not antibiotics) for administered organism reported? CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes, 2 _____
n/a - no probiotics ..... ☐

Did the study describe methods for recovery of the administered organism from the gastrointestinal tract, serum, mouth, vagina? [1h] CIRCLE ONE

No 0
Unclear – somewhat unclear 1
Yes 2
n/a, no probiotics ..... ☐

Add additional result pages and staple to the back of this form if there is more than one treatment group using probiotics

Quality Assessment

Level of evidence

Level of evidence CIRCLE ONE
I (RCT, CCT) 1
II (Cohort, case-control) 2
III (case series, case studies, mechanistic studies) 3
Unclear ☐

Reporting

Product reporting: Was the consumed genus, species and strain clearly reported or could be ascertained from the authors? CIRCLE ONE
No.....0
No, but info received from author 1
Yes 2
n/a (e.g. varies by participant) ☐

Assessment reporting: Were the assessed harms clearly reported? CIRCLE ONE
No (not clear what was monitored) 0
Somewhat unclear 1
Yes 2

Harms reporting: Were the observed (or the absence of) harms clearly reported?
CIRCLE ONE
No 0
Somewhat unclear 1
Yes (n for all groups, for all AE) 2

Susceptibility to bias

Sample selection: Does the study design protect against selection bias?
CIRCLE ONE
No (e.g. case study, opportunity sample) 0
To some extent (e.g. all patients in unit) 1
Yes (e.g. consecutive patients; explicitly representative).....2

Comparability of groups: Were the compared groups similar with regard to prognostic factors for AEs, were they sampled from the same population; or were there other differences apart from the intervention? CIRCLE ONE
No, not fully comparable 0
Probably but somewhat unclear 1
Yes (e.g. baseline values reported and comparable) 2
n/a (no control, not even pre in pre-post)..... ☐

Power: Was there a power calculation reported that considered an adverse event?
CIRCLE ONE
No 0
Very large sample or significant AE differences reported 1
Yes 2

Exposure / compliance: Can we be certain that the participants consumed probiotics as described and intended? CIRCLE ONE
No, information on compliance missing and exposure unclear 0
Probably 1
Yes, e.g. via catheter in hospital; assessed; ~80%

Surveillance: Was there a standardized and prompted assessment of harms?
CIRCLE ONE

No, passive surveillance only, spontaneously reported AE were recorded 0
Possible 1
Yes, active surveillance, structured assessment, part of protocol 2

Randomization: Was the study described as randomized and was the sequence generation for the randomization appropriate?

CIRCLE ONE

No, not described as randomized 0
Randomized but sequence unclear or not adequate (allocated alternately, or according to date of birth, hospital number) 1
Yes, randomized and adequate (table of random numbers, computer generated) 2

Allocation concealment: If study was randomized, was the treatment allocation concealed?

CIRCLE ONE

No (study personnel can predict group).....0
Unclear (possible, not enough information) 1
Yes (cannot be predicted) 2
n/a (not randomized)..... ☐

Participant blinding: CIRCLE ONE

No, unlikely 0
Possible, but unclear 1
Yes 2

Outcome assessor blinding: CIRCLE ONE

No, unlikely 0
Possible, but unclear 1
Yes 2

Dropouts: Are withdrawals and dropouts reported, including their original group assignment, were the reason described and is the drop-out rate acceptable, e.g. 20% short term, 30% long term? CIRCLE ONE

No.....0
Partially (e.g. n reported, some reasons described) 1
Yes – reported, reason described, acceptable, no dr.o.

Rate adjustment: When calculating rates of adverse events, were dropouts and withdrawals analyzed as if they remained in the study for the whole duration (unfair)? CHECK DIRECTION OF ANSWER MODE AND CIRCLE ONE

Yes 0
Possible 1
No, adjusted or no drop-outs 2
n/a (case study) ..... ☐

ITT: Was an intention to treat (ITT) analysis described for the effectiveness data? (Were all participants' data included in the analysis, according to the treatment group to which they were originally assigned, regardless of whether they completed the treatment/study? CIRCLE ONE

No, unlikely.....0
Possible 1
Yes 2
n/a (no controls, no effectiveness analysis) ☐

Confounding – confounding factors were considered in the design or analysis CIRCLE ONE

No, unlikely 0
Possible, but unclear 1
Yes (e.g. multivariate analysis, RCT with explicit similar co-interventions etc.) 2

Conflict: Is there potentially a conflict of interest CIRCLE ONE

Yes (funded by manufacturer) 0
Unclear (university aff. but no info on funding; meds donated) 1
No ('no conflict' clearly stated) 2

General Applicability

Relevance: Is the study directly relevant to answering the review questions? CIRCLE ONE

Problematic study (e.g. doubts if AE is associated with probiotics, e.g. case study, infection strain and probiotics could not be shown as being identical)
Unclear (cocktail of meds, a number of alternative explanations for AE or different AE rates; cross-over studies) 1
Yes (specific probiotic only difference between groups) 2

Appendix C. Evidence Tables

Evidence Table C1. Participant and study detail

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Abrahamsson, 2007	Sweden	L	RCT 100+	Journal		Prenatal Newborn Infant	48	Infants with family history of allergic disease	n/a		Prevention	Antibiotics Steroids
Agerbaek, 1995	Denmark	St E	RCT 11-100	Journal		Adults	0	Healthy participants	Healthy		None - nutrition	
Aihara, 2005	Japan	L	RCT 11-100	Journal	Yes	Adults	30	High-normal blood pressure; Mild hypertension	n/a	Milk protein allergy; Lactose intolerance	Treatment	
Alberda, 2007	Canada	L B St	RCT 11-100	Journal		Adults Elderly	57	Critically ill;			Prevention	Antibiotics
Allen, 2010	UK	L B	RCT 100+	Journal	Yes	Newborn Infant		Risk of atopy-infants	n/a		Prevention	
Anderson, 2003	n/a	L B St	RCT 100+	Journal		Adults Elderly	42	Elective abdominal surgery	n/a		Prevention	Antibiotics
Andriulli, 2008	Italy	L	RCT 100+	Journal		Adults Elderly	69	IBS	n/a		Treatment	
Anukam, 2006	Nigeria	L	RCT 100+	Journal		Adults Black African	100	Bacterial vaginosis	n/a	Elderly High risk	Treatment	Antibiotics
Anukam, 2008	Nigeria	L St	RCT 11-100	Journal		Adults	100	Diarrhea; Immuno-compromised			Treatment	
Anukam, 2009	Nigeria	L	RCT 11-100	Journal		Adults	100	Vaginal yeast infection	n/a	Pregnancy	Treatment	Antibiotics
Arunachalam, 2000	New Zealand	B	RCT 11-100	Journal		Adults Elderly	64	Healthy participants	Healthy	Elderly	Treatment	
Aso, 1992	Japan	L	RCT 11-100	Journal	Yes	Adults Elderly	13	Cancer	n/a		Prevention	
Aso, 1995	Japan	L	RCT 100+	Journal		Teens Adults Elderly	16	Cancer	n/a		Prevention	
Awad, 2010	Egypt	L	RCT 100+	Journal		Newborn	50	Neonate admitted to the NICU			Prevention	Antibiotics
Baerheim, 1994	Norway	L	RCT 11-100			Adults	100	Urinary tract infection	n/a	Pregnancy	Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Bajaj, 2008	USA	L B St	RCT 11-100	Journal		Adults 22 White, 3 Black		Nonalcoholic minimal hepatic encephalopathy cirrhotics	n/a		Treatment	
Banaszkiewicz, 2005	Poland	L	RCT 11-100	Journal		Toddler Children Teens		Constipation	n/a		Treatment	Lactulose
Barraud, 2010	France	L B	RCT 100+	Journal		Adults Elderly	59	Patients under mechanical ventilation		High risk Pregnancy	Treatment	Antibiotics
Barreto-Zuniga, 2001	n/a	L B	RCT 11-100	Journal		Adults Elderly	21	Alcohol-related liver cirrhosis	n/a		Treatment	
Basu, 2007	India	L	RCT 100+	Journal		Infant Toddler	47	Acute watery diarrhea	n/a		Treatment	
Basu, 2007	India	L	RCT 100+	Journal		Children	74	Persistent diarrhea	n/a		Treatment	
Basu, 2009	India	L	RCT 100+	Journal		Infant Toddler Children	51	Diarrhea	n/a		Treatment	
Beausoleil, 2007	Canada	L	RCT 11-100	Journal	Yes	Adults Elderly	52	Hospitalized patients on antibiotics	n/a	High risk	Prevention	Antibiotics
Bellomo, 1979 #13195	Switzerland	E	RCT 11-100	Journal		Newborn Infant Toddler Children	36	Diarrhea; Gastroenteritis/ enteritis; toxic dyspepsia; Diarrhea following respiratory infection	Healthy		Treatment	Antibiotics
Bertolami, 1999	Brazil	St E	C-RCT 11-100	Journal		Adults	66	Mild to moderate primary hypercholesterolemia	n/a		Treatment	Diet
Besselink, 2008	The Netherlands	L B	RCT 100+	Journal		Adults Elderly	41	Acute pancreatitis	n/a		Prevention	Antibiotics
Bin-Nun, 2005	Israel	B St	RCT 100+	Journal		Infant	44	Very low birth weight			Prevention	
Black, 1997	n/a	L B	CCT 11-100	Journal		Adults	50	Healthy participants	Healthy		None - nutrition	Antibiotics
Boge, 2009 pilot	France	L St	RCT 11-100	Journal		Elderly	65	Healthy participants	Healthy		5	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Boge, 2009	France	L St	RCT 100+	Journal		Elderly	63	Healthy participants	Healthy		5	
Borgia, 1982	Italy	St	RCT 100+	Journal		Adults Elderly	50	Chronic pulmonary tuberculosis	n/a		Treatment	Antibiotics
Bousvaros, 2005	USA	L	RCT 11-100	Journal		Children Teens White 85%, Hispanic 4%, Black 8%	37	Crohn's disease	n/a		Treatment	Steroids
Bravo, 2008	Chile	S	RCT 11-100	Journal	Yes	Adults Elderly	77	Acute infectious disease	n/a	High risk Pregnancy	Treatment	Antibiotics
Brophy, 2008	UK	L B	RCT 100+	Journal		Adults	30	Spondylarthropathy	n/a	High risk	Treatment	
Bruno, 1981	Italy	E	RCT 11-100	Journal		Adults	41	Enteritis	n/a		Treatment	
Bruzzese, 2007	n/a	L	C-RCT 11-100	Journal		Children Teens Adults	58	Cystic fibrosis; Chronically infected with pseudomonas	n/a		Treatment	Antibiotics
Bu, 2007	Taiwan	L	RCT 11-100	Journal		Toddler Children	49	Chronic constipation	n/a		Treatment	
Chen, 2005	Taiwan	L	RCT 100+	Journal		Adults Elderly	45	Partial adhesive small-bowel obstruction	n/a		Prevention	
Chen, 2010	Taiwan	L	RCT 100+	Journal		Children Teens	43	Asthma and allergic rhinitis	n/a		Treatment	Steroids
Chou, 2010	Taiwan	L B	RCT 100+	Journal	Unclear	Newborn Infant Toddler Children	56	Preterm very low birth weight infant	n/a		Prevention	
Chouraqui, 2004	France	L B St	RCT 11-100	Journal		Infant	50	Healthy participants	Healthy		Prevention	
Chouraqui, 2008	France	L B	RCT 100+	Journal	Yes	Newborn Infant	51	Healthy participants	Healthy		None - nutrition	
Chui, 2009	China	L B E	RCT 11-100	Unclear		Adults Elderly	27	Severe acute pancreatitis	n/a		Treatment	
Coccorullo, 2010	Italy	L	RCT 11-100	Journal		Infant	45	Functional chronic constipation	n/a		Treatment	
Connolly, 2005	Sweden	L	RCT 11-100	Journal	Yes	Infant		Family history of allergy	Healthy		None - nutrition	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Cooper, 2006	n/a	B	RCT 100+	Journal		Newborn Infant		Infant of HIV positive mother			None - nutrition	
Correa, 2005	Brazil	B St	RCT 100+	Journal		Infant Toddler Children	42	Inpatients receiving antibiotics	n/a	Breast feeding	Prevention	Antibiotics
Cui, 2004	China	Ba	RCT 100+	Journal	Yes	Adults	30	Diarrhea	n/a		Treatment	
Cunningham-Rundles, 2000	USA	L	CCT 11-100	Journal		Other		Immuno-compromised			Treatment	
Czaja, 2007	USA	L	RCT 11-100	Journal	Yes	Adults 83% White, 13% Asian, 3% Native American, 3% Hispanic	100	Recurrent urinary tract infection	n/a	High risk Pregnancy Lactating	Prevention	
Dadak, 2006	Czech Republic	L	RCT 11-100	Journal		Adults	17	Long-term ICU patients			Treatment	
De Preter, 2006	Belgium	S	C-RCT 11-100	Journal		Adults	51	Healthy participants	Healthy		None - nutrition	
de Roos, 1999	The Netherlands	L St	RCT 11-100	Journal		Adults	72	Healthy participants	Healthy		Treatment	
De Simone, 1992	Italy	L B	RCT 11-100	Journal		Elderly	48	Healthy participants	Healthy		None - nutrition	
De Simone, 2001	Italy	L B St	CCT 100+			Adults Elderly	50	IBS	n/a		Treatment	
Dekker, 2009	New Zealand	L	RCT 100+	Journal	Yes	Prenatal Newborn Infant Toddler 10% Maori, 79% European, 11% Other	49	Parent with allergic disease	n/a		Prevention	
Delia, 2002	Italy	L B St	RCT 100+					Cancer; Radiotherapy	n/a		Prevention	
Delia, 2007	Italy	L B St	RCT 100+	Journal				Cancer		Elderly	Treatment	Radiation therapy

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Dewan, 2007	India	L St	RCT 11-100	Journal		Toddler Children		Moderately to severely malnourished	n/a	High risk	Treatment	Antibiotics Diet
Dolin, 2009	USA	Ba	RCT 11-100	Journal	Yes	Adults Elderly 82% Caucasian	76	IBS	n/a	High risk Pregnancy Lactating	Treatment	
Dubey, 2008	India	L B St	RCT 100+	Journal	Yes	Infant Toddler		Rotavirus diarrhea	n/a		Treatment	
Duman, 2005	Turkey	S	RCT 100+	Journal	Yes	Adults	51	H. pylori; Non-ulcer dyspepsia; Peptic ulcer disease	n/a		Treatment	Antibiotics
Dupont, 2010	France	L B	RCT 11-100	Journal	Yes	Newborn Infant		Colic	n/a		Treatment	
Dylewski, 2010	Canada	L	RCT 100+	Journal		Adults Elderly	49	Taking antibiotics	n/a	High risk Pregnancy Breast feeding	Treatment	Antibiotics
Ehrstrom, 2010	Sweden	L	RCT 11-100	Journal		Adults	100	Bacterial vaginosis Vulvovaginal candidiasis	n/a	Pregnancy Breast feeding	Treatment	
Eriksson, 2005	Finland, Norway, Sweden	L	RCT 100+	Journal		Adults Caucasian 95%	100	Bacterial vaginosis	n/a	Pregnancy Breast feeding	Treatment	Antibiotics
Falck, 1999	Sweden	St	RCT 100+	Journal	Yes	Children Teens Adults		Tonsillitis	n/a	High risk	Treatment	Antibiotics
Felley, 2001	Switzerland	L	RCT 11-100	Journal		Adults	34	H. pylori	n/a	Elderly Pregnancy	Treatment	Antibiotics
Feng, 1999	China	L B St	RCT 11-100	Journal	Yes	Teens Adults	60	Diarrhea	n/a		Treatment	
Folster-Holst, 2006	Germany	L	RCT 11-100	Journal		Infant Toddler Children	36	Atopic Dermatitis	n/a		Treatment	Steroids
Forestier, 2008	France	L	RCT 100+	Journal		Adults Elderly	30	ICU patients with nasogastric feeding tube		High risk	Prevention	Antibiotics
French, 2009	Australia	L	RCT 11-100	Journal		Adults	58	Healthy participants	Healthy	Pregnancy	None - nutrition	Flu vaccination
Frohmader, 2010	Australia	L B St	RCT 11-100	Journal		Adults Elderly	33	ICU patients requiring enteral nutrition through feeding tube			Treatment	Antibiotics

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Fujimori, 2009	Japan	B	RCT 100+	Journal		Adults	58	Colitis; Ulcerative colitis	n/a		Treatment	Steroids
Gade, 1989	Denmark	St	RCT 11-100	Journal		Adults	78	IBS	n/a	Pregnancy	Treatment	
Galpin, 2005	Malawi	L	RCT 100+	Journal		Children	54	Healthy participants	Healthy	Elderly	Prevention	
Gao, 2010	China	L	RCT 100+	Journal		Adults Elderly 10% Asian	49	Diarrhea	n/a	High risk	Prevention	Antibiotics
Garcia Vilela, 2008	Brazil	S	RCT 11-100	Journal		Adults		Crohn's disease in remission	n/a	Elderly Pregnancy Breast feeding	None - nutrition	Antibiotics Steroids
Gerasimou, 2010	Ukraine	L B	RCT 11-100	Journal		Toddler Children	38	Atopic Dermatitis	n/a	High risk	Treatment	Diet Steroids
Gibson, 2008	Australia	B	RCT 100+	Journal	Yes	Infant Toddler	77	Healthy participants	Healthy	Elderly	None - nutrition	
Gill, 2001	New Zealand	B	RCT 11-100	Journal		Elderly	60	Healthy participants	Healthy		None - nutrition	
Gionchetti, 2000	Italy	L B St	RCT 11-100	Journal		Adults	43	Ulcerative colitis; Relapsing pouchitis	n/a	Infants Elderly	Treatment	
Gionchetti, 2003	Italy	L B S St	RCT 11-100	Journal		Adults	42	Ulcerative colitis	n/a	Elderly Pregnancy	Treatment	
Goossens, 2003	The Netherlands	L	RCT 11-100	Journal		Adults	55	Healthy participants	Healthy		None - nutrition	
Gracheva, 1999	Russia	B	CCT 100+	Journal	Yes			GI unspecific; Hepatitis B; Acute intestinal infections; Chronic intestinal and digestive tract conditions			Treatment	Vitamins; Symptomatic treatment
Gruber, 2007	Germany	L	RCT 100+	Journal		Infant	32	Atopic Dermatitis	Healthy	High risk	Treatment	Steroids
Guillemard, 2010	France	L St	RCT 100+	Journal		Elderly	63	Healthy participants	Healthy	High risk	Prevention	
Guyonnet, 2009	UK	L B St	RCT 100+	Journal		Adults	23	Healthy participants	Healthy	Elderly Pregnancy Breast feeding	None - nutrition	
Habermann, 2001	Germany	E	RCT 100+	Journal		Adults Elderly	50	Chronic infection; Chronic recurrent bronchitis	n/a	Pregnancy	Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Habermann, 2002	Germany	E	RCT 100+	Journal		Adults	71	Recurrent sinusitis	Healthy	Pregnancy	Treatment	
Haschke-Becher, 2008	Chile	L	RCT 11-100	Journal	Yes	Infant		Healthy participants	Healthy		None - nutrition	
Hatakka, 2008	Finland	L	C-RCT 11-100	Journal		Adults	0	Hypercholesterolemia	n/a		Treatment	
Heimburger, 1994	USA	L	RCT 11-100	Journal			20	Tube-fed patients	n/a		Prevention	Antibiotics
Hemmerling, 2009	USA	L	RCT 11-100	Journal	Yes	Adults 83% white	100	Healthy participants	Healthy	High risk Pregnancy	None - nutrition	
Higashikawa, 2009	Japan	L	RCT 11-100	Journal		Adults 97% Japanese, 3% Chinese	72	Diarrhea; Constipation	n/a	Pregnancy	Treatment	
Hilton, 1997	USA	L	RCT 100+	Journal		Teens Adults Elderly	48	Healthy participants	Healthy	Infants Elderly High risk	Treatment	
Hirata, 2002	Japan	L S	CCT 11-100	Journal		Adults	53	Hypertension	n/a		Treatment	
Hochter,1990	Germany	S	RCT 11-100	Journal			45	Diarrhea	n/a	Elderly	Treatment	
Honeycutt, 2007	n/a	L	RCT 11-100	Journal		Newborn Infant Toddler Children	34	ICU patients			Prevention	Antibiotics Steroids
Hong, 2010	Korea	L B	RCT 11-100	Journal		Adults Elderly	33	IBS	n/a	Pregnancy Breast feeding	Treatment	
Horvat, 2010	Slovenia	L	RCT 11-100	Journal		Adults Elderly	56	Adenocarcinoma of the colon	n/a	Infants	Treatment	
Ishikawa, 2002	Japan	L B S	RCT 11-100	Journal		Adults	48	Ulcerative colitis	n/a		Treatment	Steroids
Ishikawa, 2003	Japan	L	RCT 11-100	Journal		Adults	26	n/a	n/a		Prevention	
Ishikawa, 2005	Japan	L	RCT 100+	Journal		Adults Elderly	18	History of colorectal tumors	n/a	High risk	Prevention	Diet
Isolauri, 1991	Finland	L	RCT 11-100	Journal		Infant Toddler Children		Diarrhea	n/a		Treatment	
Isolauri,1995	Finland	L	RCT 11-100			Infant		Healthy participants	Healthy		Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Jirapinyo, 2002	Thailand	L B	RCT 11-100	Journal		Infant Toddler Children	33	Sepsis; Meningitis		High risk	Treatment	Antibiotics
Johansson, 1998	Sweden	L	RCT 11-100	Journal		Adults	77	Healthy participants	Healthy		None - nutrition	
Kadooka, 2010	Japan	L St	RCT 11-100	Journal		Adults	33	Over weight	n/a		Treatment	
Kajander, 2005	Finland	L B	RCT 100+	Journal		Adults	76	IBS	n/a	Pregnancy Lactating	Treatment	IBS meds, other regular medications
Kajander, 2008	Finland	L B	RCT 11-100	Journal			93	IBS	n/a	Pregnancy Lactating	Treatment	
Kajimoto, 2002	Japan	L S St	RCT 11-100	Journal		Adults	49	Mild hypertension	n/a		Treatment	
Karvonen, 2001	n/a	L	RCT 11-100		Yes	Newborn		Healthy participants	Healthy		Treatment	
Kerac, 2009	Malawi	L	RCT 100+	Journal		Infant Toddler Children Teens	46	Severe acute malnutrition			Treatment	Antibiotics Diet
Kianifar, 2009	Iran	L B	RCT 11-100	Journal		Infant Toddler Children		Moderate dehydration	n/a		Treatment	
Kim, 2006 additional groups described in #3610	USA	L B S Ba	RCT 11-100	Journal	Yes	Adults Elderly White 93%, Black 6%, Hispanic 1%	71	Functional GI disorder	n/a		Treatment	
Kim, 2006	USA	L B Ba	RCT 11-100	Journal	Yes	Adults Elderly White 93%, Black 6%, Hispanic 1%	71	Functional GI disorder	n/a		Treatment	
Kim, 2008	South Korea	L B St	RCT 100+	Journal		Adults Elderly	53	H. pylori	n/a	Pregnancy Lactating	Treatment	Antibiotics Proton pump inhibition
Kirjavainen, 2003	Finland	L	RCT 11-100	Journal		Infant		Cow's milk allergy	n/a		Treatment	
Klarin, 2008	Sweden	L	RCT 11-100	Journal		Adults Elderly	50	Intubated, ventilated, critically ill		High risk	Prevention	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Klarin,2005	Sweden	L	RCT 1-10	Journal		Adults Elderly	47	Enterally fed, critically ill			None - nutrition	Antibiotics Prokinetic agents
Knight, 2007	UK	L	RCT 100+	Journal		Adults Elderly	38	Ventilator associated pneumonia		Infants High risk Pregnancy	Prevention	
Koning, 2008	The Netherlands	L B E	RCT 11-100	Journal		Adults	63	Healthy participants	Healthy	Pregnancy Lactating	None - nutrition	Antibiotics
Kopp, 2008	Germany	L	RCT 100+	Journal		Prenatal Newborn Infant	55	Family history of atopic disease	n/a		Prevention	
Kotzampassi, 2006	Greece	L	RCT 11-100	Journal		Adults Elderly	18	Severe multiple trauma victims		High risk Pregnancy	Prevention	Antibiotics
Krasse, 2005	Sweden	L	RCT 11-100	Journal		Adults Elderly	50	Gingivitis	Healthy		Treatment	
Kuitunen, 2009	Finland	L B	RCT 100+	Journal	Yes	Prenatal Newborn Infant Toddler	44	High risk for allergy	Healthy		Prevention	
Kurugol, 2005	Turkey	S	RCT 100+	Journal		Infant Toddler Children	38	Diarrhea	n/a		Treatment	
La Rosa, 2003	Italy	Ba	RCT 100+	Journal		Infant Toddler Children Teens	44	Infection requiring antibiotics	n/a		Treatment	Antibiotics
Laitinen, 2008	Finland	L B	RCT 100+	Journal		Adults	100	Pregnant	Healthy		Treatment	Dietary counseling
Langhendries, 1995	Belgium	L B St	RCT 11-100	Journal	Yes	Newborn Infant		Healthy participants	Healthy		None - nutrition	
Larsen, 2006	Denmark	L B	RCT 11-100	Journal		Adults	65	Healthy participants	Healthy	Elderly Pregnancy	None - nutrition	
Larsson, 2008	Norway	L	RCT 11-100	Journal		Adults	100	Bacterial vaginosis	n/a	Pregnancy Breast feeding	Treatment	Antibiotics
Lata, 2009	n/a	L B	RCT 11-100	Journal		Adults Elderly	0	Acute Pancreatitis	n/a	High risk	Prevention	Antibiotics
Lawrence, 2005	USA	L	RCT 11-100	Journal		Adults Elderly	87	Diarrhea	n/a	High risk	Treatment	Antibiotics
Li, 2004	Japan	B	RCT 11-100	Journal		Newborn Infant		Low birth weight			None - nutrition	Antibiotics

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Ligaarden, 2010	Norway	L	C-RCT 11-100	Journal		Adults	69	IBS	n/a	Pregnancy Breast feeding	Treatment	
Lighthouse, 2004	n/a	L B	RCT 11-100	Journal		Adults Elderly	43	HCV-related Child B liver cirrhosis	n/a		Treatment	Antibiotics
Lin, 1989	USA	L	C-RCT 100+	Journal				n/a	n/a		None - nutrition	
Lin, 2005	Taiwan	L B	RCT 100+	Journal			50	Very low birth weight			Treatment	
Lin, 2008	Taiwan	L B	RCT 100+	Journal		Newborn Infant	45	Very low birth weight, preterm			Prevention	Antibiotics
Ljungberg, 2006	Sweden	L B	RCT 100+	Journal	Yes	Infant Toddler		Children with HLA risk genotype	n/a		Prevention	
Loguercio, 1987	Italy	E	RCT 11-100	Journal		Adults Elderly	35	Hepatic encephalopathy			Treatment	
Lonnermark, 2010	Sweden	L	RCT 100+	Journal		Adults	58	Infections requiring antibiotics	n/a	High risk	Treatment	Antibiotics
Lu, 2004	Taiwan	L	CCT 11-100		Yes			Healthy participants	Healthy		None - nutrition	
Luoto, 2010	Finland	L B	RCT 100+	Journal	Yes	Prenatal Newborn Infant Toddler Adults Caucasian	100	Healthy participants	Healthy		None - nutrition	
Mäkeläinen, 2003	Finland	B	RCT 11-100	Journal	Yes	Adults	59	Healthy participants	Healthy		None - nutrition	
Malaguarnera, 2007	Italy	B	RCT 11-100	Journal		Adults	45	Cirrhosis	n/a		Treatment	Diuretics, Beta-blockers
Malaguarnera, 2010	Italy	B	RCT 100+	Journal		Adults	50	Hepatic encephalopathy	n/a		Treatment	
Maldonado, 2009	Spain	L	RCT 11-100	Journal	Yes	Infant	51	Healthy participants	Healthy		None - nutrition	
Mandel, 2010	n/a	Ba	RCT 11-100	Journal		Adults Elderly 100% Caucasian	82	Rheumatoid arthritis	n/a	Pregnancy	Treatment	
Manley, 2007	Australia	L	C-RCT 11-100	Journal		Adults Elderly	33	Vancomycin-resistant Enterococcus	n/a		Treatment	Antibiotics

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Manzoni, 2006	Italy	L	RCT 11-100	Journal		Newborn Infant 85% White	49	Very low birth weight			Prevention	
Margreiter, 2006	Austria	L B	RCT 100+	Journal		Adults Elderly 99% Caucasian, 0.6% Black	52	Diarrhea	n/a		Treatment	
Marotta, 2003	n/a	L B	C-RCT 11-100	Journal		Adults		Ulcerative colitis	n/a		Treatment	
Marrazzo, 2006	USA	L	RCT 100+	Journal		Adults	100	Bacterial vaginosis	n/a	Pregnancy	Treatment	Antibiotics
Marseglia, 2007	Italy	B Ba	RCT 11-100	Journal	Yes	Children	51	Recurrent respiratory infections	n/a	High risk Hypersensitivity to study treatment	Prevention	
Marteau, 2004	France	L	RCT 11-100	Journal		Adults	52	Crohn's disease	n/a	Elderly Pregnancy	Prevention	Antibiotics Steroids
Martiney, 2009	Brazil	L St	RCT 11-100	Journal		Children Teens	43	Respiratory allergy	n/a		Treatment	
Martinez, 2008	Brazil	L	RCT 11-100	Journal		Teens Adults	100	Vaginal yeast Infection	n/a	High risk Pregnancy	Treatment	Antibiotics
Martinez, 2009	Brazil	L	RCT 11-100	Journal		Teens Adults	100	Bacterial vaginosis	n/a	High risk	Treatment	Antibiotics
Mayanagi, 2009	Japan	L	RCT 11-100	Journal		Adults	14	Healthy participants	Healthy		None - nutrition	
McFarland, 1994	USA	S	RCT 100+	Journal	Yes	Adults Elderly	77	Clostridium difficile-associated disease	n/a	High risk Pregnancy	Treatment	Antibiotics
McFarland, 1995	USA	S	RCT 100+	Journal	Yes	Adults Elderly	35	Patients on beta-lactam antibiotics	n/a		Treatment	Antibiotics
McNaught, 2002	UK	L	RCT 100+	Journal		Adults Elderly	42	Undergoing major elective abdominal surgery	n/a		Treatment	Antibiotics
Merenstein, 2009	USA	L B S	RCT 100+	Journal		Toddler Children	49	Treated with antibiotics for upper respiratory tract infection	n/a		Treatment	Antibiotics
Merenstein, 2010	USA	L St	RCT 100+	Journal		Children	49	Healthy participants	Healthy		Prevention	Antibiotics

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Metts, 2003	USA	L	RCT 11-100	Journal		Adults	100	Recurrent Candida vulvovaginitis	n/a	High risk Pregnancy	Prevention	
Miele, 2009	Italy	L B St	RCT 11-100	Journal	Yes	Toddler Children Teens	45	Ulcerative colitis	n/a		Treatment	Steroids
Millar, 1993	UK	L	RCT 11-100	Journal				Preterm infant			Prevention	
Mimura, 2004	Italy, UK	L B St	RCT 11-100	Journal		Adults	44	Pouchitis	n/a		Prevention	Antibiotics
Miyaji, 2006	Japan	L	RCT 11-100	Journal		Adults Elderly	59	H. pylori; Upper gastrointestinal symptoms	n/a		Treatment	
Morrow, 2010	USA	L	RCT 100+	Journal	Yes	Adults Elderly Caucasian 79%, Black 13%, Hispanic 8%	41	Mechanical ventilation		High risk Pregnancy	Prevention	Antibiotics
Mukerji, 2009	USA	L	RCT 11-100	Journal		Adults 93% White	57	Chronic inflammatory rhinosinusitis	n/a	High risk Pregnancy	Treatment	Steroids
Naito, 2008	Japan	L	RCT 100+	Journal		Adults Elderly	19	Cancer	n/a		Prevention	
Newcomer, 1983	USA	L	RCT 11-100	Journal	Yes	Adults Elderly		Lactase-deficiency	n/a		None - nutrition	
Niers, 2009	The Netherlands	L B	RCT 100+	Journal		Prenatal Newborn Infant Toddler	60	Family history of allergic disease	n/a		Prevention	
Niv, 2005	Israel	L	RCT 11-100	Journal		Teens Adults	67	IBS	n/a	Pregnancy	Treatment	
Nobuta, 2009 RCT (effect on bowel movement), 5 groups, group 3 not extracted (AE not mentioned)	Japan	L	RCT 11-100	Journal		Adults Elderly	73	Tendency to constipation	Healthy		None - nutrition	
O'Mahony, 2005	Ireland	L	RCT 11-100	Journal		Adults Elderly White	64	IBS	n/a	High risk Pregnancy	Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Ojetti, 2010	Italy	L	RCT 11-100	Journal		Adults	85	Lactose intolerant	n/a	Infants Elderly	Treatment	
Olah, 2005	Hungary	L	RCT 11-100	Journal		Adults Elderly	84	Pancreatitis			Treatment	Antibiotics
Olivares, 2006	Spain	L St	RCT 11-100	Journal		Adults	50	Healthy participants	Healthy		None - nutrition	
Osterlund, 2007	Finland	L	RCT 100+	Journal		Adults Elderly	49	Cancer	n/a	Pregnancy Lactating	Treatment	Diet Chemotherapy
Ouwehand, 2009	Finland	L B	RCT 11-100	Journal		Children Teens	60	Birch pollen allergy	n/a		Treatment	
Ozkinay, 2005	Turkey	L	RCT 100+	Journal		Adults Elderly	100	Vaginal infection	n/a	High risk Pregnancy	Treatment	Antibiotics
Panigrahi, 2008	India	L	RCT 11-100	Journal	Yes	Newborn	61	Healthy participants	Healthy		None - nutrition	
Parent, 1996	Belgium	L	RCT 11-100	Journal		Adults	100	Bacterial vaginosis	n/a		Treatment	
Parfenov, 2005	Russia	L B St	CCT 11-100	Journal		Adults	75	Hemorrhoids	n/a		Treatment	Antiacids and vitamins if needed
Parfenov, 2005	Russia	L St	CCT 11-100	Journal		Adults	60	Hemorrhoids	n/a		Treatment	Vitamins (both groups)
Parra, 2004	Spain	L	RCT 11-100	Journal		Adults	53	Healthy participants	Healthy		5	
Passeron, 2005	France	L	RCT 11-100	Journal		Children		Atopic Dermatitis	n/a	High risk	Treatment	Steroids Immune suppressant
Peral, 2009	Argentina	L	RCT 11-100	Journal		Adults		Burn patients		Pregnancy Breast feeding	Treatment	
Pereg, 2010	Israel	L B St	RCT 11-100			Adults Elderly		Cirrhosis	n/a		Treatment	
Petschow, 2005	USA	L	RCT 11-100	Journal		Newborn Infant	49	Healthy participants	Healthy		None - nutrition	
Prantera, 2002	n/a	L	RCT 11-100	Journal		Adults Elderly	36	Crohn's disease	n/a	Pregnancy	Treatment	Antidiarrhoeals; Colestyramine
Pregliasco, 2008 #5328 stage 1	Italy	L B	RCT 100+	Journal				Healthy participants	Healthy	Pregnancy Breast feeding	Prevention	
Pregliasco, 2008 #5328, 3 studies, same with multiple arms reported in 1 publication; stage 3	Italy	L B	RCT 100+	Journal				Healthy participants	Healthy	Pregnancy Breast feeding	Prevention	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Pregliasco, 2008 stage 1	Italy	L B	RCT 100+	Journal		Teens Adults		Healthy participants	Healthy	Pregnancy Breast feeding	Prevention	
Puccio, 2007	Italy	B	RCT 100+	Journal	Yes	Newborn Infant	54	Healthy participants	Healthy		None - nutrition	
Rampengan, 2010	Indonesia	L	RCT 11-100	Journal		Children Teens	48	Lactose malabsorption	n/a		Treatment	
Ranganathan	Canada	L B St	C-RCT 11-100	Journal		Adults Elderly White 4, Hispanic 1; Asian 10, Black 1	25	Chronic kidney disease stage 3 and 4	n/a	Pregnancy	Treatment	
Rautava, 2008	Finland	L B	RCT 11-100	Journal		Infant	51	Healthy participants	Healthy		Prevention	
Rayes, 2002	n/a	L	RCT 11-100	Journal		Adults Elderly	47	Undergoing major abdominal surgery;	n/a		Prevention	Antibiotics Diet
Rayes, 2002	Germany	L	RCT 11-100	Journal		Adults Elderly	48	Liver transplant; Stomach, pancreas or liver surgery		Sever renal insufficiency; Cerebral disorders; Emergency operation	Treatment	Antibiotics
Rayes, 2005	n/a	L	RCT 11-100	Journal		Adults	42	Liver transplant		Decompensated renal insufficiencies	Prevention	Antibiotics Immune suppressant
Rayes, 2007	n/a	L	RCT 11-100	Journal		Adults Elderly	44	Undergoing pylorus-preserving pancreticoduodenectomy	n/a		Prevention	Antibiotics
Reid, 1992	Canada	L	RCT 11-100	Journal		Adults	100	Acute lower urinary tract infection	n/a	Pregnancy	Prevention	Antibiotics
Reid, 1995	Canada	L	RCT 11-100	Journal		Adults	100	Recurrent urinary tract infections	n/a		Prevention	
Ren, 2010	China	B	RCT 11-100	Journal		Prenatal	44	Premature infants			Prevention	Antibiotics
Reuman, 1986	USA	L	RCT 11-100	Journal		Newborn		Premature infants			None - nutrition	Antibiotics
Richelsen, 1996	Denmark	St E	RCT 11-100	Journal		Adults Elderly	48	Healthy participants	Healthy		None - nutrition	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Rio, 2002	Argentina	L	RCT 11-100	Journal		Infant Toddler		Undernourished	n/a		Prevention	
Roos, 1996	Sweden	St	RCT 100+	Journal		Children Teens Adults	65	Recurrent streptococcal pharyngotonsillitis	n/a	High risk	Prevention	
Roos, 2001	Sweden	St	RCT 100+	Journal		Infant Toddler Children		Recurrent otitis media	n/a	High risk	Prevention	Antibiotics
Rose, 2010	Germany	L	RCT 100+	Journal		Infant Toddler	0	Wheezing episodes; Family history of atopic disease	n/a		Prevention	Antibiotics Steroids
Rosenfeldt, 2002	Denmark	L	RCT 11-100	Journal		Infant Toddler Children	60	Diarrhea	n/a	Elderly	Treatment	
Rosenfeldt, 2003 2 studies in 1 paper #13297	Denmark	L	C-RCT 11-100	Journal	Yes	Teens Adults	0	Healthy participants	Healthy		None - nutrition	
Rouge, 2009	France	L B	RCT 11-100	Journal		Newborn	43	Very low birth weight preterm infants			Treatment	
Ruiz-Palacios, 1996	n/a	L B	RCT 11-100		Yes	Infant Toddler Children		Healthy participants	Healthy		Prevention	
Saavedra, 2004	USA	B St	RCT 100+	Journal	Yes	Infant Toddler	51	Healthy participants	Healthy		None - nutrition	
Safdar, 2008	USA	L	RCT 11-100	Journal	Yes	Adults Elderly	2	Inpatients receiving or expected to receive antibiotics	n/a		Prevention	Antibiotics
Sahagun-flores, 2007	Mexico	L	RCT 11-100	Journal		Adults	48	H. pylori	n/a	Pregnancy	Treatment	Antibiotics
Saint-Marc, 1995	France	S	RCT 11-100	Journal		Adults	6	Immuno-compromised; AIDS-related diarrhea		Infants	Treatment	Necessary medications
Salminen, 1988	Finland	L	RCT 11-100	Journal		Adults Elderly	100	Gynecologic malignancies	n/a		Prevention	Radiation
Salminen, 2004	Finland	L	C-RCT 11-100	Journal	Yes	Adults	18	Diarrhea; Immuno-compromised	n/a	Pregnancy	Treatment	Antibiotics HAART

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Samanta, 2008	India	L B	RCT 100+	Journal		Newborn		Preterm infant; very low birth weight			Prevention	
Satokari, 2001 13281	Finland	B	RCT 11-100	Journal		Adults	90	Healthy participants	Healthy		5	
Savino, 2006	Italy	L	RCT 11-100	Journal		Newborn Infant	47	Colic	n/a		Treatment	
Sazawal, 2010	India	B	RCT 100+	Journal		Toddler Children		n/a	n/a	High risk	Prevention	
Scalabrin, 2009	USA	L	RCT 100+	Journal	Yes	Newborn Infant	50	Healthy participants	Healthy	High risk	None - nutrition	
Schrezenmeir, 2004	Germany	L B	RCT 100+	Journal		Toddler Children Caucasian	44	Acute bacterial infection	n/a		Treatment	Antibiotics
Schultz, 2004	n/a	L	RCT 11-100	Journal				Crohn's disease	n/a		Treatment	Antibiotics Steroids
Seppo, 2003	Finland	L	RCT 11-100	Journal		Adults	51	Hypertension	n/a		Treatment	
Sierra, 2010	Spain	L	RCT 11-100	Journal	Yes	Adults	50	Healthy participants	Healthy		None - nutrition	
Simons, 2006	Australia	L	RCT 11-100	Journal		Adults	64	Healthy participants	Healthy		None - nutrition	
Simren, 2010	Sweden	L B St	RCT 11-100	Journal		Adults	70	IBS	n/a	Pregnancy	Treatment	
Song, 2010	Korea	S	RCT 100+	Journal		Teens Adults Elderly	40	H. pylori	n/a	High risk Pregnancy Lactating	Treatment	Antibiotics
Songisepp, 2005	Estonia	L	RCT 11-100	Journal		Adults	38	Healthy participants	Healthy		None - nutrition	
Songisepp, 2005	Estonia	L	CCT 11-100	Journal		Adults	56	Healthy participants	Healthy		None - nutrition	
Sood, 2009	India	L B St	RCT 100+	Journal	Yes	Adults	19	Ulcerative colitis	n/a	Pregnancy	Treatment	
Spanhaak, 1998	The Netherlands	L	RCT 11-100	Journal		Adults	0	Healthy participants	Healthy		None - nutrition	
Stockert, 2007	n/a	E	RCT 11-100	Journal		Children Teens		Asthma	n/a	High risk	Treatment	Steroids
Stotzer, 1996	n/a	L	C-RCT 11-100	Journal		Elderly		Small intestinal bacterial overgrowth	n/a		Treatment	Antibiotics
Stratiki, 2007	Greece	B	RCT 11-100	Journal		Newborn		Preterm infant			None - nutrition	
Sullivan, 2003	Sweden	L B	RCT 11-100	Journal		Adults	91	Healthy participants	Healthy	Pregnancy	None - nutrition	Antibiotics

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Sykora, 2005	Czech Republic	L	RCT 11-100	Journal		Children Teens	60	H. pylori	n/a		Treatment	Antibiotics Proton pump inhibition
Tamura, 2007	Japan	L	RCT 100+	Journal		Adults	61	Allergic rhinitis	n/a		Prevention	
Taylor, 2007	Australia	L	RCT 100+	Journal		Newborn Infant		Risk for atopic dermatitis	n/a		Prevention	
Tempe, 1985	France	S	RCT 11-100	Journal		Adults Elderly		ICU patients on enteral feeding		Illnesses of digestive tract	Prevention	
Teran, 2008	Bolivia	L B S	RCT 11-100	Journal		Newborn Infant Toddler	47	Acute rotavirus diarrhea	n/a		Treatment	
Thomas, 2001	USA	L	RCT 100+	Journal		Adults Elderly	46	Hospitalized	n/a	InfantsHigh risk	Treatment	Antibiotics
Tomoda, 1991	Japan	L B St	CCT 1-10	Journal		Adults	50	Healthy participants	Healthy		None - nutrition	
Tsuchiya, 2004	n/a	L B	CCT 11-100	Journal		Adults	80	IBS	n/a	Elderly	Treatment	
Turchet, 2003	Italy	L	RCT 100+	Journal		Adults Elderly	67	Healthy participants	Healthy	High risk	Prevention	Flu vaccine
Tursi, 2004	Italy	L B St	RCT 11-100	Journal	Yes	Adults Elderly	36	Ulcerative colitis	n/a	Pregnancy	Treatment	
Tursi, 2008	Italy	L	CCT 11-100	Journal		Adults Elderly	56	Diverticular disease of the colon	n/a		Prevention	
Tursi, 2010	Italy	L B St	RCT 100+	Journal		Adults	35	Ulcerative colitis	n/a		Treatment	Immune suppressant
Underwood, 2009	USA	L	RCT 11-100	Journal		Newborn	34	Premature infants			None - nutrition	Antibiotics
Urban, 2008	South Africa	B	RCT 100+	Journal		Newborn Infant	48	Infant of HIV infected mother;	n/a		None - nutrition	
Urbansek, 2001	Hungary	L	RCT 100+	Journal	Yes	Adults Elderly	74	Cancer; Diarrhea; Radiation induced diarrhea			Treatment	Radiation
Van der Aa, 2010	The Netherlands	B	RCT 11-100	Journal		Infant	34	Atopic Dermatitis	n/a		Treatment	Steroids
Van Gossum, 2007	n/a	L	RCT 11-100	Journal		Adults	47	Crohn's disease	n/a		Prevention	Antibiotics Steroids
Velaphi, 2008	South Africa	B	RCT 100+	Journal		Infant	50	Infant of HIV mother	n/a	High risk	None - nutrition	Nevirapine
Vendt, 2006	Estonia	L	RCT 100+	Journal		Infant	50	Healthy participants	Healthy		None - nutrition	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Vleggaar, 2008	The Netherlands	L B	C-RCT 11-100	Journal		Adults Elderly	7	Primary sclerosing cholangitis	n/a	Pregnancy	Treatment	
Vlieger, 2009	The Netherlands	L B	RCT 100+	Journal	Yes	Newborn Infant	53	Healthy participants	Healthy		None - nutrition	
Wada, 2010	Japan	B	RCT 11-100	Journal		Toddler Children Teens	60	Malignancy, receiving chemotherapy		Pregnancy	Prevention	Chemo-therapy
Wang, 2004	China	L St	RCT 11-100	Journal		Children Teens	48	Perennial allergic rhinitis	n/a	High risk Pregnancy	Treatment	
Wang, 2007	Japan	B	RCT 11-100	Journal		Newborn	49	Low birth weight infant			None - nutrition	Antibiotics
Weizman, 2005	Israel	B	RCT 100+	Journal		Infant	52	Healthy participants	Healthy		Prevention	
Weizman, 2006	Israel	B	RCT 11-100	Journal	Yes	Newborn Infant	32	Healthy participants	Healthy	Elderly	None - nutrition	
Weston, 2005	Australia	L	RCT 11-100	Journal		Infant Toddler	46	Atopic Dermatitis	n/a		Treatment	Steroids
Wewalka, 2002	Austria	L	RCT 11-100	Journal	Yes	Adults	100	Bacterial vaginosis	n/a	Pregnancy	Treatment	
Wheeler, 1997	USA	L St	C-RCT 11-100	Journal		Teens Adults	67	Asthma	n/a		Treatment	Anti-inflammatories
Wildt, 2006	Denmark	L B	RCT 11-100	Journal		Adults Elderly	7	Collagenous colitis	n/a	Elderly Pregnancy	Treatment	Anti-diarrheal drugs
Williams, 2008	UK	L B	RCT 11-100	Journal		Adults	86	IBS	n/a	Pregnancy Lactating	Treatment	
Wind, 2010	The Netherlands	L	RCT 11-100	Journal	Yes	Adults	59	Healthy participants	Healthy	Pregnancy	None - nutrition	
Wolf, 1994	USA	L	RCT 11-100	Journal	Yes	Adults Elderly	0	Healthy participants	Healthy		None - nutrition	
Wolf, 1998	USA	L	RCT 11-100	Journal	Yes	Adults		Immuno-compromised		InfantsElderly	Treatment	
Worthley, 2009	Australia	B	C-RCT 11-100	Journal		Adults Elderly	35	Healthy participants	Healthy		None - nutrition	
Xia, 2010	China	L	RCT 11-100	Journal		Adults Elderly	42	Cancer	n/a		Treatment	
Xiang, 2006	China	E Ba	RCT 11-100	Journal		Adults	54	Ulcerative colitis	n/a		Treatment	Antibiotics
Xiao, 2003	Japan	L B St	RCT 11-100	Journal		Adults	0	Healthy participants	Healthy		None - nutrition	
Xiao, 2003	China	L	RCT 100+	Journal		Teens Adults Elderly	39	Chronic diarrhea	n/a		Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Yang, 2008	China	L B St	RCT 100+	Journal		Adults	100	Constipation	n/a		Treatment	
Yao-Zong, 2004	China	L E	RCT 100+	Journal		Adults Elderly Chinese/Asian	37	Diarrhea	n/a	Pregnancy Lactating	Treatment	
Yonekura	Japan	L	RCT 100+	Journal		Adults Asian	69	Cedar pollinosis	n/a	Pregnancy	Treatment	
Zhang, 2010	China	B	RCT 11-100	Journal	Yes	Adults Elderly	50	Cancer	n/a		Prevention	Antibiotics
Ziegler, 2003	USA	B	RCT 100+	Journal		Newborn Infant Caucasian		Healthy participants	Healthy		None - nutrition	
Zocco, 2003 #3960	Italy	L	RCT 11-100			Adults	44	Ulcerative colitis	n/a	High risk Pregnancy Antibiotic treatment	Treatment	
An, 2010	Korea	L B	Case Series 11-100	Journal		Elderly	58	Chronic constipation	n/a		Treatment	
Barrett, 2008	Australia	L	Case Series 11-100	Journal		Adults Elderly	72	IBS	n/a		Treatment	
Beck, 1961	USA	L	Case Series 11-100	Journal		Children Teens Adults Elderly	54	Various abdominal symptoms	n/a		Treatment	
Bekkali, 2007	The Netherlands	L B	Case Series 11-100	Journal		Children Teens	50	Constipation	n/a		Treatment	
Bellomo, 1979	Switzerland	E	Case Series 100+	Journal		Mixed	44	Gastroenteritis; Enteritis; Toxic dyspepsia; Enteritis following respiratory infection	Healthy		Treatment	Antibiotics
Benchimol, 2004	Canada	L B	Case Series 1-10	Journal		Children	50	Cancer; Diarrhea; Colitis			Treatment	Antibiotics Immune suppressant
Berman, 2006	USA	L B	Case Series 1-10	Journal		Adults	0	Healthy participants	Healthy	High risk Pregnancy Lactating	Treatment	
Bibiloni, 2005	Canada, Italy, US	L B St	Case Series 11-100	Journal	Yes	Adults	53	Ulcerative colitis	n/a		Treatment	Steroids Azathioprine or 6-mercaptopurine

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Bruce, 1988	Canada	L	Case Series 1-10	Journal		Teens Adults	100	Recurrent urinary tract infections	n/a		Treatment	
Bruni, 2008	Italy	L	Case Series 11-100	Journal	Yes	Infant Toddler Children Teens		Atopic Dermatitis; Cow's milk allergy	n/a		None - nutrition	
Carlsson, 2009	Sweden	L	Case Series 11-100	Journal		Elderly	87	Dementia; Constipation	n/a	High risk	Treatment	Antibiotics
Cobo Sanz, 2006	Spain	L St	Case Series 100+	Journal		Children		Healthy participants	Healthy		None - nutrition	
Colecchia, 2006	Italy	B	Case Series 100+	Journal	Yes	Adults Elderly	61	IBS	n/a		Treatment	
Di Pierro, 2009	Italy	L	Case Series 100+	Journal		Adults	100	Acute vulvovaginal affection	n/a	High risk Pregnancy	Treatment	
Dughera, 2007	Italy	B	Case Series 100+	Journal		Adults	71	IBS	n/a		Treatment	
Elmer, 1995	USA	S	Case Series 1-10	Journal	Yes	Adults	0	Diarrhea; Immuno-compromised			Treatment	Antifungal
Fukuda, 2008	Japan	B	Case Series 100+	Journal	Yes	Adults Elderly	84	Constipation and abdominal disorder	n/a	Pregnancy	Treatment	
Gabrielli, 2009	Italy	Ba	Case Series 11-100		Yes	Adults	65	Small intestinal bacterial over growth	n/a		Treatment	
Garrido, 2005	n/a	L Ba	Case Series 1-10	Unclear		Adults	50	Healthy participants	Healthy		None - nutrition	
Gionchetti, 2007	Italy	L B St	Case Series 11-100	Journal			44	Ulcerative colitis; Mild pouchitis	n/a	High risk Pregnancy	Treatment	
Glintborg, 2006	Denmark	L	Case Series 11-100	Journal		Adults		H. pylori	n/a		Treatment	
Gniwotta, 1977	Germany	S	Case Series 100+	Journal				Diarrhea			Treatment	
Gotteland, 2003	Chile	L	Case Series 11-100			Adults	83	H. pylori	n/a		Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Gruenwald, 2002	Germany	L B	Case Series 11-100	Journal		Adults	81	Stress and exhaustion	Healthy	Elderly High risk	Treatment	Vitamins
Hensgens, 1976	Belgium	L	Case Series 1-10	Journal		Adults Elderly	17	Granulopenia			Prevention	Antibiotics
Huynh, 2009	Canada	L B St	Case Series 11-100	Journal	Yes	Children Teens	61	Ulcerative colitis	n/a	Pregnancy Severe disease; Lactating	Treatment	Steroids Immune suppressant
Karimi, 2005	The Netherlands	L B St	Case Series 11-100	Journal	Yes	Adults	59	Crohn's disease; Ulcerative colitis	n/a	Pregnancy	Treatment	Immune suppressant
Kawamura,1981	Japan	L	Case Series 11-100	Journal		Adults Elderly	53	Irregular bowel movement and abdominal discomfort	n/a		Treatment	
Kirchhelle, 1996	Germany	S	Case Series 11-100	Journal		Adults Elderly	52	Persistent traveler's diarrhea	Healthy		Treatment	Antibiotics
Kitajima, 1997	Japan	B	Case Series 11-100	Journal	Yes	Newborn		Preterm infant			None - nutrition	
Lamiki, 2010	Italy	L B	Case Series 11-100	Journal	Yes	Adults Elderly	1	Diverticular disease of the colon	n/a		Prevention	
Lee, 2010	New Zealand	L B S St	Case Series 11-100	Journal		Adults Elderly	0	Rheumatoid arthritis	n/a	Pregnancy	None - nutrition	
Lombardo, 2009	Italy	L	Case Series 11-100	Journal	Yes	Adults Elderly	62	IBS	n/a		Treatment	
Luoto, 2010	Finland	L	Case Series 100+		Yes	Newborn		Very low birth weight			Prevention	
Malin, 1996 Study 2	Finland	L	Case Series 11-100	Journal		Children Teens	50	Juvenile chronic arthritis	n/a		Treatment	
Malkov, 2006	Russia	Ba	Case Series 1-10	Journal		Adults Elderly	70	Cancer			Treatment	
Mego, 2005	Slovak Republic	E	Case Series 11-100	Journal	Yes	Adults		Cancer; Relapsed acute leukemia	n/a		Treatment	Antibiotics Chemotherapy; immunomodulants

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Mego, 2006	Slovak Republic	E	Case Series 11-100	Journal		Adults Elderly		Cancer			Prevention	
Michetti, 1999	Switzerland	L	Case Series 11-100	Journal		Adults	40	H. pylori	n/a	Pregnancy Breast feeding	Treatment	
Muting, 1968	Germany	B	Case Series 11-100	Journal		Children Teens Adults		Chronic liver disease	n/a		Treatment	
Nobuta, 2009 #13315	Japan	L	Case Series 11-100	Journal	Yes	Adults		Cancer	Healthy		None - nutrition	
Reid, 2001	Canada	L	Case Series 1-10	Journal			100	Bacterial vaginosis	n/a		Treatment	
Rosenfeldt, 2003 #6738 2 studies in 1 paper	Denmark	L	Case Series 11-100	Journal	Yes	Adults Elderly		Previous benign polyps or family history of polyposis	n/a		None - nutrition	
Sakamoto, 2001	n/a	L	Case Series 11-100	Journal		Adults	6	H. pylori	n/a		Treatment	
Schneider, 2005	n/a	S	Case Series 11-100	Journal		Adults	28	Healthy participants; Patient on long term total enteral nutrition	n/a		None - nutrition	
Shen, 2005	USA	L B St	Case Series 11-100	Journal		Adults	42	Ulcerative colitis Antibiotic dependent pouchitis	n/a		Treatment	Antibiotics
Srinivasan, 2006	UK	L	Case Series 11-100	Journal	Yes	Infant Toddler Children Teens	43	Critically ill children in ICU		High risk	Treatment	
Tasli, 2006	Turkey	L	Case Series 11-100	Journal		Adults	56	Behcet's syndrome	n/a		Treatment	
van Bodegraven 2004	n/a	L B St	Case Series 11-100			Adults	83	IBD related spondyloarthropathy	n/a		Treatment	
Weiss, 2010	Israel	L B St	Case Series 1-10	Journal		Teens Adults	30	Cystic fibrosis	n/a		Treatment	Antibiotics

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Yim, 2006	Korea	L B	Case Series 11-100	Journal	Yes	Children Teens Adults		Atopic Dermatitis	n/a		Treatment	
Zahradnik, 2009	USA	St	Case Series 11-100	Journal	Yes	Adults		Healthy participants	Healthy		None - nutrition	
Zahradnik, 2009	USA	St	Case Series 11-100	Journal	Yes	Adults		Healthy participants	Healthy		None - nutrition	
Barton, 2001	n/a	L E	Case Study 1-10	Journal	Yes	Infant	100	Gastroschisis; Preterm infant			Treatment	Antibiotics
Bassetti, 1998	Switzerland	S	Case Study 1-10	Journal	Yes	Adults	100	Arthritis, polyarteritis nodosa; Livedo reticularis; Raynaud's phenomenon; Renal failure	n/a		Treatment	Antibiotics Immune suppressant
Burkhardt, 2005	n/a	S	Case Study 1-10	Journal	Yes	Adults White	0	Spastic tetra paresis	n/a		Prevention	
Cesaro, 2000	Italy	S	Case Study 1-10	Journal	Yes	Infant	0	Acute myeloid leukemia			Prevention	Antibiotics Chemotherapy
Cherifi, 2004	Belgium	S	Case Study 1-10	Journal		Elderly	100	Colitis	n/a		Treatment	Antibiotics
Conen, 2009	Switzerland	L	Case Study 1-10		Yes	Adults	100	Diarrhea; Ulcerative colitis	n/a		Treatment	Steroids Immune suppressant
De Groote, 2005	USA	L	Case Study 11-100	Journal	Yes	Infant	0	Short gut syndrome			Treatment	Antibiotics
Force, 1995	France	S	Case Study 1-10	Journal	Yes	Adults	100	AIDS; Chronic diarrhea			Treatment	
Fredenucci, 1998	France	S	Case Study 1-10	Journal	Yes	Adults	0	Diarrhea	n/a		Treatment	Antibiotics Steroids
Hennequin, 2000	France	S	Case Study 1-10	Journal	Yes	Toddler Adults Elderly	25	Cancer; Ileal atresia; COPD			Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Henry, 2004	Belgium	S	Case Study 1-10	Journal	Yes	Elderly	0	Cancer; Diarrhea			Treatment	Antibiotics Chemotherapy; Radiation
Hwang, 2009	Korea	S	Case Study 1-10	Unclear	Yes	Infant	0	Soy-induced food protein-induced enterocolitis syndrome	n/a		Treatment	Antibiotics
Jensen, 1974	USA	S	Case Study 1-10	Journal	Yes	Elderly	0	Healthy participants	Healthy		None - nutrition	
Kniehl, 2003	Germany	Ba	Case Study 1-10	Journal	Yes	Adults Elderly	0	Myocardial infarction and upper GI bleeding; Coronary bypass surgery, caecal perforation; Tachyarrhythmia, fever, and diarrhea			Treatment	Antibiotics
Ku, 2006	China	L B	Case Study 1-10	Journal	Yes	Children Chinese	0	Cancer; Short bowel syndrome			Treatment	
Kunz, 2004	USA	L	Case Study 1-10	Journal	Yes	Newborn Infant	0	Short gut syndrome; Gastroschisis			Treatment	Antibiotics
Land, 2005	n/a	L	Case Study 1-10	Journal	Yes	Infant Children 100% White	50	Diarrhea			Varies	Antibiotics
LeDoux, 2006	USA	L	Case Study 1-10	Journal	Yes	Adults	0	AIDS; Hodgkin's disease			5	Antibiotics
Lestin, 2003	Germany	S	Case Study 1-10	Journal	Yes	Adults	0	Diabetes; Peripheral arterial disease; Bypass (after PB admin)			Treatment	Antibiotics
Lherm, 2002	France	S	Case Study 1-10	Journal	Yes			Diarrhea; Hospitalized in medical and surgical ICU			Treatment	
Lolis, 2008	Greece	S	Case Study 1-10	Journal	Yes	Adults	0	Acute pulmonary edema			Treatment	Antibiotics

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Lungarotti, 2003	Italy	S	Case Study 1-10		Yes	Newborn	0	Preterm infant	n/a		Prevention	
Mackay, 1999	n/a	L St	Case Study 1-10	Journal	Yes	Elderly	0	Mitral valve prolapse; Mild mitral value regurgitation	n/a		None - nutrition	Antibiotics
Munakata, 2010	Japan	L St	Case Study 1-10	Journal	Yes	Children	100	Short bowel syndrome	n/a		Treatment	
Muñoz, 2005	Spain	S	Case Study 1-10	Journal	Yes	Elderly	100	Diarrhea; Heart surgery	n/a		Treatment	Antibiotics
Niault, 1999	France	S	Case Study 1-10	Unclear	Yes		100	COPD	n/a		Treatment	Antibiotics
Oggioni, 1998	Italy	Ba	Case Study 1-10	Journal	Yes	Elderly	0	Cancer; Chronic lymphocytic leukemia			5	
Oh, 1979	USA	L	Case Study 1-10	Journal	Yes	Adults	0	Diarrhea; Short bowel syndrome	n/a		Treatment	
Ohishi, 2010	Japan	B	Case Study 1-10	Journal	Yes	Newborn	100	Omphalocele			None - nutrition	
Perapoch, 2000	Spain	S	Case Study 1-10	Journal	Yes	Infant	0	Congenital cardiopathy			Treatment	
Piarroux, 1999	France	S	Case Study 1-10		Yes			n/a	n/a		5	
Piechno, 2007	France	S	Case Study 1-10		Yes	Adults	0	Cancer; Diarrhea; Colitis			Treatment	Antibiotics
Pletinex, 1995	Belgium	S	Case Study 1-10	Journal	Yes	Toddler	100	Diarrhea	n/a		Treatment	Antibiotics
Presterl, 2001	n/a	L	Case Study 1-10	Journal	Yes	Adults White	0	Diabetes insipidus; Biscuspid aortic valve	n/a		None - nutrition	Intranasal octreotide
Rautio, 1999	Finland	L	Case Study 1-10		Yes	Elderly	100	Hypertension; Diabetes	n/a		Treatment	

Evidence Table C1. Participant and study detail (continued)

Author, Year	Country	Gen-era	Study Design Sample Size Category	Source	Safety Assess-ment Main Aim	Age Ethnicity	% Female	Disease/ Immunologic Status Subgroups	General Health	Exclusion Criteria	Probiotic Function	Cotreatments
Richard, 1988	Belgium	Ba	Case Study 1-10	Journal	Yes	Adults Elderly	50	Head trauma; Endometrial carcinoma; Stroke			Treatment	
Rijnders, 2000	n/a	S	Case Study 1-10	Journal	Yes	Elderly	0	Diarrhea; Subarachnoid hematoma; Hemiplegia			Treatment	
Riquelme, 2003	n/a	S	Case Study 1-10	Journal	Yes	Adults	50	Immuno-compromised			Treatment	Antibiotics
Tommasi, 2008	Italy	L	Case Study 1-10	Journal	Yes	Elderly	0	Hypertension; Diverticulosis; Hemorrhoidal bleeding; COPD	n/a		Treatment	
Trautmann, 2008	Germany	S	Case Study 1-10	Journal	Yes	Teens	100	Subarachnoid bleed			Treatment	Antibiotics
Viggiano, 1995	France	S	Case Study 1-10	Journal	Yes	Teens	0	Severe burns			Treatment	Antibiotics
Zein, 2008	Lebanon	L B St	Case Study 1-10	Journal	Yes	Adults	100	Diabetes; Hypertension			Treatment	
Zunic, 1991	France	S	Case Study 1-10		Yes	Adults	0	H. pylori; Colectomy / colostomy; Septic shock			Treatment	Antibiotics Steroids Immune suppressant Daktarin (antifungal)

*Abbreviations
Ba=Bacillus
B=Bifidobacterium
CCT=Controlled Clinical Trials
C-RCT=Cross-over Randomized Controlled Trial
E=Enterococcus
GI=Gastrointestinal
IBS=Irritable Bowel Syndrome
L=Lactobacillus
n/a=not available or not applicable
RCT=Randomized Controlled Trial
S=Saccharomyces
St=Streptococcus

Evidence Table C2. Intervention

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Abrahamsson, 2007 RCT	1	n/a Oil droplets Patient Mother	Lactobacillus, reuteri, ATCC 55730, Lyophilized, 10^8 cfu	5 days 1 per day	Oral	Long term	Placebo
Agerbaek, 1995 RCT	1	Gaio Fermented milk Patient	Enterococcus, faecium, n/a, n/a, 2*10^8 cfu/ml Streptococcus, thermophilus, n/a, n/a, 7*10^8 cfu/ml Streptococcus, thermophilus, n/a, n/a, 7*10^8 cfu/ml	200 ml 1 per day	Oral	1.5 months Medium term	Placebo
Aihara, 2005 RCT	1	n/a Pill Patient	Lactobacillus, helveticus, CM4, n/a, n/a	6 tablets 1 per day	Oral	1 month Short term	Placebo
Alberda, 2007 RCT	1	n/a Sachet Patient	Lactobacillus, casei, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Lactobacillus, Plantarum, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Lactobacillus, Acidophilus, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Bifidobacterium, longum, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Bifidobacterium, breve, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Bifidobacterium, Infantis, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Streptococcus, salivarius thermophilus, n/a, Lyophilized, viable, 9*10^11 cfu/sachet	2 sachets 2 per day	Enteral	0.25 months Short term	Placebo
Alberda, 2007 RCT	3	VSL#3 Sachets Patient	Lactobacillus, casei, n/a, Sonicated, n/a Lactobacillus, plantarum, n/a, Sonicated, n/a Lactobacillus, acidophilus, n/a, Sonicated, n/a Lactobacillus, delbrueckii acidophilus, n/a, Sonicated, n/a Bifidobacterium, longum, n/a, Sonicated, n/a Bifidobacterium, infantis, n/a, Sonicated, n/a Bifidobacterium, breve, n/a, Sonicated, n/a Streptococcus, salivarius thermophilus, n/a, Sonicated, n/a	1 sachet 2 per day	Enteral		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Allen, 2010 RCT	1	n/a Pill Patient Mother	Lactobacillus, salivarius, CUL 61, n/a, 6.25*10^9 cfu Lactobacillus, paracasei, CUL 08, n/a, 1.25*10^9 cfu Bifidobacterium, animalis lactis, CUL 34, n/a, 1.25*10^9 cfu Bifidobacterium, bifidum, CUL 20, n/a, 1.25*10^9 cfu	n/a	Oral	Medium term	Placebo
Anderson, 2003 RCT	1	Trevis Pill Patient	Lactobacillus, acidophilus, LA-5, n/a, 4*10^9 cfu Lactobacillus, bulgaricus, n/a, n/a, 4*10^9 cfu Bifidobacterium, lactis, BB-12, n/a, 4*10^9 cfu Streptococcus, thermophilus, n/a, n/a, 4*10^9 cfu	1 capsule 3 per day	Oral	Medium term	Placebo
Andriulli, 2008 RCT	1	Flontec Powder, sachet Patient	Lactobacillus, paracasei, B21060, Lyophilized, 5*10^9 cfu/7g sachet	7 g 2 per day	Oral	3 months Medium term	Placebo
Anukam, 2006 RCT	1	n/a Mix Patient	Lactobacillus, rhamnosus, GR-1, Viable, 10^9 cfu Lactobacillus, reuteri, RC-14, Viable, 10^9 cfu	2 per day n/a	Oral	1 month Short term	Placebo
Anukam, 2008 RCT	1	n/a Yogurt Patient	Lactobacillus, delbrueckii bulgaricus, n/a, n/a, n/a Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, rhamnosus, 6R-1, n/a, 2.5*10^9 cfu/ml Lactobacillus, reuteri, RC-14, n/a, 2.5*10^9 cfu/ml	100 ml 1 per day	Oral	0.5 months Short term	Yogurt only
Anukam, 2009 RCT	1	n/a Mix Patient	Lactobacillus, rhamnosus, GR-1, Live, 5*10^9 cfu/dose Lactobacillus, reuteri, RC-14, Live, 5*10^9 cfu/dose	1 capsule 1 per day	Oral	3 months Medium term	Placebo
Arunachalam, 2000 RCT	1	DR10 Drink Patient	Bifidobacterium, lactis, HN019, Lyophilized, 1.5*10^11 cfu	180 ml 2 per day	Oral	1.5 months Medium term	Placebo
Aso, 1992 RCT	1	BiolActis Powder Powder Patient	Lactobacillus, casei, n/a, Viable, 1*10^10 cfu/g	1 g 3 per day	Oral	12 months Long term	No medication or placebo
Aso, 1995 RCT	1	BLP Patient	Lactobacillus, casei, n/a, Viable, 10^10	1 g 3 per day	Oral	12 months Long term	Placebo
Awad, 2010 RCT	1	Lacteol fort Eppendorf tube Patient	Lactobacillus, acidophilus, GG, Living, 6*10^9 cfu/g	2 per day n/a	Enteral	Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Awad, 2010 RCT	3	n/a Eppendorf tube Patient	Lactobacillus, rhamnosus, GG, Heat-killed, 6*10^9 cfu	1 tube 2 per day	Enteral		
Baerheim, 1994 RCT	1	Gynophilus Vaginal suppository Patient	Lactobacillus, casei rhamnosus, n/a, live, 7.5*10^8 cfu	1 suppository 2 per week	Vaginal	6.5 months Medium term	Placebo
Bajaj, 2008 RCT	1	CC Jersey Crème Yogurt Patient	Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, bulgaricus, n/a, n/a, n/a Lactobacillus, acidophilus, n/a, n/a, n/a Lactobacillus, casei, n/a, n/a, n/a Bifidobacterium, n/a, n/a, n/a, n/a	12 oz 1 per day	Oral	2 months Medium term	No treatment
Banaszkiewicz, 2005 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, ATCC GG 53103, n/a, 10^9 cfu	10^9 cfu 2 per day Varies by participant	Oral	3 months Medium term	Placebo
Barraud, 2010 RCT	1	Ergyphilus Pill Patient	Lactobacillus, rhamnosus, GG, Revivable, 2*10^10 cfu/capsule Lactobacillus, casei, n/a, Revivable, 2*10^10 cfu/capsule Lactobacillus, acidophilus, n/a, Revivable, 2*10^10 cfu/capsule Bifidobacterium, bifidum, n/a, Revivable, 2*10^10 cfu/capsule	5 capsule 1 per day	Enteral	Short term	Placebo
Barreto-Zuniga, 2001 RCT	1	Microflorana-F Oral mix Patient	Lactobacillus, acidophilus, n/a, n/a, n/a Lactobacillus, helveticus, n/a, n/a, n/a Bifidobacterium, n/a, n/a, n/a, n/a	10 ml 3 per day	Oral	0.75 months Short term	Non-probiotic
Basu, 2007 RCT	1	n/a Powder in ORS Patient	Lactobacillus, rhamnosus, GG, n/a, 6*10^7 cfu	6*10^7 cells 2 per day	Oral	Medium term	Placebo
Basu, 2007 RCT	1	n/a Powder packet Patient	Lactobacillus, rhamnosus, GG, n/a, 6*10^7 cfu/100ml	100 ml 2 per day	Oral	Short term	ORS only
Basu, 2009 RCT	1	n/a Powder Patient	Lactobacillus, rhamnosus, GG, n/a, 10^10 cfu	100 ml 2 per day	Oral	Medium term	Glucose-electrolyte rehydration solution only
Basu, 2009 RCT	3	n/a Powder Patient	Lactobacillus, rhamnosus, GG, n/a, 10^12 cfu	100 ml 2 per day	Oral		
Beausoleil, 2007 RCT	1	n/a Drink Patient	Lactobacillus, acidophilus, CL1285, n/a, 5*10^10 cfu Lactobacillus, casei, n/a, n/a, 5*10^10 cfu	Varies over time	Oral	Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Bellomo, 1979 RCT	1	Bioflorin Mix Powder Patient	Enterococcus, faecium, SF-68, Lyophilized, 3*10^7 cfu/dose	1-3 dose 2-3 per day Varies by participant	Oral	Short term	Placebo
Bertolami, 1999 C-RCT	1	Gaio Fermented milk Patient	Streptococcus, thermophilus, n/a, n/a, 5-20*10^8 cfu/ml Streptococcus, thermophilus, n/a, n/a, 5-20*10^8 cfu/ml Enterococcus, faecium, n/a, n/a, 10^5-10^9 cfu/ml	200 g 1 per day	Oral	2 months Medium term	Placebo
Besselink, 2008 RCT	1	Ecologic 641 Sachet dissolved in water Patient	Lactobacillus, acidophilus, n/a, Lyophilized, viable, 10^10 cfu/daily dose Lactobacillus, casei, n/a, Lyophilized, viable, 10^10 cfu/daily dose Lactobacillus, salivarius, n/a, Lyophilized, viable, 10^10 cfu/daily dose Bifidobacterium, bifidum, n/a, Lyophilized, viable, 10^10 cfu/daily dose Bifidobacterium, lactis, n/a, Lyophilized, viable, 10^10 cfu/daily dose	2 per day n/a	Enteral	1 month Short term	Placebo
Bin-Nun, 2005 RCT	1	ABC Dophilus Formula Powder in breast milk or formula Patient	Bifidobacterium, infantis, n/a, n/a, 0.35*10^9 cfu Bifidobacterium, bifidum, n/a, n/a, 0.35*10^9 cfu Streptococcus, thermophilus, n/a, n/a, 0.35*10^9 cfu	Varies by participant	Enteral	Medium term	Feeding supplement only
Black, 1997 CCT	1	BioTura Pill Patient	Lactobacillus, acidophilus, n/a, Lyophilized, 4*10^9 cfu/capsule Bifidobacterium, bifidum, n/a, Lyophilized, 4*10^9 cfu/capsule	1 capsule 3 per day	Oral	0.75 months Short term	Placebo
Boge, 2009 RCT	1	Actimel Drink Patient	Lactobacillus, casei, DN-114 001 (CNCMI-1518), n/a, n/a Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, bulgaricus, n/a, n/a, n/a	100 g 2 per day	Oral	1.75 months Medium term	Placebo
Boge, 2009 RCT	1	Actimel Drink Patient	Lactobacillus, casei, DN-114001(CNCM1-1518), n/a, n/a Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, bulgaricus, n/a, n/a, n/a	100 g 2 per day	Oral	3.25 months Short term	Placebo
Borgia, 1982 RCT	1	n/a Pill Patient	Streptococcus, faecium, SF-68, Lyophilized, >7.5*10^7 cfu/capsule	1 capsules 1 per day	Oral	2 months Medium term	Antibiotics only

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Borgia, 1982 RCT	3	n/a Pill Patient	Streptococcus, faecium, SF68, Lyophilized, >=75ml 1 cfu/capsule	2 capsule 1 per day	Oral		
Borgia, 1982 RCT	4	n/a Pill Patient	Streptococcus, faecium, SF68, Lyophilized, >=75ml 1 bacteria/capsule	3 capsules 1 per day	Oral		
Bousvaros, 2005 RCT	1	LGG Pill Patient	Lactobacillus, rhamnosus, GG, n/a, >=10^10	1 capsule 2 per day	Oral	24 months Long term	Placebo
Bravo, 2008 RCT	1	n/a Pill Patient	Saccharomyces, boulardii, n/a, Lyophilized, 5.1*10^9 cells/ capsule	1 capsule 2 per day	Oral	0.5 months Short term	Placebo
Brophy, 2008 RCT	1	n/a Pill Patient	Lactobacillus, salivarius, CUL 61, Lyophilized, 6.25*10^9 cfu Lactobacillus, paracasei, CUL 08, Lyophilized, 6.25*10^9 cfu Bifidobacterium, infantis, CUL 34, Lyophilized, 6.25*10^9 cfu Bifidobacterium, bifidum, CUL 20, Lyophilized, 6.25*10^9 cfu	1 capsule 1 per day	Oral	3 months Medium term	Placebo
Bruno, 1981 RCT	1	n/a Pill Patient	Enterococcus, faecalis, SF-68, Lyophilized, 7.5*10^7 cfu/capsule	7.5*10^7 cfu capsule 3 per day n/a	Oral	0.33 months Short term	Placebo
Bruzzese, 2007 C-RCT	1	n/a LGG dissolved in ORS Patient	Lactobacillus, rhamnosus, GG, n/a, 6*10^9 cfu/d	6*10^9 cfu 1 per day	Oral	6 months Medium term	Non-probiotic
Bu, 2007 RCT	1	Antibiophilus Pill Patient	Lactobacillus, casei rhamnosus, LCR 35, n/a, 8*10^8 cfu/day	2 capsules 2 per day	Oral	1 month Short term	Placebo
Chen, 2005 RCT	1	n/a Tablet Patient	Lactobacillus, acidophilus, n/a, n/a, n/a	1 tablet 3 per day	Oral	Medium term	Non-probiotic
Chen, 2010 RCT	1	n/a Pill Patient	Lactobacillus, gasseri, PM-A 0005, Lyophilized, 2*10^9 cfu/capsule	1 capsule 2 per day	Oral	2 months Medium term	Placebo
Chou, 2010 RCT	1	Infloran Breast milk Patient	Lactobacillus, acidophilus, n/a, n/a, 10^9 cfu/dose Bifidobacterium, infantis, n/a, n/a, 10^9 cfu/dose	2 per day Varies by participant	Oral	Medium term	Placebo
Chouraqui, 2004 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, BB-12, Dried, viable, 1.5*10^8 cfu Streptococcus, thermophilus, n/a, Dried, viable, n/a Lactobacillus, helveticus, n/a, Dried, viable, n/a	Varies by participant	Oral	Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Chouraqui, 2008 RCT	1	n/a Formula Patient	Bifidobacterium, longum, BL-999, n/a, 1.29*10^8 cfu/100ml Lactobacillus, rhamnosus, LPR, n/a, 1.29*10^8 cfu/100ml	Varies by participant	Oral	4 months Medium term	Placebo
Chouraqui, 2008 RCT	3	n/a Formulal	Bifidobacterium, longum, BL999, n/a, 1.29 * 10^8 cfu/100ml Lactobacillus, rhamnosus, LPR, n/a, 6.45 * 10^8 cfu/100ml	Varies by participant	Oral		
Chouraqui, 2008 RCT	4	n/a Formulal Patient	Bifidobacterium, longum, BL999, n/a, 1.29 * 10^8 cfu/100ml Lactobacillus, paracasei, ST11, n/a, 2.58 * 10^8 cfu/100ml	Varies by participant	Oral		
Chui, 2009 RCT	1	Bifid Triple Pill Patient	Lactobacillus, n/a, n/a, Live, n/a Bifidobacterium, n/a, n/a, Live, n/a Enterococcus, n/a, n/a, Live, n/a n/a, n/a, n/a, Live, n/a	4 capsules 2 per day	Enteral	0.5 months Short term	Placebo
Coccorullo, 2010 RCT	1	Reuterin Oil suspension Patient	Lactobacillus, reuteri, DSM 17938, n/a, 10^8 cfu/5 drops	5 drops 1 per day	n/a	2 months Medium term	Placebo
Connolly, 2005 RCT	1	n/a Mixed in peanut oil Patient	Lactobacillus, reuteri, ATCC 55730, n/a, 1*10^8 cfu/dose	5 drops 1 per day	n/a	12 months Long term	Placebo
Cooper, 2006 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, n/a, n/a, 2*10^7 cfu/g	n/a	Oral	Medium term	Formula only
Correa, 2005 RCT	1	Nan Probiotico Formula Patient	Bifidobacterium, lactis, n/a, n/a, 10^7 cfu/g Streptococcus, thermophilus, n/a, n/a, 10^7 cfu/g	>500 ml 1 per day	Oral	0.5 months Short term	Placebo
Cui, 2004 RCT	1	n/a Tablet Patient	Bacillus, coagulans, n/a, n/a, 10^8 cfu	10^8 cfu 3 per day	Oral	Short term	Other probiotic
Cui, 2004 RCT	2	n/a Pill Patient	Bifidobacterium, longum, n/a, n/a, 10^8 cfu	10^8 cfu 3 per day	Oral		
Cunningham-Rundles, 2000 CCT	1	n/a Mix Patient	Lactobacillus, plantarum, 299v, Lyophilized, n/a	1 packet 1 per day	Oral Enteral	Medium term	Placebo
Czaja, 2007 RCT	1	n/a Vaginal suppository Patient	Lactobacillus, crispatus, CTV-05, n/a, 5*10^8 cfu/suppository	1 suppository 1 per day	Vaginal	0.25 months Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Dadak, 2006 RCT	1	Synbiotic 2000 Forte Patient	Lactobacillus, Plantarum, 2362, n/a, 10^10 cfu Lactobacillus, paracasei paracasei, 19, N/A, 10^10 cfu	n/a	n/a	Medium term	Placebo
De Preter, 2006 C-RCT	1	Perenterol Patient	Saccharomyces, boulardii, n/a, Lyophilized, viable, 1-2.5*10^9 cells/250mg	250 mg 4 per day	Oral	1 month Short term	Placebo
De Preter, 2006 C-RCT	3	Perenterol Patient	Saccharomyces, boulardii, n/a, Lyophilized, viable, 1-2.5*10^9 cells/250 mg	250 mg 2 per day	Oral		
de Roos, 1999 RCT	1	n/a Yogurt Patient	Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, acidophilus, L-1, n/a, 4.8*10^9-2.7*10^10 cfu/500ml	2 per day Varies over time	Oral	2 months Medium term	Yogurt only
De Simone, 1992 RCT	1	Infloran Pill Patient	Lactobacillus, acidophilus, n/a, n/a, 10^9 cfu Bifidobacterium, bifidum, n/a, n/a, 10^9 cfu	2 capsules 4 per day	Oral	1 month Short term	Placebo
De Simone, 2001 CCT	1	VSL#3-Yoris Patient	Streptococcus, thermophilus, n/a, Live, 10^11 cfu/g Bifidobacterium, n/a, n/a, Living, 10^11 cfu/g Lactobacillus, acidophilus, n/a, Live, 10^11 cfu/g Lactobacillus, plantarum, n/a, Live, 10^11 cfu/g Lactobacillus, casei, n/a, Live, 10^11 cfu/g Lactobacillus, delbrueckii bulgaricus, n/a, Live, 10^11 cfu/g Streptococcus, faecium, n/a, Live, 10^11 cfu/g	3 g 1 per day	Oral	0.33 months Short term	Other probiotic
De Simone, 2001 CCT	2	Bioflorin Pill Patient	Enterococcus, faecium, n/a, Live, 2.5*10^7 cfu/capsule	3 capsules 1 per day			
Dekker, 2009 RCT	1	Fonterra NZ Pill Patient Mother	Lactobacillus, rhamnosus, HN001, n/a, 6*10^9 cfu	1 capsule 1 per day	Oral	Long term	Placebo
Dekker, 2009 RCT	3	n/a Drink Patient Mother	Bifidobacterium, animalis lactis, HN019, n/a, 9*10^9 cfu	1 capsule 1 per day	Oral		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Delia, 2002 RCT	1	VSL#3 Sachet Patient	Lactobacillus, casei, n/a, Lyophilized, 4.5*10^8 cfu/g Lactobacillus, plantarum, n/a, Lyophilized, 4.5*10^8 cfu/g Lactobacillus, acidophilus, n/a, Lyophilized, 4.5*10^8 cfu/g Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, 4.5*10^8 cfu/g Bifidobacterium, longum, n/a, Lyophilized, 4.5*10^8 cfu/g Bifidobacterium, breve, n/a, Lyophilized, 4.5*10^8 cfu/g Bifidobacterium, infantis, n/a, Lyophilized, 4.5*10^8 cfu/g Streptococcus, salivarius thermophilus, n/a, Lyophilized, 4.5*10^8 cfu/g	1 sachet 3 per day	Oral	Medium term	Placebo
Delia, 2007 RCT	1	VSL#3 Sachet Patient	Lactobacillus, casei, n/a, Lyophilized, viable, 4.5*10^8 cfu/g Lactobacillus, plantarum, n/a, Lyophilized, viable, 4.5*10^8 cfu/g Lactobacillus, acidophilus, n/a, Lyophilized, viable, 4.5*10^8 cfu/g Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, viable, 4.5*10^8 cfu/g Bifidobacterium, longum, n/a, Lyophilized, viable, 4.5*10^8 cfu/g Bifidobacterium, breve, n/a, Lyophilized, viable, 4.5*10^8 cfu/g Bifidobacterium, infantis, n/a, Lyophilized, viable, 4.5*10^8 cfu/g Streptococcus, saliva, n/a, Lyophilized, viable, 4.5*10^8 cfu/g	1 sachet 3 per day	n/a	Medium term	Placebo
Dewan, 2007 RCT	1	n/a Curd Patient	Lactobacillus, bulgaricus, n/a, n/a, 10^8 Streptococcus, thermophilus, n/a, n/a, 10^8 cfu	100 g 2 per day	Oral	0.5 months Short term	Non-probiotic
Dolin, 2009 RCT	1	GanedenBC Pill Patient	Bacillus, coagulans, GB1-30 6086, n/a, 2*10^9 cfu/capsule	1 capsule 1 per day	Oral	2 months Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Dubey, 2008 RCT	1	VSL#3 Sachet Patient	Lactobacillus, acidophilus, n/a, n/a, 9*10^10 cfu/sachet Lactobacillus, paracasei, n/a, n/a, 9*10^10 cfu/sachet Lactobacillus, bulgaricus, n/a, n/a, 9*10^10 cfu/sachet Lactobacillus, plantarum, n/a, n/a, 9*10^10 cfu/sachet Bifidobacterium, breve, n/a, n/a, 9*10^10 cfu/sachet Bifidobacterium, infantis, n/a, n/a, 9*10^10 cfu/sachet Bifidobacterium, longum, n/a, n/a, 9*10^10 cfu/sachet Streptococcus, thermophilus, n/a, n/a, 9*10^10 cfu/sachet	Varies by participant	Oral	Medium term	Placebo
Duman, 2005 RCT	1	Reflor Pill Patient	Saccharomyces, boulardii, n/a, n/a, n/a	500 mg 2 per day	n/a	0.5 months Short term	Triple therapy only
Dupont, 2010 RCT	1	Modilac Digest 1 Formula Patient	Lactobacillus, rhamnosus, n/a, n/a, n/a Bifidobacterium, infantis, n/a, n/a, n/a	n/a	Oral	1 month Short term	Formula only
Dylewski, 2010 RCT	1	BIO K+ CL1285 Fermented milk Patient	Lactobacillus, acidophilus, CL1285, n/a, 5*10^10 cfu/g Lactobacillus, casei, n/a, n/a, 5*10^10 cfu/g	49-98 g 1 per day Varies over time	Oral	Medium term	Placebo
Ehrstrom, 2010 RCT	1	n/a Pill Patient	Lactobacillus, gasseri, LN40, Lyophilized, viable, 10^8-10^10 cfu/capsule Lactobacillus, fermentum, LN-99, Lyophilized viable, 10^8-10^10 cfu/capsule Lactobacillus, casei rhamnosus, LN113, Lyophilized, viable, 10^8-10^10 cfu/capsule Pediococcus, acidilactici, LN 23, Lyophilized, viable, 10^8-10^10 cfu/capsule	1 capsule 2 per day	Vaginal	0.2 months Short term	Placebo
Eriksson, 2005 RCT	1	n/a Tampon Patient	Lactobacillus, gasseri, n/a, Lyophilized, live, 10^8 cfu/tampon Lactobacillus, casei rhamnosus, n/a, Lyophilized, live, 10^8 cfu/tampon Lactobacillus, fermentum, n/a, Lyophilized, live, 10^8 cfu/tampon	Varies by participant	Vaginal	1 month Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Falck, 1999 RCT	1	Bactonormal Suspension spray Patient	Streptococcus, mitis, n/a, n/a, 7*10^6 cfu/ml Streptococcus, sanguis II, n/a, n/a, 7*10^6 cfu/ml Streptococcus, sanguis II, n/a, n/a, 7*10^6 cfu/ml Streptococcus, sanguis II, n/a, n/a, 7*10^6 cfu/ml	150 ml 2 per day	Topical	0.33 months Short term	Placebo
Felley, 2001 RCT	1	LC-1 Drink Patient	Lactobacillus, johnsonii, LA-1, n/a, 1*10^7 cfu/ml	180 ml 2 per day	Oral	0.75 months Short term	Placebo
Feng, 1999 RCT	1	Golden Bifido Pill Patient	Lactobacillus, n/a, n/a, Live, 1*10^9 cfu/g Bifidobacterium, longum, n/a, Live, 1*10^9 cfu/g Streptococcus, thermophilus, n/a, Live, 1*10^9 cfu/g	4 capsules 2 per day	Oral	 Short term	Other probiotic
Folster-Holst, 2006 RCT	1	LGG Mixed with mile on water Patient	Lactobacillus, rhamnosus, GG, n/a, 5*10^9 cfu/dose	5*10^9 cfu 2 per day	Oral	2 months Medium term	Placebo
Forestier, 2008 RCT	1	n/a Varies Patient	Lactobacillus, casei rhamnosus, n/a, n/a, 10^9 cfu	10^9 cfu 2 per day	Oral Enteral	 Medium term	Placebo
French, 2009 RCT	1	PCC Pill Patient	Lactobacillus, fermentum, VRI 003, Lyophilized, 10^9 cfu/capsule	1 capsule 1 per day	Oral	1.5 months Medium term	Placebo
Frohmader, 2010 RCT	1	VSL#3 Sachet Patient	Lactobacillus, acidophilus, n/a, Lyophilized, live, n/a Lactobacillus, casei, n/a, Live lyophilized, n/a Lactobacillus, bulgaricus, n/a, Lyophilized, live, n/a Lactobacillus, plantarum, n/a, Lyophilized, live, n/a Bifidobacterium, longum, n/a, Lyophilized, live, >10^10 cfu/g Bifidobacterium, infantis, n/a, Lyophilized, live, >10^10 cfu/g Bifidobacterium, breve, n/a, Lyophilized, live, >10^10 cfu/g Streptococcus, salivarius thermophilus, n/a, Lyophilized, live, >10^11 cfu/g	4.5*10^11 cfu 2 per day	Enteral	 Short term	Placebo
Fujimori, 2009 RCT	1	Bificolon Pill Patient	Bifidobacterium, longum, n/a, n/a, 2*10^9 cfu	1 capsule 1 per day	Oral	1 month Short term	Prebiotic
Fujimori, 2009 RCT	3	n/a Water Patient	Bifidobacterium, longum, n/a, n/a, 2*10^9 cfu	1 capsule 1 per day	Oral		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Gade, 1989 RCT	1	n/a Pill Patient	Streptococcus, faecium, n/a, Lyophilized, n/a	4 tablets 2 per day	n/a	1 month Short term	Placebo
Galpin, 2005 RCT	1	LGG Pill Mix Patient	Lactobacillus, rhamnosus, GG, n/a, 5^10 cfu	2 capsules 1 per day	Oral	1 month Short term	Placebo
Gao, 2010 RCT	1	n/a Pill Patient	Lactobacillus, acidophilus, CL1285, Live, 5*10^10 cfu/capsule Lactobacillus, casei, LBC80R, Live, 5*10^10 cfu/capsule	1 capsule 1 per day	Oral	Short term	Placebo
Gao, 2010 RCT	3	n/a Pill Patient	Lactobacillus, acidophilus, CL1285, Live, 5*10^10 cfu/capsule Lactobacillus, casei, LBC80R, Live, 5*10^10 cfu/capsule	2 capsule 1 per day	Oral		
Garcia Vilela, 2008 RCT	1	Floratil Pill Patient	Saccharomyces, boulardii, 17, Lyophilized, 4*10^8 cells/capsule	1 capsule 3 per day	Oral	3 months Medium term	Placebo
Gerasimou, 2010 RCT	1	DDS(R) Junior Mix Powder Patient	Bifidobacterium, lactis, UABLA-12, n/a, 5*10^9 cfu/g Lactobacillus, acidophilus, DDS-1, n/a, 5*10^9 cfu/g	1 gram 2 per day	Oral	2 months Medium term	Placebo
Gibson, 2008 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, CNCM I-3446, n/a, 3.85*10^8 cfu	Varies by participant	Oral	7 months Medium term	Formula only
Gill, 2001 RCT	1	n/a Sachet Patient	Bifidobacterium, lactis, HN019, Lyophilized, 1*10^9 cfu	5*10^10 organisms 1 per day	Oral	0.75 months Short term	Other probiotic
Gill, 2001 RCT	2	n/a Patient	Bifidobacterium, lactis, HN019, Lyophilized, 1*10^8 cfu/g	1*10^8 organisms 1 per day	Oral		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Gionchetti, 2000 RCT	1	n/a Bag Patient	Lactobacillus, casei, n/a, Lyophilized, viable, 3*10^11 cfu/g Lactobacillus, plantarum, n/a, Lyophilized, viable, 3*10^11 cfu/g Lactobacillus, acidophilus, n/a, Lyophilized, viable, 3*10^11 cfu/g Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, viable, 3*10^11 cfu/g Bifidobacterium, longum, n/a, Lyophilized, viable, 3*10^11 cfu/g Bifidobacterium, breve, n/a, Lyophilized, viable, 3*10^11 cfu/g Bifidobacterium, infantis, n/a, Lyophilized, viable, 3*10^11 cfu/g Streptococcus, salivarius thermophilus, n/a, Lyophilized, viable, 3*10^11 cfu/g	3 g bags 2x per day	Oral	9 months Medium term	Placebo
Gionchetti, 2003 RCT	1	VSL#3 Packet Patient	Lactobacillus, casei, n/a, Lyophilized, 9*10^11 cfu Lactobacillus, plantarum, n/a, Lyophilized, 9*10^11 cfu Lactobacillus, acidophilus, n/a, Lyophilized, 9*10^11 cfu Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, 9*10^11 cfu Bifidobacterium, longum, n/a, Lyophilized, 9*10^11 cfu Bifidobacterium, breve, n/a, Lyophilized, 9*10^11 cfu Bifidobacterium, infantis, n/a, Lyophilized, 9*10^11 cfu Saccharomyces, salivarius thermophilus, n/a, Lyophilized, 9*10^11	1 packet 1 per day	n/a	12 months Long term	Placebo
Goossens, 2003 RCT	1	n/a In fermented oatmeal drink Patient	Lactobacillus, Plantarum, 299v, n/a, 1*10^9 cfu/ml	100 ml 2 per day	Oral	1 month Short term	Placebo
Gracheva, 1999 CCT	1	Bifidumbacterin-forte Patient	Bifidobacterium, bifidum, n/a, n/a, n/a	45 doses 2-3 per day	Oral	Short term	Other probiotic
Gracheva, 1999 CCT	2	n/a Patient	Bifidobacterium, bifidum, n/a, Active, n/a	5 doses 2 per day	n/a		
Gruber, 2007 RCT	1	Valio Pill Patient	Lactobacillus, rhamnosus, GG, n/a, 5*10^9 cfu	1 capsule 2 per day	Oral	3 months Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Guillemard, 2010 RCT	1	Actimel Drink Patient	Lactobacillus, casei paracasei, DN-114001, n/a, >=10^10 cfu/100g Streptococcus, thermophilus, n/a, n/a, >=10^9 cfu/100g Lactobacillus, delbrueckii, bulgaricus, n/a, >=10^9 cfu/100g	100 g 2 per day	Oral	3 months Medium term	Placebo
Guyonnet, 2009 RCT	1	Activia Drink Patient	Bifidobacterium, lactis, DN-173010, n/a, 1.25*10^10 cfu/pot Streptococcus, thermophilus, n/a, n/a, 1.2*10^9 cfu/pot Lactobacillus, bulgaricus, n/a, n/a, 1.2*10^9 cfu/pot	1 pot 1 per day	Oral	0.5 months Short term	No intervention
Guyonnet, 2009 RCT	3	Activia Drink Patient	Bifidobacterium, lactis, DN-173 010, n/a, 1.25*10^10 cfu/pot Streptococcus, thermophilus, n/a, n/a, 1.2*10^9 cfu/pot Lactobacillus, bulgaricus, n/a, n/a, 1.2*10^9 cfu/pot	2 pots 1 per day	Oral		
Habermann, 2001 RCT	1	Symbioflor Taken orally, gargled, swallowed Patient	Enterococcus, faecalis, n/a, Active cells + autolysis, 1.5-4.5*10^7 cfu/ml	30 drops 3 per day	Oral	6 months Medium term	Placebo
Habermann, 2002 RCT	1	Symbioflor Salt solution Patient	Enterococcus, faecalis, Group D, Active, 1.5-4.5*10^7 cfu/ml	3.75-11.25*10^7 cfu 3 per day	Enteral	6 months Medium term	Placebo
Haschke-Becher, 2008 RCT	1	Nan 2 Formula Patient	Lactobacillus, johnsonii, LA-1, Live, 1*10^8 cfu/g	Varies by participant	Oral	1 month Short term	Placebo
Hatakka, 2008 C-RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, LC705 DSM 7061, Lyophilized, 2*10^10 cfu/2 capsules Propionibacterium, freudenreichii shermanii, JS, Lyophilized, 2*10^10 cfu	2 capsules 1 per day	Oral	1 month Short term	Placebo
Heimburger, 1994 RCT	1	Laxtinex Granules Patient	Lactobacillus, acidophilus, n/a, Viable, n/a Lactobacillus, bulgaricus, n/a, Viable, n/a	1 g 3 per day	Enteral	Short term	Placebo
Hemmerling, 2009 RCT	1	LACTIN-V Single use vaginal applications Patient	Lactobacillus, crispatus, CTV-05, n/a, 5*10^8 cfu/dose	1 dose 1 per day	Vaginal	0.13 months Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Hemmerling, 2009 RCT	3	n/a Single use vaginal applications Patient	Lactobacillus, crispatus, CTV-05, n/a, 10^9 cfu/dose	1 dose 1 per day	Vaginal		
Hemmerling, 2009 RCT	4	n/a Patient	Lactobacillus, crispatus, CTV-05, n/a, 2*10^9 cfu/dose	1 dose 1 per day	Vaginal		
Higashikawa, 2009 RCT	1	n/a Yogurt Patient	Lactobacillus, plantarum, SN35N, Viable, 1.9*10^8 cfu/g Lactobacillus, plantarum, SN13T, Viable, 0.2*10^8 cfu/g	100 g 1 per day	Oral	1.5 months Medium term	Other probiotic
Higashikawa, 2009 RCT	2	n/a Yogurt Patient	Lactobacillus, plantarum, SN35N, Viable, 1.96*10^8 cfu/g Lactobacillus, plantarum, SN13T, Viable, 0.04*10^8 cfu/g	100 g 1 per day	Oral		
Higashikawa, 2009 RCT	3	n/a Yogurt Patient	Lactobacillus, lactis, A6, Viable, 1.722*10^8 cfu/g Bifidobacterium, thermophilus, 510, Viable, 0.276*10^8 cfu/g Lactobacillus, bulgaricus, C6, Viable, 0.002*10^8 cfu/g	100 g 1 per day	Oral		
Hilton, 1997 RCT	1	LGG Mix Patient	Lactobacillus, GG, n/a, n/a, 2*10^9 cfu	2*10^9 cfu 1 per day	Oral	Medium term	Placebo
Hirata, 2002 CCT	1	n/a Sour milk Patient	Lactobacillus, helveticus, n/a, n/a, n/a Saccharomyces, cerevisiae, n/a, n/a, n/a Lactobacillus, helveticus, CM4, n/a, n/a	120 g 1 per day	Oral	2 months Medium term	Placebo
Hochter,1990 RCT	1	Perenterol Pill Patient	Saccharomyces, boulardii, n/a, n/a, 50ml	3 capsules 2-4 per day	Oral	0.25 months Short term	Placebo
Honeycutt, 2007 RCT	1	Culturelle Pill Patient	Lactobacillus, rhamnosus, GG, n/a, 10^9 cfu/capsule	1 capsule 1 per day	Varies	Medium term	Placebo
Hong, 2010 RCT	1	n/a Packet of powder with water Patient	Bifidobacterium, bifidum, BGN4, Lyophilized, 5*10^9 cfu/packet Bifidobacterium, lactis, AD011, Lyophilized, 5*10^9 cfu/packet Lactobacillus, acidophilus, AD031, Lyophilized, 5*10^9 cfu/packet Lactobacillus, casei, IBS041, Lyophilized, 5*10^9 cfu/packet	1 packet 2 per day	Oral	2 months Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Horvat, 2010 RCT	1	Synbiotic 2000 Sachet Patient	Lactobacillus, paracasei, paracasei 19, Active, 10^10 cfu/sachet Lactobacillus, plantarum, 2362, Active, 10^10 cfu/sachet Pediococcus, pentosaceus, 5-33:3, Active, 10^10 cfu/sachet Leuconostoc, mesenteroides, 32-77:1, Active, 10^10 cfu/sachet	1 sachet 2 per day	Oral	0.1 month Short term	Other probiotic
Horvat, 2010 RCT	2	n/a Patient	Lactobacillus, paracasei paracasei, 19, Heat-inactivated, n/a Lactobacillus, plantarum, 2362, Heat-inactivated, n/a Pediococcus, pentosaceus, 5-33:3, Heat-inactivated, n/a Leuconostoc, mesenteroides, 32-77:1, Heat-inactivated, n/a	1 sachet 2 per day	Oral		
Ishikawa, 2002 RCT	1	BFM Drink Patient	Lactobacillus, acidophilus, YIT 0168, Live, >10^9 cfu/100ml Bifidobacterium, breve, n/a, Live, >10^9 cfu/100ml Bifidobacterium, bifidum, n/a, Live, >10^9 cfu/100ml	100 ml 1 per day	Oral	12 months Long term	No treatment
Ishikawa, 2003 RCT	1	n/a Tablet Patient	Lactobacillus, salivarius, TI 2711, Lyophilized, 1*10^8 cfu	5 tablets 5 per day	Oral	2 months Medium term	No treatment
Ishikawa, 2003 RCT	3	n/a Pill Patient	Lactobacillus, salivarius, TI 2711, Lyophilized, 2*10^7 cfu	5 tablets 5 per day	Oral		
Ishikawa, 2005 RCT	1	n/a Powder Patient	Lactobacillus, casei, Shirota, n/a, 10^10 cfu/g	1 g	n/a	48 months Long term	Dietary instructions only
Ishikawa, 2005 RCT	3	n/a Powder Patient	Lactobacillus, casei, Shirota, n/a, 10^10 cfu/g	1 g 3 per day	n/a		
Isolauri, 1991 RCT	1	LGG Fermented milk Patient	Lactobacillus, casei, GG, n/a, 10^10-11 cfu	125 g 2 per day	Oral	0.25 months Short term	Non-probiotic
Isolauri, 1991 RCT	3	LGG Powder Patient	Lactobacillus, casei, GG, Lyophilized, 10^10-11 cfu	1 dose 2 per day	n/a		
Isolauri,1995 RCT	1	LGG Dry powder mixed with water Patient	Lactobacillus, casei, ATCC 53103, Lyophilized, 5*10^9 cfu	0.1 g 2 per day	Oral	0.25 months Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Jirapinyo, 2002 RCT	1	Infloran Pill Patient	Lactobacillus, acidophilus, n/a, Lyophilized, n/a Bifidobacterium, infantis, n/a, Lyophilized, n/a	1 capsule 3 per day	Oral	0.25 months Short term	Placebo
Johansson, 1998 RCT	1	ProViva Rose-hip drink fermented oats Patient	Lactobacillus, plantarum, DSM 9843, 299v, n/a, 5*10^7 cfu/ml	400 ml 1 per day	Oral	0.75 months Short term	Placebo
Kadooka, 2010 RCT	1	n/a Fermented milk Patient	Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, delbrueckii bulgaricus, n/a, n/a, n/a Lactobacillus, gasseri, SBT 2055(LG2055), Viable, 5*10^10 cfu/100g	100 g 2 per day	Oral	3 months Medium term	Fermented milk only
Kajander, 2005 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, LC 705, n/a, 8-9*10^9 cfu/capsule Bifidobacterium, breve, BB 99, n/a, 8-9*10^9 cfu/capsule Lactobacillus, rhamnosus, GG, n/a, 8-9*10^9 cfu/capsule	1 capsule 1 per day	n/a	6 months Medium term	Placebo
Kajander, 2008 RCT	1	LGG Drink Patient	Lactobacillus, rhamnosus, GG ATCC 53103, n/a, 10^7 cfu Lactobacillus, rhamnosus, LC 705 DSM 7061, n/a, 10^7 cfu Bifidobacterium, animalis lactis, BB-12 DSM 15954, n/a, 10^9 cfu	1.2 daily 1 per day	Oral	5 months Medium term	Placebo
Kajimoto, 2002 RCT	1	n/a Yogurt Patient	Lactobacillus, helveticus, n/a, n/a, n/a Saccharomyces, cerevisiae, n/a, n/a, n/a Lactobacillus, helveticus, CM4, n/a, n/a Lactobacillus, delbrueckii bulgaricus, n/a, n/a, n/a Streptococcus, thermophilus, n/a, n/a, n/a	150 g 2 per day	Oral	2 months Medium term	Yogurt only
Karvonen, 2001 RCT	1	n/a Varies Patient	Lactobacillus, reuteri, n/a, Lyophilized, 10^5 cfu	20 ml 1 per day	Oral	1 month Short term	Placebo
Karvonen, 2001 RCT	3	n/a Varies Patient	Lactobacillus, reuteri, n/a, Lyophilized, 10^7 cfu	20 ml 1 per day	Oral		
Karvonen, 2001 RCT	4	n/a Varies Patient	Lactobacillus, reuteri, n/a, Lyophilized, 10^9 cfu	20 ml 1 per day	Oral		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Kerac, 2009 RCT	1	Synbiotic 2000 Forte Ready-to-use food Patient	Lactobacillus, paracasei paracasei, F-19 LM6 P-17806, Lyophilized, 2.5*10^10 cfu Lactobacillus, plantarum, 2362 LM6 P-20606, Lyophilized, 2.5*10^10 cfu/dose Leuconostoc, mesenteroides, 23-77:1LMGP-20607, Lyophilized, 2.5*10^10 cfu/dose Pediococcus, pentosaceus, 16:1 LMG P-20608, Lyophilized, 2.5*10^10 cfu/dose	>10^10 cfu 1 per day Varies by participant	Oral	Medium term	Placebo
Kianifar, 2009 RCT	1	Infloran Powder Patient	Lactobacillus, acidophilus, n/a, n/a, 1*10^9 cfu/dose Bifidobacterium, bifidum, n/a, n/a, 1*10^9 cfu/dose	1 dose 3 per day	Oral	0.2 months Short term	Placebo
Kim, 2006 RCT	1	n/a Pill Patient	Lactobacillus, acidophilus, n/a, n/a, 5*10^7 cfu/dose Bifidobacterium, bifidum, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, bulgaricus, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, lactis + leichmannii, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, brevis + caseii, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, caucasicus + plantarum, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, fermenti + helveticus, n/a, n/a, 5*10^7 cfu/dose Saccharomyces, boulardii, n/a, n/a, 5*10^7 cfu/dose	Varies over time	Oral	2 months Medium term	Other probiotic
Kim, 2006 RCT	2	n/a Pill Patient	Lactobacillus, acidophilus, n/a, n/a, 5*10^7 cfu/dose Bifidobacterium, bifidum, n/a, n/a, 5*10^7 cfu/dose Bacillus, subtilis, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, bulgaricus, n/a, n/a, 5x10^7 cfu/dose Lactobacillus, lactis, n/a, n/a, 5*10^7 cfu/dose Bacillus, lichenformis, n/a, n/a, 5*10^7 cfu/dose	Varies over time	Oral		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Kim, 2006 RCT	1	n/a Pill Patient	Lactobacillus, acidophilus, n/a, n/a, 1*10^7 cfu/dose Bifidobacterium, bifidum, n/a, n/a, 1*10^7 cfu/dose Bacillus, subtilis, n/a, n/a, 1*10^7 cfu/dose Lactobacillus, bulgaricus, n/a, n/a, 1*10^7 cfu/dose Lactobacillus, lactis, n/a, n/a, 1*10^7 cfu/dose Bacillus, licheniformis, n/a, n/a, 1*10^7 cfu/dose	Varies over time	Oral	2 months Medium term	Placebo
Kim, 2006 RCT	3	n/a Caplet Patient	Bacillus, coagulans, n/a, n/a, 5*10^7 cfu/dose Saccharomyces, boulardii, n/a, n/a, 5*10^7 cfu/dose Bacillus, subtilis, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, salivarius, n/a, n/a, 5*10^7 cfu/dose Lactobacillus, plantarum, n/a, n/a, 5*10^7 cfu/dose	Varies over time	Oral		
Kim, 2008 RCT	1	Will Yogurt Yogurt Patient	Lactobacillus, acidophilus, HY 2177, n/a, >10^5 cfu/ml Lactobacillus, casei, HY 2177, n/a, >10^5 cfu/ml Bifidobacterium, longum, HY 8001, n/a, >10^5 cfu/ml Streptococcus, thermophilus, B-1, n/a, >10^5 cfu/ml	150 ml 1 per day	Oral	0.75 months Short term	Triple therapy only
Kirjavainen,2003 RCT	1	n/a Formula Patient	Lactobacillus, rhamnosus, GG, Lyophilized, viable, 1*10^9 cfu/g	3*10^10 cfu/kg	Oral	Medium term	Placebo
Kirjavainen,2003 RCT	3	n/a Formulal Patient	Lactobacillus, rhamnosus, GG, Heat-killed, 10^9 cfu/g	3*10^10 cfu/g	Oral		
Klarin, 2008 RCT	1	n/a Gauze swabs Patient	Lactobacillus, plantarum, 299, n/a, 10^10 cfu/10 ml	2 swabs 2 per day	Topical	Medium term	Non-probiotic
Klarin,2005 RCT	1	Probi AB Fermented oatmeal formula Patient	Lactobacillus, plantarum, 299v, n/a, 10^9 cfu/ml	Varies by participant	Enteral	Medium term	Placebo
Knight, 2007 RCT	1	Synbiotic 2000 Sachet Patient	Lactobacillus, paracasei paracasei, n/a, n/a, 10^10 cfu/sachet Lactobacillus, plantarum, n/a, n/a, 10^10 cfu/sachet	2 per day n/a	Enteral	Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Koning, 2008 RCT	1	Ecologic AAD Sachet Patient	Bifidobacterium, bifidum, W 23, n/a, 10^9 cfu/g Bifidobacterium, lactis, W 18, n/a, 10^9 cfu/g Bifidobacterium, longum, W 51, n/a, 10^9 cfu/g Enterococcus, faecium, W54, n/a, 10^9 cfu/g Lactobacillus, acidophilus, W37, n/a, 10^9 cfu/g Lactobacillus, acidophilus, W55, n/a, 10^9 cfu/g Lactobacillus, paracasei, W72, n/a, 10^9 cfu/g Lactobacillus, plantarum, W62, n/a, 10^9 cfu/g	5 g 2 per day	Oral	0.5 months Short term	Placebo
Kopp, 2008 RCT	1	n/a Pill Patient Mother	Lactobacillus, rhamnosus GG, ATCC 53103, n/a, 5*10^9 cfu	2 capsules 1 per day	Oral	Medium term	Placebo
Kotzampassi, 2006 RCT	1	Synbiotic 2000 Forte Sachet Patient	Lactobacillus, paracasei paracasei, 19, n/a, 10^11 cfu Lactobacillus, plantarum, 2362, n/a, 10^11 cfu	12 g 1 per day	Enteral	0.5 months Short term	Placebo
Krasse, 2005 RCT	1	n/a Chewing gum Patient	Lactobacillus, reuteri, n/a, Live, 1*10^8 cfu	1 g 2 per day	Oral	0.5 months Short term	Placebo
Krasse, 2005 RCT	3	n/a Chewing gum Patient	Lactobacillus, reuteri, n/a, Live, 1*10^8 cfu	1 gum 2 per day	Oral		
Kuitunen, 2009 RCT	1	n/a Patient Mother	Lactobacillus, rhamnosus, GG (ATCC 53103), n/a, 5*10^9 cfu Lactobacillus, rhamnosus, LC 705 (DSM 7061), n/a, 5*10^9 cfu Bifidobacterium, breve, Bb 99 (DSM 13692), n/a, 2*10^8 cfu Propionibacterium, freudenreichii, shermanii JS (DSM 7076), n/a, 2*10^9 cfu	1 dose 1-2 per day Varies by participant	n/a	6 months Medium term	Placebo
Kurugol, 2005 RCT	1	n/a Diluted with water or juice Patient	Saccharomyces, boulardii, n/a, n/a, n/a	250 mg 1 per day	Oral	0.17 months Short term	Placebo
La Rosa, 2003 RCT	1	n/a Pill Patient	Lactobacillus, sporogenes, n/a, n/a, 5.5*10^8 cfu	1 capsule 1 per day	Oral	0.3 months Short term	Placebo
Laitinen, 2008 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, GG ATCC-55 103, n/a, 10^10 cfu/day Bifidobacterium, lactis, BB-12, n/a, 10^10 cfu/day	n/a	Oral	Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Langhendries, 1995 RCT	1	n/a Formula Patient	Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, helveticus, n/a, n/a, n/a Bifidobacterium, bifidum, n/a, Viable, 10^6 cfu/g	Varies by participant	Oral	2 months Medium term	Formula only
Larsen, 2006 RCT	1	n/a Pill Patient	Lactobacillus, paracasei paracasei, CRL-431, n/a, 10^8 cfu/day Bifidobacterium, animals lactis, BB-12, n/a, 10^8 cfu/day	2 capsules 1 per day	Oral	0.75 months Short term	Placebo
Larsen, 2006 RCT	3	n/a Pill Patient	Lactobacillus, paracasei paracasei, CRL-431, n/a, 1*10^9 cfu Bifidobacterium, animalis lactis, n/a, n/a, 1*10^9 cfu	2 capsules 1 per day	Oral		
Larsen, 2006 RCT	4	10^10 Pill Patient	Lactobacillus paracasei paracasei, CRL-431, n/a, n/a, 1*10^10 Bifidobacterium, animalis lactis, n/a, n/a, 1*10^10	2 capsules 1 per day	Oral		
Larsson, 2008 RCT	1	EcoVag Pill Patient	Lactobacillus, gasseri, Lba EB01-DSM 14869, Lyophilized, >=10^8-9 cfu Lactobacillus, rhamnosus, Lba EBD1-DSM 14870, Lyophilized, >=10^8-9 cfu	n/a	Vaginal	3 months Medium term	Placebo
Lata, 2009 RCT	1	n/a Patient	Bifidobacterium, infantis, n/a, n/a, n/a Bifidobacterium, bifidum, n/a, n/a, n/a Lactobacillus, acidophilus, n/a, n/a, n/a Lactobacillus, casei, n/a, n/a, n/a Lactobacillus, salivarius, n/a, n/a, n/a Lactobacillus, lactis, n/a, n/a, n/a	n/a	Enteral	Medium term	Placebo
Lawrence, 2005 RCT	1	LGG Pill Patient	Lactobacillus, rhamnosus, GG, Lyophilized, 2.8*10^11-4*10^10 cfu	40 mg 2 per day	Oral	Medium term	Placebo
Li, 2004 RCT	1	n/a Dissolved in water Patient	Bifidobacterium, breve, n/a, n/a, 1.6*10^8 cells/0.5ml	0.5 ml 2 per day	Enteral	Medium term	No supplement
Ligaarden, 2010 C-RCT	1	n/a Pill Patient	Lactobacillus, plantarum, MF 1298, Lyophilized, live, 10^10 cfu/capsule	1 capsule 1 per day	Oral	0.75 months Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Lighthouse, 2004 RCT	1	SCM-III Patient	Lactobacillus, acidophilus, n/a, n/a, n/a Lactobacillus, helveticus, n/a, n/a, n/a Bifidobacterium, n/a, n/a, n/a, n/a	10 ml 3 per day	n/a	0.5 months Short term	Non-probiotic
Lin, 1989 C-RCT	1	Lactinex Tablet Patient	Lactobacillus, acidophilus, ATCC 4962, Viable, 2*10^6 cfu/tablet Lactobacillus, bulgaricus, ATCC 33409, Viable, 2*10^6 cfu/tablet	1 tablet 4 per day	Oral	1.5 months Medium term	Placebo
Lin, 2005 RCT	1	Infloran Mixed with breast milk Patient	Lactobacillus, acidophilus, n/a, n/a, >=1,004,356 Bifidobacterium, infantis, n/a, n/a, >=1,004,356	125 mg/kg 2 per day	Oral	Medium term	Breast milk only
Lin, 2008 RCT	1	Infloran; Bifidum Formula Added to breast milk or formula Patient	Lactobacillus, acidophilus, NCDD 1748, n/a, 10^9 cfu Bifidobacterium, bifidum, NCDD 1453, n/a, 10^9 cfu	125 mg/kg 2 per day	Oral	1.5 months Medium term	Placebo
Ljungberg, 2006 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, GG, n/a, 5*10^9 cfu Lactobacillus, rhamnosus, LC705, n/a, 5*10^9 cfu Bifidobacterium, breve, Bbi99, n/a, 2*10^8 cfu	1 per day n/a	Oral	Medium term	Placebo
Loguercio, 1987 RCT	1	Bioflorin Pill Patient	Enterococcus, faecium, SF-68, n/a, 7.5*10^7 cfu/capsule	2 capsule 3 per day	Oral	0.33 months Short term	Non-probiotic
Lonnermark, 2010 RCT	1	n/a Drink with Blueberries + oats gruel Patient	Lactobacillus, plantarum, 299v, n/a, 5*10^7 cfu/ml	200 ml 1 per day	Oral	Short term	Placebo
Lu, 2004 CCT	1	n/a Patient	Lactobacillus, rhamnosus, n/a, n/a, 1.5*10^8 cfu/day	1.5*10^8 cfu 1 per day	n/a	1 month Medium term	Placebo
Lu, 2004 CCT	3	n/a Patient	Lactobacillus, rhamnosus, n/a, n/a, 2.7*10^8 cfu	4*10^8 cfu 1 per day	n/a		
Lu, 2004 CCT	4	n/a Patient	Lactobacillus, rhamnosus, n/a, n/a, 4*10^8 cfu	4*10^8 cfu 1 per day	n/a		
Luoto, 2010 RCT	1	n/a Pill Patient Mother	Lactobacillus, rhamnosus, GG (ATCC 53103), n/a, 10^10 cfu/capsule Bifidobacterium, lactis, BB-12, n/a, 10^10 cfu/capsule	1 capsule 1 per day	Oral	Short term	Dietary counseling only

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Mäkeläinen, 2003 RCT	1	n/a Pill Patient	Bifidobacterium, longum, 2C, n/a, 10^9 cfu Bifidobacterium, longum, 46, n/a, 10^9 cfu	2 capsules 1 per day	n/a	0.75 months Short term	Placebo
Malaguarnera, 2007 RCT	1	n/a Patient	Bifidobacterium, longum, W11, n/a, n/a	n/a	n/a	3 months Medium term	Placebo
Malaguarnera, 2010 RCT	1	n/a Patient	Bifidobacterium, n/a, n/a, n/a, n/a	n/a	n/a	2 months Medium term	Non-probiotic
Maldonado, 2009 RCT	1	n/a Formula Patient	Lactobacillus, salivarius, CECT5713, n/a, >=2*10^6 cfu/g	n/a	Oral	6 months Medium term	Placebo
Mandel, 2010 RCT	1	n/a Caplet Patient	Bacillus, coagulans, GBI-30, 6086, n/a, 2*10^9 cfu/caplet	1 caplet 1 per day	Oral	2 months Medium term	Placebo
Manley, 2007 C-RCT	1	Vaalia yoghurt Yogurt Patient	Lactobacillus, rhamnosus, GG, n/a, n/a	100 g yogurt 1 per day	Oral	1 month Short term	Yogurt only
Manzoni, 2006 RCT	1	Dicoflor 60 Packet mixed with milk Patient	Lactobacillus, rhamnosus, GG, n/a, 6*10^9 cfu/ml	n/a	Enteral	Medium term	Milk only
Margreiter, 2006 RCT	1	Omniflora Pill Patient	Lactobacillus, gasseri, n/a, Lyophilized, 2*10^7-2*10^8 cfu/capsule Bifidobacterium, longum, n/a, Lyophilized, 2*10^7-2*10^8 cfu/capsule	50 mg 3 per day	Oral	Short term	Other probiotic
Margreiter, 2006 RCT	2	Bioflorin Pill Patient	Enterococcus, faecium, Cernelle 68, n/a, 7.5*10^7 cfu/capsule	3 per day n/a	Oral		
Marotta, 2003 C-RCT	1	SCM-III Patient	Lactobacillus, acidophilus, n/a, n/a, n/a Lactobacillus, helveticus, n/a, n/a, n/a Bifidobacterium, brevis, n/a, n/a, n/a	3 ml 3 per day	Oral	0.5 months Short term	Non-probiotic
Marrazzo, 2006 RCT	1	n/a Pill Patient	Lactobacillus, crispatus, n/a, n/a, 10^8	1 capsule 2 per day	Vaginal	3 months Medium term	Placebo
Marseglia, 2007 RCT	1	n/a Suspension Patient	Bifidobacterium, clausii, n/a, n/a, 2*10^9 cfu/5 ml	1 vial 2 per day	Oral	3 months Medium term	No treatment

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Marteau, 2004 RCT	1	n/a Packet Patient	Lactobacillus, johnsonii, LA-1, Lyophilized, 2*10^9 cfu/packet	2 packets 1 per day	Oral	6 months Medium term	Placebo
Martiney, 2009 RCT	1	n/a Yogurt Patient	Lactobacillus, gasseri, CECT5714, n/a, >=10^6 cfu/g Lactobacillus, coryniformis, CECT5711, n/a, >=10^6 cfu/g Streptococcus, thermophilus, n/a, n/a, 10^7 cfu/g	200 ml 1 per day	Oral	3 months Medium term	Yogurt only
Martinez, 2008 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, GR-1, Viable, 1*10^9 cfu Lactobacillus, reuteri, RC-14, Viable, 1*10^9	2 capsule 1 per day	Oral	1 month Short term	Placebo
Martinez, 2009 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, 6R-1, Dried, 1*10^7 cfu/capsule Lactobacillus, reuteri, RC-14, Dried, 1*10^9 cfu/capsule	2 capsules 1 per day	Oral	1 month Short term	Placebo
Mayanagi, 2009 RCT	1	n/a Tablet Patient	Lactobacillus, salivarius, WB21, n/a, 6.7*10^8 cfu/tablet	1 tablet 3 per day	Oral	2 months Medium term	Placebo
McFarland, 1994 RCT	1	n/a Pill Patient	Saccharomyces, boulardii, n/a, Lyophilized, 3*10^10 cfu	2 capsules 2 per day	Oral	1 month Short term	Placebo
McFarland, 1995 RCT	1	n/a Pill Patient	Saccharomyces, Boulardii, n/a, n/a, 3*10^10 cfu/g	2 capsules 2 per day	Oral	Short term	Placebo
McNaught, 2002 RCT	1	ProViva Oatmeal based drink Patient	Lactobacillus, plantarum, 299v, n/a, 5*10^9 cfu/ml	500 ml 1 per day	Oral	Short term	No treatment
Merenstein, 2009 RCT	1	Probugs Fermented milk drink Patient	Bifidobacterium, longum, n/a, Active, live, n/a Bifidobacterium, breve, n/a, Active, live, n/a Lactobacillus, acidophilus, n/a, Active, live, n/a Saccharomyces, florentinus, n/a, Active, live, n/a Lactococcus, lactis diacetylactis, n/a, Active, live, n/a Lactococcus, plantarum, n/a, Active, live, n/a Lactococcus, rhamnosus, n/a, Active, live, n/a Lactococcus, casei, n/a, Active, live, n/a	1 per day Varies by participant	Oral	0.3 months Short term	Other probiotic

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Merenstein, 2009 RCT	2	Probugs Patient	Bifidobacterium, longum, n/a, Heat-killed, n/a Bifidobacterium, breve, n/a, Heat-killed, n/a Lactobacillus, acidophilus, n/a, Heat-killed, n/a Saccharomyces, florentinus, n/a, Heat-killed, n/a Lactococcus, lactis diacetylactis, n/a, Heat-killed, n/a Lactococcus, plantarum, n/a, Heat-killed, n/a Lactococcus, rhamnosus, n/a, Heat-killed, n/a Lactococcus, casei, n/a, Heat-killed, n/a	1 per day Varies by participant	Oral		
Merenstein, 2010 RCT	1	Dan Active (Actimel) Drink Patient	Lactobacillus, paracasei paracasei, DN-114 001/CNCM-578, n/a, 10^8 cfu/g Streptococcus, thermophilus, n/a, n/a, >10^7 cfu/g Lactobacillus, bulgaricus, n/a, n/a, >10^7 cfu/g	1 bottle 1 per day	Oral	3 months Medium term	Placebo
Metts, 2003 RCT	1	n/a Vaginal Suppository Patient	Lactobacillus, acidophilus, S, n/a, 2*10^9 cfu/capsule	3 per week n/a	Vaginal	3.3 months Medium term	Placebo
Metts, 2003 RCT	3	n/a Pill Vaginal suppository Patient	Lactobacillus, acidophilus, S, n/a, 2*10^9 cfu/capsule Lactobacillus, acidophilus, S, n/a, 5*10^9 cfu/capsule Bifidobacterium, bifidum, Malyoth, n/a, 2*10^10 cfu/capsule Lactobacillus, bulgaricus, LB-51, n/a, 5*10^9 cfu	n/a	Oral Vaginal		
Miele, 2009 RCT	1	VSL#3 Packet mixed with beverage Patient	Lactobacillus, paracasei, n/a, Lyophilized, 9*10^8 cfu Lactobacillus, plantarum, n/a, Lyophilized, 9*10^8 cfu Lactobacillus, acidophilus, n/a, Lyophilized, 9*10^8 cfu Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, 9*10^8 cfu Bifidobacterium, longum, n/a, Lyophilized, 9*10^8 cfu Bifidobacterium, breve, n/a, Lyophilized, 9*10^8 cfu Bifidobacterium, infantis, n/a, Lyophilized, 9*10^8 cfu Streptococcus, salivarius thermophilus, n/a, Lyophilized, 9*10^8 cfu	1 per day Varies by participant	Oral	12 months Long term	Placebo
Millar, 1993 RCT	1	LGG Formula Patient	Lactobacillus, rhamnosus, GG, n/a, 10^8 cfu	10^8 cfu 2 per day	Oral	0.5 months Short term	Milk only

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Mimura, 2004 RCT	1	VSL#3 Sachet Patient	Lactobacillus, acidophilus, n/a, n/a, n/a Lactobacillus, delbrueckii bulgaricus, n/a, n/a, n/a Lactobacillus, casei, n/a, n/a, n/a Lactobacillus, plantarum, n/a, n/a, n/a Bifidobacterium, breve, n/a, n/a, n/a Bifidobacterium, longum, n/a, n/a, n/a Bifidobacterium, infantis, n/a, n/a, n/a Streptococcus, salivarius thermophilus, n/a, n/a, n/a	6 g 1 per day	n/a	12 months Long term	Placebo
Miyaji, 2006 RCT	1	n/a Yogurt Patient	Lactobacillus, gasseri, OLL2716 LG21, n/a, 1*10^9 cfu/g	90 g 2 per day	Oral	3 months Medium term	Placebo
Morrow, 2010 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, GG, n/a, 10^9 cfu/capsule	2 capsule 2 per day	Oral Enteral	Medium term	Placebo
Mukerji, 2009 RCT	1	n/a Chewable tablet Patient	Lactobacillus, rhamnosus, Roo11, Active, 5*10^8 cfu	2 per day n/a	Oral	1 month Short term	Placebo
Naito, 2008 RCT	1	n/a Powder Patient	Lactobacillus, casei, Shirota, n/a, 1*10^10 cfu/g	3 g 1 per day	Oral	12 months Long term	Chemotherapy only
Newcomer, 1983 RCT	1	Acidophilus milk Drink Patient	Lactobacillus, acidophilus, n/a, n/a, 4*10^6 cfu/ml	6 oz 3 per day	Oral	0.5 months Short term	Placebo
Niers, 2009 RCT	1	Ecologic Panda Powder Patient Mother	Bifidobacterium, bifidum, W23, Lyophilized, 1*10^9 cfu Bifidobacterium, lactis, W52, Lyophilized, 1*10^9 cfu Lactobacillus, lactis, W58, Lyophilized, 1*10^9 cfu	Varies by participant	Oral	13.5 months Short term	Placebo
Niv, 2005 RCT	1	BioGaia AB Pill Patient	Lactobacillus, reuteri, ATCC 55730, n/a, 10^8 cfu	Varies over time	Oral	5.75 months Medium term	Placebo
Nobuta, 2009 RCT	1	n/a Pill Patient	Lactobacillus, brevis, KB290, Viable, 3*10^9 cfu/capsule	3 capsule 1 per day	Oral	1 month Short term	Placebo
Nobuta, 2009 RCT	3	n/a Pill Patient	Lactobacillus, brevis, KB290, Viable, 6*10^9 cfu/capsule	3 capsules 1 per day	Oral		
Nobuta, 2009 RCT	4	n/a Pill Patient	Lactobacillus, brevis, KB290, Viable, 3*10^10 cfu/capsule	3 capsules 1 per day	Oral		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
O'Mahony, 2005 RCT	1	Lactobacillus Drink Patient	Lactobacillus, salivarius, VCC 4331, Live, 10^10 cfu	10^10 bacterial cells 1 per day	n/a	2 months Medium term	Placebo
O'Mahony, 2005 RCT	3	n/a Drink Patient	Bifidobacterium, infantis, 35624, Live, 10^10 cfu	10^10 cfu 1 per day	n/a		
Ojetti, 2010 RCT	1	Reuterin Pill Patient	Lactobacillus, reuteri, n/a, n/a, 2*10^8 cfu/pill	2 pills 2 per day	Oral	0.3 months Short term	Placebo
Olah, 2005 RCT	1	Synbiotic 2000 Enteral feed Patient	Lactobacillus, n/a, 4 strains, n/a, 10^10 cfu	Varies by participant	Enteral	Short term	Prebiotic
Olivares, 2006 RCT	1	n/a Yogurt Patient	Streptococcus, thermophilus, n/a, n/a, 10^8 cfu Lactobacillus, coryniformis, CECT5711, n/a, 2*10^9 cfu Lactobacillus, gasseri, CECT5714, n/a, 2*10^9 cfu	200 ml 1 per day	Oral	1 month Short term	Yogurt only
Osterlund, 2007 RCT	1	Gefilus Pill Patient	Lactobacillus, rhamnosus, 66 ATCC 53103, n/a, 1-2*10^10 cfu	2 per day n/a	Oral	6 months Medium term	Chemotherapy only
Ouwehand, 2009 RCT	1	n/a Pill Patient	Lactobacillus, acidophilus, NCFM ATCC 700396, Viable, 1.25*10^9 cfu/capsule Bifidobacterium, lactis, BI-04 (ATCC SD5219), Viable, 3.75*10^9 cfu/capsule	1 capsule 1 per day	Oral	4 months Medium term	Placebo
Ozkinay, 2005 RCT	1	Gynoflor Vaginal tablet Patient	Lactobacillus, acidophilus, n/a, Live, >10^7 cfu/tub	1 tablet 1 per day	Vaginal	Short term	Placebo
Panigrahi, 2008 RCT	1	GastroPlan Synbiotics in dextrose saline Patient	Lactobacillus, plantarum, ATCC 20195, n/a, 10^9 cfu/2ml	2 ml 1 per day	Oral	0.25 months Short term	Placebo
Parent, 1996 RCT	1	Gynoflor Vaginal tablet Patient	Lactobacillus, acidophilus, n/a, Lyophilized, viable, 10^7 cfu/tablet	Varies by participant	Vaginal	0.25 months Short term	Placebo
Parfenov, 2005 CCT	1	Activia Yogurt Patient	Lactobacillus, bulgaricus, n/a, n/a, n/a Streptococcus, thermophilus, n/a, n/a, n/a	2 200ml 2 per day	Oral	0.75 months Short term	No treatment

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Parfenov, 2005 CCT	1	Actimel Yogurt Patient	Lactobacillus, bulgaricus, n/a, Active, 10^7 cfu/100 g Lactobacillus, casei, Defensis, Active, 10^7 cfu/100g Streptococcus, thermophilus, n/a, Active, 10^8 cfu/100 g	1 100 grams 2 per day	Oral	0.75 months Short term	
Parra, 2004 RCT	1	n/a Patient	Lactobacillus, casei, DN-114001, n/a, 10^8-10^10 cfu/g	95 g 3 per day	Oral	2 months Medium term	Milk only
Passeron, 2005 RCT	1	n/a Alu-bag Patient	Lactobacillus, rhamnosus, Lcr35, n/a, 1.2*10^9 cfu/dose	1.5 q 3 per day	Oral	3 months Medium term	Prebiotic
Peral, 2009 RCT	1	n/a Culture on gauze pad Patient	Lactobacillus, plantarum, ATCC 10 241, n/a, 10^5 cfu/ml	1 pad 1 per day	Topical	0.33 months Short term	Non-probiotic
Pereg, 2010 RCT	1	Bio-plus Pill Patient	Lactobacillus, acidophilus, n/a, Lyophilized, 2*10^10 cfu/dose Lactobacillus, bulgaricus, n/a, Lyophilized, 2*10^10 cfu/dose Bifidobacterium, bifidum, n/a, Lyophilized, 2*10^10 cfu/dose Streptococcus, thermophilus, n/a, Lyophilized, 2*10^10 cfu/dose	1 dose 1 per day	Oral	6 months Medium term	Placebo
Petschow, 2005 RCT	1	n/a Formula Patient	Lactobacillus, rhamnosus, GG, Active, live, 1*10^4 cfu/g	Varies by participant	Oral	0.5 months Short term	Formula only
Petschow, 2005 RCT	3	Nutramigen Formulal Patient	Lactobacillus, rhamnosus, GG, Active, live, 10^7 cfu/g	Varies by participant	Oral		
Petschow, 2005 RCT	4	Nutramigen Formulal Patient	Lactobacillus, rhamnosus, GG, Active, live, 10^8 cfu/g	Varies by participant	Oral		
Prantera, 2002 RCT	1	Dicoflor 60 Bags - dissolved in water Patient	Lactobacillus, casei rhamnosus, n/a, n/a, 6*10^9 cfu	2.46 g 2 per day	Oral	12 months Long term	Placebo
Pregliasco, 2008 RCT	1	n/a Sachet Patient	Lactobacillus, plantarum, LP 02 LMG P-21020, Live, 10^10 cfu/0.1g Lactobacillus, rhamnosus, LR 04-DSM 16605, Live, 10^10 cfu/0.1g Bifidobacterium, lactis, BS-01-LMG P-21384, Live, 10^10 cfu/0.1g	1 sachet 1 per day	Oral	3 months Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Pregliasco, 2008 RCT	3	n/a Sachets Patient	Lactobacillus, plantarum, LP 02-LMG P-21020, Live, 10^10 cfu/0.1g Lactobacillus, rhamnosus, LR 04-DSM 16605, Live, 10^10 cfu/0.1g Bifidobacterium, lactis, BS 01-LMG P-21384, Live, 10^10 cfu/0.1g	1 sachet 1 per day	Oral		
Pregliasco, 2008 RCT	1	n/a Sachet Patient	Lactobacillus, plantarum, LP 01-LMG P-21021, n/a, 5*10^9 cfu Lactobacillus, plantarum, LP 01-LMG P-21020, n/a, 5*10^9 cfu Lactobacillus, rhamnosus, LR 04-DSM 16605, n/a, 5*10^9 cfu Lactobacillus, rhamnosus, LR 05 - DSM 19739, n/a, 5*10^9 cfu Bifidobacterium, lactis, BS 01-LMG P-21384, n/a, 5*10^9 cfu	1 sachet 1 per day	Oral	3 months Medium term	Placebo
Pregliasco, 2008 RCT	3	n/a Sachets Patient	Lactobacillus, plantarum, LP 02-LMG P-21020, Live, 10^10 cfu/0.1g Lactobacillus, rhamnosus, LR 04-DSM 16605, Live, 10^10 cfu/0.1g Bifidobacterium, lactis, BS 01-LMG P-21384, Live, 10^10 cfu/0.1g Lactobacillus, plantarum, LP 01-LMG P-21021, Live, 10^10 cfu/0.1g	1 sachet 1 per day	Oral		
Pregliasco, 2008 RCT	1	n/a Sachet Patient	Lactobacillus, plantarum, LP 02-LMG P-21020, Live, 10^10 cfu/0.1g Lactobacillus, rhamnosus, LR 04-DSM 16605, Live, 10^10 cfu/0.1g Bifidobacterium, lactis, BS 01-LM6 P-21384, Live, 10^10 cfu/0.1g	1 sachet 1 per day	Oral	3 months Medium term	Placebo
Puccio, 2007 RCT	1	Nan Formula Patient	Bifidobacterium, longum, BL-999, Live, 2*10^7 cfu	Varies by participant	Oral	3.7 months Medium term	Placebo
Rampengan, 2010 RCT	1	Lacidofil Pill Patient	Lactobacillus, n/a, n/a, Live, n/a	1 capsule 1 per day	Oral	0.5 months Short term	Other probiotic
Rampengan, 2010 RCT	2	Dialac Patient	Lactobacillus, n/a, n/a, Heat-killed, n/a	2 sachets 1 per day	Oral		
Ranganathan C-RCT	1	Kibow Biotics Pill Patient	Lactobacillus, acidophilus, KB31, n/a, 5*10^9 cfu/capsule Bifidobacterium, longum, KB35, n/a, 5*10^9 cfu/capsule Streptococcus, thermophilus, KB27, n/a, 5*10^9 cfu/capsule	2 capsule 3 per day	Oral	3 months Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Rautava, 2008 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, GG ATCC 53103, n/a, 10^10 cfu Bifidobacterium, lactis, BB-12, n/a, 10^10 cfu	1*10^10 cfu 1 per day	Oral	Medium term	Placebo
Rayes, 2002 RCT	1	n/a Enteral formula Patient	Lactobacillus, plantarum, 299, Live, 1*10^9 cfu	10^9 cfu 2 per day	Enteral	0.25 months Short term	Standard crystalloid solution only
Rayes, 2002 RCT	3	n/a Enteral formula Patient	Lactobacillus, plantarum, 299, Heat-killed, 1*10^9 cfu	10^9 cfu 2 per day	Enteral		
Rayes, 2002 RCT	1	n/a Enteral formula Patient	Lactobacillus, plantarum, 299, Live, 10^9 cfu	10^9 cfu 2 per day	Enteral	0.3 months Short term	Parenteral or enteral nutrition only
Rayes, 2002 RCT	3	n/a Enteral formula Patient	Lactobacillus, plantarum, 299, Heat-killed, n/a	10^9 cfu 2 per day	Enteral		
Rayes, 2005 RCT	1	Synbiotic 2000 Sachet Patient	Lactobacillus, paracasei paracasei, F-19, n/a, n/a Lactobacillus, plantarum, 2362, n/a, n/a	2 per day n/a	Varies	0.5 months Short term	Placebo
Rayes, 2007 RCT	1	n/a Sachet Patient	Lactobacillus, paracasei paracasei, F-19, n/a, n/a Lactobacillus, plantarum, 2362, n/a, n/a	1 sachet 2 per day	Varies	0.3 months Short term	Placebo
Reid, 1992 RCT	1	n/a Pill Patient	Lactobacillus, casei rhamnosus, GR-1, Lyophilized, 1.6*10^9 cfu/vial Lactobacillus, fermentum, B-54, Lyophilized, 1.6*10^9 cfu/vial	1 capsule	Vaginal	2 months Medium term	Placebo
Reid, 1995 RCT	1	n/a Suppository Patient	Lactobacillus, casei, GR-1, Lyophilized, 1*10^9 cfu Lactobacillus, fermentum, B-54, Lyophilized, 1*10^9	1 suppository 1 per week	Vaginal	12 months Long term	Prebiotic
Ren, 2010 RCT	1	Charge Le Kang Powder Patient	Bifidobacterium, n/a, n/a, Live, ?1.0*10^6 cfu/g Clostridium, butyricum, n/a, n/a, n/a	250 mg 2 per day	Oral	Short term	Non-probiotic
Reuman, 1986 RCT	1	n/a Formula Patient	Lactobacillus, acidophilus, n/a, n/a, 5*10^10 cfu/ml	1 ml 2 per day	Enteral	Medium term	Placebo
Richelsen, 1996 RCT	1	Gaio Fermented milk Patient	Enterococcus, faecium, n/a, n/a, 10^5-10^9 cfu/ml Streptococcus, thermophilus, n/a, n/a, 5-20*10^8 cfu/ml Streptococcus, thermophilus, n/a, n/a, 5-20*10^8 cfu/ml	200 ml 1 per day	Oral	6 months Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Rio, 2002 RCT	1	n/a Drink Patient	Lactobacillus, acidophilus, n/a, Viable, 10^7-10^8 cfu/ml Lactobacillus, casei, n/a, Viable, 10^8 cfu/ml	Varies by participant	Oral	3 months Medium term	Placebo
Roos, 1996 RCT	1	n/a Suspension spray Patient	Streptococcus, sanguis, n/a, Lyophilized, 10^6 cfu/50ml Streptococcus, mitis, n/a, Lyophilized, 10^6 cfu/50ml Streptococcus, sanguis, n/a, Lyophilized, 10^6 cfu/50ml Streptococcus, sanguis, n/a, Lyophilized, 10^6 cfu/50ml	3 puffs 2 per day	Topical	0.33 months Short term	Placebo
Roos, 2001 RCT	1	n/a Spray Patient	Streptococcus, sanguis, 2 strains, Lyophilized, 5*10^6 cfu/ml Streptococcus, mitis, 2 strains, Lyophilized, 5*10^6 5*10^6 5*10^6 cfu/ml Streptococcus, oralis, n/a, Lyophilized, 5*10^6 cfu/ml	6 puffs 2 per day	Other	2 months Medium term	Placebo
Rose, 2010 RCT	1	LGG Pill Capsule contents reconstituted in water Patient	Lactobacillus, rhamnosus, ATCC 53103 GG, n/a, 10^10 cfu/capsule	1 capsule 2 per day	Oral	6 months Medium term	Placebo
Rosenfeldt, 2002 RCT	1	n/a Patient	Lactobacillus, rhamnosus, 19070-Z, Lyophilized, 10^10 cfu Lactobacillus, reuteri, DSM 12246, Lyophilized, 10^10 cfu	10^10 cfu 2 per day	n/a	0.17 months Short term	Placebo
Rosenfeldt, 2003 C-RCT	1	n/a Powder mixed in water on milk Patient	Lactobacillus, casei alactus, CHCC 3137, Lyophilized, 10^10 cfu Lactobacillus, delbrueckii lactis, CHCC 2329, Lyophilized, 10^10 cfu Lactobacillus, rhamnosus, 66 ATCC 53103, Lyophilized, 10^10 cfu	10^10 cfu 2 per day	Oral	0.6 months Short term	Placebo
Rosenfeldt, 2003 C-RCT	3	n/a Powder mixed with water or milk Patient	Lactobacillus, rhamnosus, 19070-2, Lyophilized, 10^10 cfu Lactobacillus, reuteri, DSM 12246, Lyophilized, 10^10 cfu	10^10 cfu 2 per day	Oral		
Rouge, 2009 RCT	1	Valio Pill Patient	Lactobacillus, rhamnosus, GG, Lyophilized, 10^8 cells/unit Bifidobacterium, longum, BB 536, Lyophilized, 10^8 cfu/unit	4 capsule 1 per day	Enteral	Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Ruiz-Palacios, 1996 RCT	1	n/a Formula Added to Pediasure Patient	Lactobacillus, reuteri, n/a, n/a, 10^6 cfu Lactobacillus, acidophilus, n/a, n/a, 10^6 cfu Bifidobacterium, infantis, n/a, n/a, 10^6 cfu	n/a	Oral	0.75 months Short term	Placebo
Ruiz-Palacios, 1996 RCT	3	n/a Added to PediaSure Patient	Lactobacillus, reuteri, n/a, n/a, 10^10 cfu Lactobacillus, acidophilus, n/a, n/a, 10^10 cfu Bifidobacterium, infantis, n/a, n/a, 10^10 cfu	n/a	Oral		
Ruiz-Palacios, 1996 RCT	4	n/a Patient	Lactobacillus, reuteri, n/a, n/a, 10^8 cfu Lactobacillus, acidophilus, n/a, n/a, 10^8 cfu Bifidobacterium, infantis, n/a, n/a, 10^8 cfu	n/a	Oral		
Saavedra, 2004 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, BB-12, n/a, 10^6 cfu/g Streptococcus, thermophilus, n/a, n/a, 10^6 cfu/g	Varies by participant	Oral	Medium term	Placebo
Saavedra, 2004 RCT	3	n/a Formulal Patient	Bifidobacterium, lactis, BB-12, n/a, 10^7 cfu/g Streptococcus, thermophilus, n/a, n/a, 10^7 cfu/g	Varies by participant	Oral		
Safdar, 2008 RCT	1	Florajen Mix Patient	Lactobacillus, acidophilus, n/a, n/a, 2*10^7 cfu/capsule	1 capsule 3 per day	Oral	0.5 months Short term	Placebo
Sahagun-flores, 2007 RCT	1	n/a Patient	Lactobacillus, casei, Shirota, n/a, 8*10^9 cfu/dose	1 dose 3 per day	Oral	0.25 months Short term	Antibiotics only
Saint-Marc, 1995 RCT	1	n/a Patient	Saccharomyces, boulardii, n/a, n/a, 500mg/sachet	1 sachet 2 per day n/a	Oral Enteral	0.25 months Short term	Placebo
Salminen, 1988 RCT	1	n/a Yogurt Patient	Lactobacillus, acidophilus, NCDO 1748, Live, 2*10^9 cfu	150 ml 1 per day	Oral	Medium term	Dietary counseling only
Salminen, 2004 C-RCT	1	Valio Drink Patient	Lactobacillus, rhamnosus, GG, n/a, 1-5*10^10 cfu/dose	2 per day n/a	Oral	0.5 months Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Samanta, 2008 RCT	1	n/a Mix Breast milk Patient	Bifidobacterium, infantis, n/a, n/a, 2.5*10^9 cfu/dose Bifidobacterium, bifidum, n/a, n/a, 2.5*10^9 cfu/dose Bifidobacterium, longum, n/a, n/a, 2.5*10^9 cfu/dose Lactobacillus, acidophilus, n/a, n/a, 2.5*10^9 cfu/dose	1 dose 2 per day	Oral	Medium term	Placebo
Satokari, 2001 RCT	1	n/a Powder added to yogurt Patient	Bifidobacterium, lactis, BB-12, Lyophilized, 3*10^10 cfu	125 ml 2 per day	Oral	0.5 months Short term	Prebiotic
Satokari, 2001 RCT	3	n/a Combo of syrup + powder in yogurt Patient	Bifidobacterium, lactis, BB-12, Lyophilized, 3*10^10 cfu	125 ml 2 per day	Oral		
Savino, 2006 RCT	1	n/a Oil suspension Patient	Lactobacillus, reuteri, ATCC 55730, n/a, 10^8 cfu/5 drops	5 drops 1 per day	Oral	1 month Short term	Non-probiotic
Sazawal, 2010 RCT	1	n/a Sachets of milk powder Patient	Bifidobacterium, lactis, HN019, n/a, 3.3*10^6 cfu/sachet	1 Sachet 3 per Day	Oral	12 months Long term	Placebo
Scalabrin, 2009 RCT	1	LGG Formula Patient	Lactobacillus, rhamnosus, GG, n/a, 10^8 cfu/g	n/a	Oral	Medium term	Formula only
Scalabrin, 2009 RCT	3	n/a Formulal Patient	Lactobacillus, rhamnosus, GG, Lyophilized, 10^8 cfu/g formula	n/a	Oral		
Schrezenmeir, 2004 RCT	1	Pediasure Protect with SmartChoice Nutritional supplement-powder mixed to milk drink Patient	Lactobacillus, acidophilus, n/a, n/a, 10^9 cfu/g Bifidobacterium, n/a, n/a, n/a, 10^9 cfu/g	120 ml	Oral	Medium term	Pediasure only
Schultz, 2004 RCT	1	LGG Patient	Lactobacillus, rhamnosus, GG, n/a, 2*10^9 cfu	2*10^9 cfu 1 per day	n/a	6 months Medium term	Placebo
Seppo, 2003 RCT	1	Evolus Drink Patient	Lactobacillus, helveticus, LBK 16H, n/a, n/a	150 ml 1 per day	Oral	5.25 months Medium term	Milk only
Sierra, 2010 RCT	1	n/a Pill Patient	Lactobacillus, salivarius, CECT5713, n/a, 10^8 cfu/capsule	2 capsule 1 per day	Oral	1 month Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Simons, 2006 RCT	1	PCC Pill Patient	Lactobacillus, fermentum, n/a, n/a, 2*10^9 cfu	2 capsule 2 per day	Oral	2.5 months Medium term	Placebo
Simren, 2010 RCT	1	Cultura Drink Patient	Lactobacillus, paracasei paracasei, F-19, n/a, >5*10^7 cfu/ml Lactobacillus, acidophilus, La 5, n/a, >5*10^7 cfu/ml Bifidobacterium, lactis, BB-12, n/a, >5*10^7 cfu/ml Lactobacillus, bulgaricus, n/a, n/a, n/a Streptococcus, thermophilus, n/a, n/a, n/a	200 ml 2 per day	Oral	2 months Medium term	Placebo
Song, 2010 RCT	1	Bioflor250 Pill Patient	Saccharomyces, boulardii, n/a, n/a, 3*10^10 cfu/g	1 capsule 3 per day	Oral	1 month Short term	Triple therapy only
Song, 2010 RCT	3	Bioflor 250 Pill Patient	Saccharomyces, boulardii, DA9601, n/a, 3*10^10 cfu/g	1 capsule 3 per day	Oral		
Songisepp, 2005 RCT	1	n/a Pill Patient	Lactobacillus, fermentum, EE-3, lyophilized, 9.2 log cfu	3 capsules 2 per day	Oral	0.75 months Short term	Placebo
Songisepp, 2005 CCT	1	n/a Drink Patient	Lactobacillus, plantarum, LB-4, n/a, n/a Lactobacillus, buchneri, S-15, n/a, n/a Lactobacillus, fermentum, ME-3, Lyophilized, 11.2-11.8 cfu	150 ml 1 per day	Oral	0.75 months Short term	Goat's milk only
Sood, 2009 RCT	1	VSL#3 Sachet Patient	Lactobacillus, paracasei, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Lactobacillus, plantarum, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Lactobacillus, acidophilus, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Lactobacillus, delbrueckii, bulgaricus, Lyophilized, viable, 9*10^11 cfu/sachet Bifidobacterium, longum, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Bifidobacterium, breve, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Bifidobacterium, infantis, n/a, Lyophilized, viable, 9*10^11 cfu/sachet Streptococcus, thermophilus, n/a, Lyophilized, viable, 9*10^11 cfu/sachet	1 Sachet 4 per Day	Oral	3 months Medium term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Spanhaak, 1998 RCT	1	Yakult Drink Patient	Lactobacillus, casei, Shirota, n/a, 10^9 cfu/ml	100 ml 3 per day	Oral	1 month Short term	Placebo
Stockert, 2007 RCT	1	Symbioflor Drops Patient	Enterococcus, faecalis, n/a, n/a, 6*10^7 cfu	20 drops 3 per day	n/a	2 months Medium term	Placebo
Stotzer, 1996 C-RCT	1	n/a Pill Patient	Lactobacillus, fermentum, KLO, Lyophilized, 1-3*10^11 cfu/capsule	1 capsule 2 per day	Oral	1 month Short term	Placebo
Stratiki, 2007 RCT	1	PreN Formula Patient	Bifidobacterium, lactis, n/a, n/a, 2*10^7 cfu/g	Varies over time	Oral	Medium term	Placebo
Sullivan, 2003 RCT	1	n/a Yogurt Patient	Lactobacillus, acidophilus, NCFB 1748, n/a, 10^8 cfu/ml Bifidobacterium, lactis, BB-12, n/a, 10^8 cfu/ml Lactobacillus, paracasei paracasei, F19, n/a, 10^8 cfu/ml	250 ml 2 per day	Oral	0.5 months Short term	Placebo
Sykora, 2005 RCT	1	Actimel Drink Patient	Lactobacillus, casei, DN-114 001, Live, 10^10 cfu/100ml	100 ml 1 per day	Oral	0.5 months Short term	Placebo
Tamura, 2007 RCT	1	n/a Fermented milk Patient	Lactobacillus, casei, Shirota, n/a, 4*10^10 cfu/80ml	80 ml 1 per day	Oral	2 months Medium term	Placebo
Taylor, 2007 RCT	1	n/a Powder Patient	Lactobacillus, acidophilus, LAVRI-A1, Lyophilized, 3*10^9 cfu/packet	1 packet 1 per day	Oral	6 months Medium term	Placebo
Tempe, 1985 RCT	1	Perenterol Dissolved in enteral nutrition solution Patient	Saccharomyces, cerevisiae, Hansen CBS5926, Active, 5*10^9 cfu/capsule	2 capsules l per day	Enteral	Short term	Placebo
Teran, 2008 RCT	1	n/a Patient	Lactobacillus, acidophilus, n/a, n/a, 1.25*10^6 cfu Lactobacillus, rhamnosus, n/a, n/a, n/a Bifidobacterium, longum, n/a, n/a, n/a Saccharomyces, boulardii, n/a, n/a, n/a	1 g 2 per day	n/a	Short term	Rehydration solution only
Thomas, 2001 RCT	1	n/a Pill Patient	Lactobacillus, rhamnosus, GG, Live, 10^10 cfu	1 capsule 2 per day	Oral	0.5 months Short term	Placebo

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Tomoda, 1991 CCT	1	n/a Yogurt Patient	Bifidobacterium, longum, n/a, n/a, 10^8 cfu Streptococcus, salivarius thermophilus, n/a, n/a, n/a Lactobacillus, delbrueckii bulgaricus, n/a, n/a, n/a	130 g 1 per day	Oral	Medium term	Yogurt only
Tomoda, 1991 CCT	3	n/a Yogurt Patient	Bifidobacterium, longum, n/a, n/a, 10^8 cfu/g Saccharomyces, salivarius thermophilus, n/a, n/a, n/a Lactobacillus, delbrueckii bulgaricus, n/a, n/a, n/a	130 g 1 per day	Oral		
Tsuchiya, 2004 CCT	1	SCM III In a vitamin and phyto-extracts enriched medium Patient	Lactobacillus, acidophilus, n/a, n/a, 1.25*10^6 cfu/100ml Lactobacillus, helveticus, n/a, n/a, 1.3*10^9 cfu/100ml Bifidobacterium, n/a, n/a, n/a, 4.95*10^9 cfu/100ml	10 ml 3 per day	n/a	3 months Medium term	Synbiotic
Tsuchiya, 2004 CCT	2	SCM III heat inactivated symbiotic Patient	Lactobacillus, acidophilus, n/a, Heat-killed, 1.25*10^6 /100ml Lactobacillus, helveticus, n/a, Heat-killed, 1.3*10^6 /100ml Bifidobacterium, n/a, n/a, Heat-killed, 4.95*10^9 /100ml	10 ml 3 per day	n/a		
Turchet, 2003 RCT	1	Actimel Drink Patient	Lactobacillus, casei, DN-114 001, n/a, 10^8 cfu/ml	100 ml 2 per day	Oral	1 month Short term	No study product
Tursi, 2004 RCT	1	VSL#3 Bag Patient	Lactobacillus, casei, n/a, Lyophilized, 3*10^8 cfu/g Lactobacillus, plantarum, n/a, Lyophilized, 3*10^8 cfu/g Lactobacillus, acidophilus, n/a, Lyophilized, 3*10^8 cfu/g Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, 3*10^8 cfu/g Bifidobacterium, longum, n/a, Lyophilized, 3*10^8 cfu/g Bifidobacterium, infantis, n/a, Lyophilized, 3*10^8 cfu/g Bifidobacterium, breve, n/a, Lyophilized, 3*10^8 cfu/g Streptococcus, salivarius thermophilus, n/a, Lyophilized, 3*10^8 cfu/g	3 g 1 per day	Oral	2 months Medium term	Balsalazide only
Tursi, 2008 CCT	1	Enterolactis Pill Patient	Lactobacillus, casei casei, DG, n/a, 8*10^6 cfu	1.6*10^7 daily 10 per day/month	n/a	24 months Long term	Mesalazine only
Tursi, 2008 CCT	3	Enterolactis Patient	Lactobacillus, casei casei, DG, n/a, 1.6*10^7 cfu/day	1.6*10^7 daily 10 per days/month	n/a		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Tursi, 2010 RCT	1	VSL#3 Sachet Patient	Lactobacillus, paracasei, n/a, Lyophilized, viable, 900*10^9 cfu/sachet Lactobacillus, plantarum, n/a, Lyophilized, viable, 900*10^9 cfu/sachet Lactobacillus, acidophilus, n/a, Lyophilized, viable, 900*10^9 cfu/sachet Lactobacillus, delbrueckii, bulgaricus, Lyophilized, viable, 900*10^9 cfu/sachet Bifidobacterium, longum, n/a, Lyophilized, viable, 900*10^9 cfu/sachet Bifidobacterium, infantis, n/a, Lyophilized, viable, 900*10^9 cfu/sachet Bifidobacterium, breve, n/a, Lyophilized, viable, 900*10^9 cfu/sachet Streptococcus, thermophilus, n/a, Lyophilized, viable, 900*10^9 cfu/sachet	2 sachet 2 per day	Oral	2 months Medium term	Placebo
Underwood, 2009 RCT	1	Culturelle Pill Patient	Lactobacillus, rhamnosus, GG, Viable, 5*10^8 cfu/dose Lactobacillus, casei, n/a, n/a, n/a	1 ml 2 per day	Varies	Short term	Placebo
Underwood, 2009 RCT	3	ProBioPlus DDS Mix Patient	Lactobacillus, acidophilus, n/a, Viable, 5*10^8 cfu/dose Bifidobacterium, longum, n/a, Viable, 5*10^8 cfu/dose Bifidobacterium, bifidum, n/a, Viable, 5*10^8 cfu/dose Bifidobacterium, infantis, n/a, Viable, 5*10^8 cfu/dose	1 ml 2 per day	Varies		
Urban, 2008 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, n/a, n/a, n/a	Varies by participant	Oral	4 months Medium term	Formula only
Urbansek, 2001 RCT	1	Antibiophilus Sachet Patient	Lactobacillus, rhamnosus, n/a, n/a, 1.5*10^9 cfu	1.5 g 3 per day	Oral	0.25 months Short term	Placebo
Van der Aa, 2010 RCT	1	n/a Formula Patient	Bifidobacterium, breve, M-16V, n/a, 1.3*10^9 cfu/100ml	Varies by participant	Oral	3 months Medium term	Placebo
Van Gossum, 2007 RCT	1	LA1 Powder/Sachets Patient	Lactobacillus, johnsonii, LA-1, Lyophilized, 10^10 cfu/sachet	n/a	Enteral	3 months Medium term	Maltodextrin only
Velaphi, 2008 RCT	1	n/a Formula Patient	Bifidobacterium, Lactis, CNCM I-3446, n/a, n/a	Varies by participant	Oral	6 months Medium term	Formula only

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Vendt, 2006 RCT	1	Tutteli Formula Patient	Lactobacillus, rhamnosus, GG, n/a, 10^7 cfu	Varies by participant	Oral	Medium term	Placebo
Vleggaar, 2008 C-RCT	1	Ecologic 641 Sachet Patient	Lactobacillus, acidophilus, n/a, Lyophilized, 10^6 cfu/daily dose Lactobacillus, casei, n/a, Lyophilized, 10^6 cfu/daily dose Lactobacillus, salivarius, n/a, Lyophilized, 10^6 cfu/daily dose Lactobacillus, lactis, n/a, Lyophilized, 10^6 cfu/daily dose Bifidobacterium, bifidum, n/a, Lyophilized, 10^6 cfu/daily dose Bifidobacterium, lactis, n/a, Lyophilized, 10^6 cfu/daily dose	1 sachet 2 per day	Oral	3 months Medium term	Placebo
Vlieger, 2009 RCT	1	Frisol Formula Patient	Bifidobacterium, animalis lactis, BB-12 ATCC 27536, n/a, 1*10^7 cfu/g Lactobacillus, paracasei paracasei/g, CRL-431 (ATCC 55 544), n/a, 1*10^7 cfu/g	Varies by participant	Oral	Medium term	Prebiotic
Wada, 2010 RCT	1	n/a Sachet Patient	Bifidobacterium, breve, BBG-01, Lyophilized, live, 10^9 cfu/sachet	1 sachet 3 per day	Enteral	Medium term	Placebo
Wang, 2004 RCT	1	n/a Drink Patient	Streptococcus, thermophilus, n/a, n/a, n/a Lactobacillus, bulgaricus, n/a, n/a, n/a Lactobacillus, paracasei, LP-33, Viable, 1*10^7 cfu/ml	Varies by participant	Oral	1 month Short term	Fermented milk only
Wang, 2007 RCT	1	n/a Suspended in water Patient	Bifidobacterium, breve, M-16v, n/a, 1.6*10^8 cfu/0.5ml	0.5 ml 2 per day	Enteral	Medium term	No supplement
Weizman, 2005 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, BB-12, n/a, 10^7 cfu/g	n/a	Oral	3 months Medium term	Placebo
Weizman, 2006 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, BB-12, n/a, 1*10^7 cfu/g	Varies by participant	Oral	1 month Medium term	Placebo
Weston, 2005 RCT	1	n/a Sachet Patient	Lactobacillus, fermentum, VRI-003 PCC, Lyophilized, 1*10^6 cfu	1*10^9 cfu 2 per day n/a	Oral	2 months Medium term	Placebo
Wewalka, 2002 RCT	1	Döderlein Med® Pill Patient	Lactobacillus, gasseri, n/a, Lyophilized, 2*10^8-2*10^9 cfu/capsule	1 capsule 1 per day	Vaginal	0.2 months Short term	Non-probiotic

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Wheeler, 1997 C-RCT	1	n/a Yogurt Patient	Lactobacillus, bulgaricus, n/a, Live, 3.4*10^8 cfu/g Streptococcus, thermophilus, n/a, Live, 3.4*10^8 cfu/g Lactobacillus, acidophilus, n/a, Live, 3.4*10^8 cfu/g	8 oz 2 per day	Oral	1 month Short term	Yogurt only
Wildt, 2006 RCT	1	AB-Cap-10 Pill Patient	Lactobacillus, acidophilus, LA-5, n/a, 0.5*10^10 cfu Bifidobacterium, animalis lactis, BB-12, n/a, 0.5*10^10 cfu	2 capsules 2 per day	Oral	3 months Medium term	Placebo
Williams, 2008 RCT	1	LAB4 Pill Patient	Lactobacillus, acidophilus, CUL 60 NCIMB 30152, n/a, 2.5*10^10 cfu/capsule Lactobacillus, acidophilus, CUL 21 NCIMB 30156, n/a, .5*10^10 cfu/capsule Bifidobacterium, lactis, CUL 34 NCIMB 30172, n/a, .5*10^10 cfu/capsule Bifidobacterium, bifidum, CUL 20 NCIMB 30153, n/a, .5*10^10 cfu/capsule	1 capsule 1 per day	Oral	2 months Medium term	Placebo
Wind, 2010 RCT	1	n/a Sachet Patient	Lactobacillus, rhamnosus, PRSF-L477, Lyophilized, 5*10^10 cfu/sachet	2 sachet 1 per day	Oral	0.75 months Short term	Placebo
Wolf, 1994 RCT	1	n/a Pill Patient	Lactobacillus, reuteri, MM53ATTCC SD 2112, Lyophilized, 5*10^10 cfu/capsule	1 capsule 2 per day	Oral	0.75 months Short term	Placebo
Wolf, 1998 RCT	1	n/a Packets to be added to beverages Patient	Lactobacillus, reuteri, SD 2112, Lyophilized, 5*10^9 cfu/packet	1 packet 2 per day	Oral	0.75 months Short term	Placebo
Worthley, 2009 C-RCT	1	n/a Pill Patient	Bifidobacterium, lactis, LAFTI B94, n/a, 5*10^9 cfu/capsule	1 capsule 1 per day	Oral	1 month Short term	Prebiotic
Worthley, 2009 C-RCT	3	n/a Pill Patient	Bifidobacterium, lactis, LAFTI B94, n/a, 10^9 cfu/g	1 capsule 1 per day	Oral		
Xia, 2010 RCT	1	n/a Sachet Patient	Lactobacillus, acidophilus, LA-11, Live, 6-10 *10^8 cfu	1 Sachet 1 per day	Oral	Short term	Placebo
Xiang, 2006 RCT	1	Medilac-S Varies Patient	Bacillus, subtilis, n/a, n/a, n/a Enterococcus, faecium, n/a, n/a, n/a	2 capsule 3 per day	Oral	1 month Short term	Sulfasalazine only

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Xiao, 2003 RCT	1	n/a Yogurt Patient	Bifidobacterium, longum, BL1, n/a, 3.7*+-1.1*10^8 cfu Streptococcus, thermophilus, n/a, n/a, 3.4+-0.7*10^8 cfu Lactobacillus, delbrueckii bulgaricus, n/a, n/a, 3.7+-1.7*10^7 cfu	100 ml 3 per day	Oral	1 month Short term	Yogurt only
Xiao, 2003 RCT	1	Lacidophilin Pill Chewable tablets Patient	Lactobacillus, acidophilus, LB, Live, n/a	5 tablets 3 per day	Oral	1 month Short term	Other probiotic
Xiao, 2003 RCT	2	Lacteol Pill Patient	Lactobacillus, acidophilus, n/a, Heat killed, lyophilized, 5*10^9 cfu	2 capsules 2 per day	Oral		
Yang, 2008 RCT	1	B10 Drink Patient	Bifidobacterium, lactis, DN-173010, n/a, 1.25*10^10 cfu/pot Streptococcus, thermophilus, n/a, n/a, 1.2*10^9 cfu/pot Lactobacillus, bulgaricus, n/a, n/a, 1.2*10^9 cfu/pot	100 g 1 per day	Oral	0.5 months Short term	Placebo
Yao-Zong, 2004 RCT	1	Bifico Pill Patient	Lactobacillus, bifidum, n/a, Live, >=10^7 cfu Lactobacillus, acidophilus, n/a, Living, >=10^7 cfu Enterococcus, n/a, n/a, Live, >=10^7 cfu	420 mg 2 per day	n/a	1 month Short term	Dioctahedral smectite
Yonekura RCT	1	n/a Powder Patient	Lactobacillus, paracasei, KW3110, n/a, 1*10^12 - 3*10^12 cfu/gm	1 g 1 per day	Oral	3 months Medium term	Placebo
Zhang, 2010 RCT	1	Bifico Pill Patient	Bifidobacterium, n/a, n/a, Viable, n/a	3 capsule 3 per day	Oral	Medium term	Non-probiotic
Ziegler, 2003 RCT	1	n/a Formula Patient	Bifidobacterium, lactis, n/a, n/a, 3.6*10^7 cfu/g	n/a	Oral	4 months Medium term	Formula only
Zocco, 2003 RCT	1	Giflorex Patient	Lactobacillus, rhamnosus, n/a, Viable, 18*10^9 cfu/day	18*10^9 bacteria 1 per day	n/a	12 months Long term	Mesalazine only
Zocco, 2003 RCT	3	Giflorex Patient	Lactobacillus, rhamnosus, GG, Viable, 18*10^9 cfu/day	18*10^9 bacteria 1 per day	n/a		

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
An, 2010 Case Series	1	n/a Patient	Lactobacillus, acidophilus, LH CBT, n/a, 3*10^11 cfu/g Bifidobacterium, longum, SPM 1205, n/a, 3*10^11 cfu/g Pediococcus, pentosaceus, PP CBT, n/a, 3*10^11 cfu/g	2 per day n/a	Oral	0.5 months Short term	None
Barrett, 2008 Case Series	1	Yakult Drink Patient	Lactobacillus, casei, Shirota, n/a, 6.5*10^6 cfu/65ml bottle	65 ml 1 per day	Oral	1.5 months Medium term	None
Beck, 1961 Case Series	1	Bacid Pill Patient	Lactobacillus, acidophilus, n/a, Dried, viable, n/a	Varies by participant	n/a	Medium term	None
Bekkali, 2007 Case Series	1	Ecologic Relief Patient	Bifidobacterium, bifidum, n/a, n/a, 4*10^9 cfu Bifidobacterium, infantis, n/a, n/a, 4*10^9 cfu Bifidobacterium, longum, n/a, n/a, 4*10^9 cfu Lactobacillus, casei, n/a, n/a, 4*10^9 cfu Lactobacillus, plantarum, n/a, n/a, 4*10^9 cfu Lactobacillus, rhamnosus, n/a, n/a, 4*10^9 cfu	4*10^9 cfu 1 per day	n/a	1 month Short term	None
Bellomo, 1979 Case Series	1	Bioflorin Mix Powder Patient	Enterococcus, faecium, SF-68, Lyophilized, 3*10^7 cfu/g	1-3 doses 2-3 per day	Oral	Short term	Placebo
Benchimol, 2004 Case Series	1	Probi Patient	Lactobacillus, plantarum, 299v, n/a, 10^10 cfu Lactobacillus, acidophilus, R0052, Lyophilized, 10^10 cfu Lactobacillus, rhamnosus, R0011, Lyophilized, 10^10 cfu Bifidobacterium, breve, R0070, Lyophilized, 10^10 cfu	10^10 cfu 1 per day	n/a	7 months Medium term	None
Berman, 2006 Case Series	1	n/a Tablet Patient	Lactobacillus, rhamnosus, n/a, n/a, 2*10^9 cfu Lactobacillus, plantarum, n/a, n/a, 2*10^9 cfu Lactobacillus, salivarius, n/a, n/a, 2*10^9 cfu Bifidobacterium, bifidum, n/a, n/a, 2*10^9 cfu	3 tablets 1 per day	Oral	2 months Medium term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Bibiloni, 2005 Case Series	1	VSL#3 Sachet Patient	Lactobacillus, casei, n/a, Lyophilized, 9*10^11 cfu/sachet Lactobacillus, acidophilus, n/a, Lyophilized, 9*10^11 cfu/sachet Lactobacillus, bulgaricus, n/a, Lyophilized, 9*10^11 cfu/sachet Lactobacillus, plantarum, n/a, Lyophilized, 9*10^11 cfu/sachet Bifidobacterium, longum, n/a, Lyophilized, 9*10^11 cfu/sachet Bifidobacterium, infantis, n/a, Lyophilized, 9*10^11 cfu/sachet Bifidobacterium, breve, n/a, Lyophilized, 9*10^11 cfu/sachet Streptococcus, salivarius thermophilus, n/a, Lyophilized, 9*10^11 cfu/sachet	2 sachets 2 per day	Oral	2 months Medium term	None
Bruce, 1988 Case Series	1	n/a Topical solution (intravaginal) Patient	Lactobacillus, casei rhamnosus, 6R-1, Active, viable, 10^11 cfu/ml	1 ml 2 per week	Vaginal	Medium term	None
Bruni, 2008 Case Series	1	Fiorilac, Dicoflor, Reuterin Sachet, diluted in water Patient	Lactobacillus, paracasei, I 1688, n/a, 0.1*10^9-10*10^9 cfu Lactobacillus, salivarius, I 1794, n/a, 0.1*10^9-10*10^9 cfu Lactobacillus, rhamnosus, GG, n/a, 3*10^9 cfu Lactobacillus, reuteri, n/a, n/a, 10^8 cfu/5 drops	1 per day n/a	Other	0.03 months Short term	None
Carlsson, 2009 Case Series	1	Verum Drickyoghurt Yogurt Patient	Lactobacillus, rhamnosus, LB-21, n/a, n/a Lactococcus, lactis, L1A, n/a, >5*10^7 cfu/ml	200 ml 1 per day	Oral	6 months Medium term	None
Cobo Sanz, 2006 Case Series	1	Actimel Drink Patient	Lactobacillus, casei, BN-114 001, n/a, n/a Lactobacillus, bulgaricus, n/a, n/a, n/a Streptococcus, thermophilus, n/a, n/a, n/a	1 per day Varies by participant	Oral	2 months Medium term	None
Colecchia, 2006 Case Series	1	Zir fos Bag Patient	Bifidobacterium, longum, W11, n/a, n/a	3 g 1 per day	n/a	1.25 months Medium term	None
Di Pierro, 2009 Case Series	1	Kramegin Vaginal tablet Patient	Lactobacillus, acidophilus, n/a, n/a, 10^9 cfu/tablet	1 tablet 1 per day	Vaginal	0.33 months Short term	None
Dughera, 2007 Case Series	1	Zir fos Bag Patient	Bifidobacterium, longum, W11, n/a, 5*10^9 cfu/3g bag	3 g 1 per day	Oral	3 months Medium term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Elmer, 1995 Case Series	1	n/a Pill Patient	Saccharomyces, boulardii, n/a, n/a, n/a	Varies over time	Oral	Medium term	None
Fukuda, 2008 Case Series	1	n/a Yogurt Patient	Bifidobacterium, lactis, DN-17B010, n/a, 10^8 cfu	85 g 1 per day	Oral	0.5 months Short term	None
Gabrielli, 2009 Case Series	1	Enterogermina Vial Patient	Bacillus, clausii, n/a, n/a, 2*10^9 spores/vial	1 vial 3 per day	n/a	1 month Short term	None
Garrido, 2005 Case Series	1	Chamyto Liquid Patient	Lactobacillus, johnsonii, LA-1, n/a, 1*10^8 cfu/ml Lactobacillus (nonprobiotic strain), helveticus, n/a, n/a, 2*10^7 cfu/ml Bacillus, stearothermophilus spores, n/a, n/a, 7*10^7 cfu/ml	Varies over time	Oral	0.75 months Short term	None
Gionchetti, 2007 Case Series	1	VSL#3 Packet Patient	Lactobacillus, casei, n/a, Lyophilized, viable, 9*10^11 cfu/packet Lactobacillus, plantarum, n/a, Lyophilized, viable, 9*10^11 cfu/packet Lactobacillus, acidophilus, n/a, Lyophilized, viable, 9*10^11 cfu/packet Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, viable, 9*10^11 cfu/packet Bifidobacterium, longum, n/a, Lyophilized, viable, 9*10^11 cfu/packet Bifidobacterium, breve, n/a, Lyophilized, viable, 9*10^11 cfu/packet Bifidobacterium, infantis, n/a, Lyophilized, viable, 9*10^11 cfu/packet Streptococcus, salivarius thermophilus, n/a, Lyophilized, viable, 9*10^11 cfu/packet	2 packets 2 per day	n/a	1 month Short term	None
Glintborg, 2006 Case Series	1	n/a Pill Patient	Lactobacillus, reuteri, ATCC 55730, n/a, 4*10^8 cfu/tablet	2 tablets 2 per day	Oral	6 months Medium term	None
Gniwotta, 1977 Case Series	1	Perenterol Pill Patient	Saccharomyces, cerevisiae, n/a, n/a, 50 mg/capsule	9-12 capsules per day Varies by participant	Oral	Short term	None
Gotteland, 2003 Case Series	1	Chamyto Drink Patient	Lactobacillus, johnsonii, LA-1, n/a, >10^7 cfu/ml	80 ml 8 per day	Oral	0.5 months Short term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Gruenwald, 2002 Case Series	1	Advanced Formula Multibionta Pill Patient	Lactobacillus, acidophilus, n/a, n/a, 10^6 cfu/1g capsule Bifidobacterium, bifidum, n/a, n/a, 10^6 cfu/1g capsule Bifidobacterium, longum, n/a, n/a, 10^6 cfu/1g capsule	1 g 1 per day	Oral	6 months Medium term	None
Hensgens, 1976 Case Series	1	n/a Drink Patient	Lactobacillus, acidophilus, n/a, Viable, 10^8-10^11 cfu/ml Lactobacillus, plantarum, n/a, Viable, 10^8-10^11 cfu/ml	500 ml 1 per day	Oral	Short term	None
Huynh, 2009 Case Series	1	VSL#3 Sachet Patient	Lactobacillus, casei, n/a, Lyophilized, 4.5*10^8 cfu Lactobacillus, plantarum, n/a, Lyophilized, 4.5*10^11 cfu/sachet Lactobacillus, acidophilus, n/a, Lyophilized, 4.5*10^11 cfu/sachet Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, 4.5*10^11 cfu/sachet Bifidobacterium, longum, n/a, Lyophilized, 4.5*10^11 cfu/sachet Bifidobacterium, breve, n/a, Lyophilized, 4.5*10^11 cfu/sachet Bifidobacterium, infantis, n/a, Lyophilized, 4.5*10^11 cfu/sachet Streptococcus, salivarius thermophilus, n/a, Lyophilized, 4.5*10^11 cfu/sachet	0.5-2.5 sachets 2 per day Varies by participant	Oral	2 months Medium term	None
Karimi, 2005 Case Series	1	VSL#3 Sachet Patient	Lactobacillus, acidophilus, n/a, Lyophilized, 4*10^11 cfu Lactobacillus, plantarum, n/a, Lyophilized, 4*10^11 cfu Lactobacillus, casei, n/a, Lyophilized, 4*10^11 cfu Lactobacillus, bulgaricus, n/a, Lyophilized, 4*10^11 cfu Bifidobacterium, longum, n/a, Lyophilized, 4*10^11 cfu Bifidobacterium, breve, n/a, Lyophilized, 4*10^11 cfu Bifidobacterium, infantis, n/a, Lyophilized, 4*10^11 cfu Streptococcus, salivarius thermophilus, n/a, Lyophilized, 4*10^11 cfu	2 sachets 2 per day	n/a	3 months Medium term	None
Kawamura,1981 Case Series	1	n/a Patient	Lactobacillus, casei, n/a, n/a, n/a	1 g 3 per day	Oral	Medium term	None
Kirchhelle, 1996 Case Series	1	n/a Pill Patient	Saccharomyces, boulardii, n/a, n/a, 50 mg/capsule	1-3 capsules 3x per day Varies by participant	n/a	Short term	Pre-test

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Kitajima, 1997 Case Series	1	Yakult Powder Patient	Bifidobacterium, breve, YIT 4010, n/a, 10^9 cfu/g	Varies by participant	n/a	Short term	None
Lamiki, 2010 Case Series	1	SCM-III Microflorana-F Patient	Lactobacillus, acidophilus, 145, n/a, 1.25*10^6 cfu/100ml Bifidobacterium, n/a, 420, n/a, 4.95*10^9 cfu/100ml Lactobacillus, helveticus, ATC 15009, n/a, 1.3*10^9 cfu/100ml	10 ml 3 per day	Oral	6 months Medium term	None
Lee, 2010 Case Series	1	BLIS BioRestor Powder Patient	Lactobacillus, acidophilus, L10, Viable, 4*10^8 cfu/g Bifidobacterium, lactis, B94, Viable, 4*10^8 cfu/g Streptococcus, salivarius, K12, Viable, 1*10^8 cfu/g	1 g 2 per day	Oral	0.25 months Short term	Pre-test
Lombardo, 2009 Case Series	1	Genefilus F19 Sachet dissolved in water Patient	Lactobacillus, paracasei paracasei, F19, n/a, 12*10^9 cfu/sachet	1 sachet 2 per day	Oral	0.5 months Short term	None
Luoto, 2010 Case Series	1	n/a Patient	Lactobacillus, rhamnosus, GG ATCC 53103, n/a, 6*10^9 cfu/dose	6*10^9 cfu 1 per day	Enteral	Medium term	None
Malin, 1996 Case Series	1	n/a Powder Patient	Lactobacillus, rhamnosus, GG ATCC 53103, Lyophilized, 10^10 cfu	10^10 cfu 2 per day	Oral	0.33 months Short term	Pre-test
Malkov, 2006 Case Series	1	n/a Patient	Bacillus, oligonitrophilus, KU-1, Active, stationary phase, 0.5-1*10^9 cells/ml	Varies by participant	Oral	Medium term	None
Mego, 2005 Case Series	1	n/a Pill Patient	Enterococcus, faecium, M-74, Lyophilized, 6*10^9-18*10^9 cfu/capsule	Varies by participant	Oral	1.5 months Medium term	None
Mego, 2006 Case Series	1	n/a Pill Patient	Enterococcus, faecium, M-74, Lyophilized, 6*10^9 cfu/capsule	6 capsules 3 per day	Oral	Medium term	None
Michetti, 1999 Case Series	1	n/a Whey based Patient	Lactobacillus, acidophilus, LA-1, n/a, supernatant	50 ml supernatant	n/a	0.5 months Short term	None
Muting, 1968 Case Series	1	n/a Milk powder in warm water solution with meals Patient	Bifidobacterium, bifidum, n/a, n/a, n/a	Varies by participant	Oral	Medium term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Nobuta, 2009 Case Series	1	n/a Beverage Patient	Lactobacillus, brevis, KB290, n/a, 1*10^10 cfu/130 ml	130 ml 3 per day	Oral	0.5 months Short term	None
Reid, 2001 Case Series	1	n/a Probiotic suspension-in milk Patient	Lactobacillus, rhamnosus, GR-1, Viable, >10*9 cfu/3ml Lactobacillus, fermentum, RC-14, Viable, >10*9 cfu/3ml	3 ml 2 per day	Enteral	0.5 months Short term	None
Rosenfeldt, 2003 Case Series	1	n/a Powder Patient	Lactobacillus, rhamnosus, 19070-2, Lyophilized, 10^10 cfu Lactobacillus, reuteri, DSM 12246, Lyophilized, 10^10 cfu	10^10 cfu 2 per day	Oral	0.33 months Short term	None
Sakamoto, 2001 Case Series	1	n/a Yogurt Patient	Lactobacillus, gasseri, OLL 2716 (LG21), n/a, 1-1.4 *10^7 cfu/g	90 g 2 per day	Oral	2 months Medium term	None
Schneider, 2005 Case Series	1	n/a Powder Patient	Saccharomyces, boulardii, n/a, Lyophilized, n/a	500 mg 2 per day	Oral Enteral	0.25 months Short term	None
Shen, 2005 Case Series	1	VSL#3 Yovis Patient	Lactobacillus, acidophilus, n/a, Lyophilized, 4.5*10^8 cfu Lactobacillus, plantarum, n/a, Lyophilized, 4.5*10^8 cfu Lactobacillus, paracasei, n/a, Lyophilized, 4.5*10^8 cfu Lactobacillus, bulgaricus, n/a, Lyophilized, 4.5*10^8 cfu Bifidobacterium, breve, n/a, Lyophilized, 4.5*10^8 cfu Bifidobacterium, infantis, n/a, Lyophilized, 4.5*10^8 cfu Bifidobacterium, longum, n/a, Lyophilized, 4.5*10^8 cfu Streptococcus, thermophilus, n/a, Lyophilized, 4.5*10^8 cfu	6 g 1 per day	Oral	8 months Medium term	None
Srinivasan, 2006 Case Series	1	Yanult-yakult Drink Patient	Lactobacillus, casei, Shirota, Live, 6.5*10^6 cfu/65ml	10^7 cfu 1 per day	Enteral	Short term	None
Tasli, 2006 Case Series	1	INERSAN VSL Lozenge Patient	Lactobacillus, brevis, CD2, n/a, n/a	1 lozenges 6 per day	Oral	0.25 months Short term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
van Bodegraven, 2004 Case Series	1	VSL#3 Patient	Lactobacillus, casei, n/a, Lyophilized, 4.5*10^8 cfu Lactobacillus, plantarum, n/a, Lyophilized, 4.5*10^8 cfu Lactobacillus, acidophilus, n/a, Lyophilized, 4.5*10^8 cfu Lactobacillus, delbrueckii bulgaricus, n/a, Lyophilized, 4.5*10^8 cfu Bifidobacterium, longum, n/a, Lyophilized, 4.5*10^8 Bifidobacterium, infantis, n/a, Lyophilized, 4.5*10^8 cfu Bifidobacterium, breve, n/a, Lyophilized, 4.5*10^8 cfu Streptococcus, salivarius thermophilus, n/a, Lyophilized, 4.5*10^8 cfu	2 per day n/a	n/a	3 months Medium term	None
Weiss, 2010 Case Series	1	Bio-plus Tablet Patient	Lactobacillus, acidophilus, n/a, n/a, 7.5*10^8 cfu/tablet Lactobacillus, bulgaricus, n/a, n/a, 7.5*10^8 cfu/tablet Bifidobacterium, bifidum, n/a, n/a, 7.5*10^8 cfu/tablet Streptococcus, thermophilus, n/a, n/a, 7.5*10^8 cfu/tablet	2 tablets 1 per day	Oral	6 months Medium term	None
Yim, 2006 Case Series	1	n/a Patient	Lactobacillus, rhamnosus, n/a, n/a, n/a Lactobacillus, plantarum, n/a, n/a, n/a Lactobacillus, casei, n/a, n/a, n/a Bifidobacterium, lactis, n/a, n/a, n/a	2 per day	n/a	2 months Medium term	None
Zahradnik, 2009 Case Series	1	ProBiora Powder, mouth wash Patient	Streptococcus, oralis, KJ3sm, Lyophilized, 10^6-10^8 cfu/bottle Streptococcus, uberis, KJ2sm, Lyophilized, 10^6-10^8 cfu/bottle Streptococcus, rattus, JH145, Lyophilized, 10^6-10^8 cfu/bottle	1 bottle 2 per day	Oral	2 months Medium term	None
Zahradnik, 2009 Case Series	1	ProBiora Mouth wash Patient	Streptococcus, oralis, KJ3sm, Lyophilized, 10^8 cfu/bottle Streptococcus, uberis, KJ2sm, Lyophilized, 10^8 cfu/bottle Streptococcus, rattus, JH145, Lyophilized, 10^8 cfu/bottle	1 bottle 2 per day	Oral	0.25 months Short term	None
Barton, 2001 Case Study	1	Bacid Capsule added to formula Patient	Lactobacillus, acidophilus, n/a, n/a, n/a Enterococcus, faecium, n/a, n/a, n/a	n/a	n/a	Medium term	None
Bassetti, 1998 Case Study	1	Perenterol Patient	Saccharomyces, boulardii, n/a, n/a, n/a	500 mg 2 per day	Oral	0.6 months Short term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Burkhardt, 2005 Case Study	1	Perenterol Patient	Saccharomyces, boulardii, n/a, n/a, n/a	150 mg 1 per day	Enteral	Medium term	None
Cesaro, 2000 Case Study	1	Codex Pill Patient	Saccharomyces, boulardii, n/a, n/a, n/a	n/a	n/a	Medium term	None
Cherifi, 2004 Case Study	1	Perenterol Patient	Saccharomyces, boulardii, n/a, n/a, n/a	300 mg 1 per day	Oral	0.25 months Short term	None
Conen, 2009 Case Study	1	Aktifit Drink Patient	Lactobacillus, n/a, n/a, n/a, n/a	n/a	Oral	Medium term	None
De Groote, 2005 Case Study	1	LGG Pill Patient	Lactobacillus, rhamnosus, GG, n/a, n/a	1/8 capsule 2 per day	Enteral	1.25 months Medium term	None
Force, 1995 Case Study	1	Ultra-Levure Patient	Saccharomyces, cerevisiae, n/a, n/a, n/a	n/a	n/a	Medium term	None
Fredenucci, 1998 Case Study	1	Ultra-Levure Package Patient	Saccharomyces, boulardii, n/a, n/a, n/a	4 package 1 per day	n/a	Short term	None
Hennequin, 2000 Case Study	1	n/a Enteral, parenteral (case1,2,4) Patient	Saccharomyces, boulardii, n/a, n/a, n/a	Varies by participant	Enteral Varies n/a	Medium term	None
Henry, 2004 Case Study	1	Perenterol Patient	Saccharomyces, boulardii, n/a, n/a, n/a	n/a	n/a	0.07 months Short term	None
Hwang, 2009 Case Study	1	Bioflor Powder Patient	Saccharomyces, boulardii, n/a, Lyophilized, n/a	n/a	Oral	0.1 month Short term	None
Jensen, 1974 Case Study	1	n/a Patient	Saccharomyces, cerevisiae, n/a, n/a, 10^7-10^9 /g	n/a	Oral	Long term	None
Kniehl, 2003 Case Study	1	Bactisubtil Varies Patient	Bacillus, IP, 5832, n/a, n/a	n/a	Varies	Short term	None
Ku, 2006 Case Study	1	Infloran Berna Pill Patient	Lactobacillus, acidophilus, n/a, n/a, n/a Bifidobacterium, infantis, n/a, n/a, n/a	n/a	n/a	Medium term	None
Kunz, 2004 Case Study	1	Culturelle; LGG Pill Patient	Lactobacillus, rhamnosus, GG, n/a, n/a	1 capsule 1 per day	Enteral	Medium term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Land, 2005 Case Study	1	Culturelle Pill Patient	Lactobacillus, rhamnosus, GG, n/a, 10*10^9 cfu/capsule	1 capsule 1 per day	Enteral	Medium term	None
Land, 2005 Case Study	3	n/a Pill Patient	Lactobacillus, rhamnosus, GG, n/a, 10*10^9 cfu/capsule	1 capsule 1 per day	Enteral		
LeDoux, 2006 Case Study	1	n/a Patient	Lactobacillus, acidophilus, n/a, n/a, n/a	3 per day n/a	n/a	0.75 months Short term	None
Lestin, 2003 Case Study	1	Perenterol Pill Patient	Saccharomyces, cerevisiae boulardii, Hansen CB55926, Lyophilized, n/a	150 mg n/a per day	Oral	0.4 months Short term	None
Lherm, 2002 Case Study	1	n/a Packet Patient	Saccharomyces, boulardii, n/a, Viable, n/a	n/a	Enteral	Medium term	None
Lolis, 2008 Case Study	1	Ultra-Levure Patient	Saccharomyces, boulardii, n/a, n/a, n/a	500 mg 4 per day	Enteral	0.25 months Short term	None
Lungarotti, 2003 Case Study	1	Codex DNB Pill Patient	Saccharomyces, boulardii, n/a, n/a, 2.5*10^9 cfu/0.5 capsule	1/2 capsules 1 per day	n/a	0.13 months Short term	None
Mackay, 1999 Case Study	1	n/a Pill Patient	Lactobacillus, rhamnosus, n/a, Lyophilized, 2*10^9 cfu Lactobacillus, acidophilus, n/a, n/a, n/a Streptococcus, faecalis, n/a, n/a, n/a n/a, n/a, n/a, n/a, n/a	1-2 capsules 1 per day	Oral	Short term	None
Munakata, 2010 Case Study	1	Lactomin Patient	Lactobacillus, acidophilus, n/a, n/a, n/a Lactobacillus, bulgaricus, n/a, n/a, n/a Streptococcus, faecalis, n/a, n/a, n/a Streptococcus, faecium, n/a, n/a, n/a	1-2 g 1 per day Varies over time	n/a	Medium term	None
Muñoz, 2005 Case Study	1	Ultra-Levure Pill Patient	Saccharomyces, boulardii, n/a, Lyophilized, n/a	Varies by participant	n/a	Short term	None
Niault, 1999 Case Study	1	n/a Patient	Saccharomyces, boulardii, n/a, n/a, n/a	1.5 g 1 per day	Enteral	0.5 months Short term	None
Oggioni, 1998 Case Study	1	Enterogermina Patient	Bacillus, subtilis, ATCC 9799, n/a, 10^9 spores/dose	n/a	Oral	1 month Medium term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Oh, 1979 Case Study	1	n/a Pill Patient	Lactobacillus, acidophilus, n/a, n/a, n/a	n/a	Oral	3 months Medium term	None
Ohishi, 2010 Case Study	1	n/a Powder Patient	Bifidobacterium, breve, BBG-01, Lyophilized, 10^9 cfu/g	2 per day n/a	Oral	0.4 months Short term	None
Perapoch, 2000 Case Study	1	n/a Sachet Patient	Saccharomyces, boulardii, n/a, n/a, n/a	1 Sachet 2 per day	n/a	0.33 months Short term	None
Piarroux, 1999 Case Study	1	n/a Patient	Saccharomyces, boulardii, n/a, n/a, n/a	n/a	n/a	Medium term	None
Piechno, 2007 Case Study	1	n/a Central line Patient	Saccharomyces, boulardii, n/a, n/a, n/a	450-600 mg n/a per day	Vein	Short term	None
Pletinex, 1995 Case Study	1	Perenterol Pill Patient	Saccharomyces, boulardii, n/a, Lyophilized, n/a	3 capsules 4 per day	Oral	Short term	None
Presterl, 2001 Case Study	1	n/a Yogurt Sour milk Patient	Lactobacillus, n/a, n/a, n/a, n/a	1.5 liter 1 per day	Oral	Medium term	None
Rautio, 1999 Case Study	1	n/a Drink Patient	Lactobacillus, rhamnosus, GG, n/a, n/a	1/2 liter 1 per day	Oral	4 months Medium term	None
Richard, 1988 Case Study	1	Bactisubtil Pill Patient	Bacillus, subtilis, n/a, n/a, 10^9 spores/tab	8 tablets 1 per day	Oral	Short term	None
Rijnders, 2000 Case Study	1	Perenterol Pill Patient	Saccharomyces, boulardii, n/a, n/a, n/a	2 capsules 6 per day	n/a	Short term	None
Riquelme, 2003 Case Study	1	Perenterol Patient	Saccharomyces, boulardii, n/a, Lyophilized, 5*1085*10^10 cells	250 mg 4 per day	Oral	Short term	None
Tommasi, 2008 Case Study	1	n/a Patient	Lactobacillus, casei, n/a, n/a, n/a	n/a	Oral	Medium term	None
Trautmann, 2008 Case Study	1	Perenterol Gastric tube Patient	Saccharomyces, boulardii, n/a, n/a, n/a	250 mg 2 per day	Enteral	1 month Short term	None
Viggiano, 1995 Case Study	1	n/a Gastric tube Patient	Saccharomyces, boulardii, n/a, n/a, n/a	4 sachet 4 per day	Enteral	0.25 months Short term	None

Evidence Table C2. Intervention (continued)

Author, Year Study Design	Arm	Product Delivery Vehicle Target	Genus, Species, Strain, Form, Potency	Dose Number/ Dose Unit Frequency Number	Route of Administration	Duration Long-Term Use	Control Category
Zein, 2008 Case Study	1	n/a Patient	Bifidobacterium, bifidum, n/a, n/a, 3*10^9 cfu/dose Bifidobacterium, longum, n/a, n/a, 8*10^7 cfu Lactobacillus, acidophilus, n/a, n/a, 7.7*10^8 cfu Lactobacillus, bulgaricus, n/a, n/a, 7.6*10^8 cfu Lactobacillus, casei, n/a, n/a, 5.4*10^8 cfu Lactobacillus, rhamnosus, n/a, n/a, 8*10^7 cfu Streptococcus, thermophilus, n/a, n/a, 8*10^7 cfu	n/a	Oral	Medium term	None
Zunic, 1991 Case Study	1	Ultra Gastric tube Patient	Saccharomyces, boulardii, n/a, Lyophilized, n/a	10 g 3 per day	Enteral	Medium term	None

*Abbreviations: C-RCT=Cross-over Randomized Controlled Trial; CCT=Controlled Clinical Trials; cfu=colony forming unit; g=gram; mg-milligram; ml=milliliter; n/a=not available or not applicable; RCT=Randomized Controlled Trial

Evidence Table C3. Assessment

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Abrahamsson, 2007 RCT	AE nonspecific	Telephone interview Provider assessment Medical record	Long-term
Agerbaek, 1995 RCT	n/a	n/a	n/a
Aihara, 2005 RCT	AE nonspecific; Dry cough; Exanthema; Skin itching; Dysgeusia; Headache; Dizziness/drift; Inappetence; Constipation; Flatulence; Abdominal discomfort	Provider assessment Patient record	n/a
Alberda, 2007 RCT	n/a	Provider assessment	n/a
Allen, 2010 RCT	Infections; AE nonspecific; Hospitalization; Microbiology lab results to identify Lactobacillus or Bifidobacteria infections	Questionnaire Telephone interview Provider assessment	Short
Anderson, 2003 RCT	n/a	Provider assessment	n/a
Andriulli, 2008 RCT	AE nonspecific	Diary Provider assessment	n/a
Anukam, 2006 RCT	n/a	n/a	n/a
Anukam, 2008 RCT	Diarrhea; n/a	Questionnaire	n/a
Anukam, 2009 RCT	AE nonspecific	Questionnaire	Short
Arunachalam, 2000 RCT	AE nonspecific	n/a	Short
Aso, 1992 RCT	AE nonspecific; Abnormal lab findings	Japan Society for Cancer Therapy Criteria Provider assessment Lab test	n/a
Aso, 1995 RCT	Lab tests	Japan Society for Cancer Therapy Criteria Lab test	n/a
Awad, 2010 RCT	n/a	Provider assessment	n/a
Baerheim, 1994 RCT	AE nonspecific	n/a	Short
Bajaj, 2008 RCT	AE nonspecific	n/a	n/a
Banaszkiewicz, 2005 RCT	n/a	Diary	n/a
Barraud, 2010 RCT	AE nonspecific	Provider assessment	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Barreto-Zuniga, 2001 RCT	n/a	n/a	Short
Basu, 2007 RCT	Death; Sepsis; Electrolyte imbalance; Renal failure	Diary Provider assessment	Short
Basu, 2007 RCT	Sepsis; Electrolyte imbalance; Renal failure; Complications of diarrhea	Diary Provider assessment	n/a
Basu, 2009 RCT	Death; Sepsis; Diarrhea; Electrolyte imbalance	Provider assessment	n/a
Beausoleil, 2007 RCT	AE nonspecific	Provider assessment	n/a
Bellomo, 1979 RCT	Diarrhea; Hematologic controls	n/a	Short
Bertolami, 1999 C-RCT	AE nonspecific	n/a	n/a
Besselink, 2008 RCT	Death; AE nonspecific; Abdominal complaints	Provider assessment	n/a
Bin-Nun, 2005 RCT	Sepsis; Abdominal Pain; Feeding intolerance; Gastric residuals; Abdominal distension; Heme positive stools; Vomiting; Sepsis due to administered strains	Provider assessment	n/a
Black, 1997 CCT	AE nonspecific	n/a	n/a
Boge, 2009 RCT	AE nonspecific; Serious adverse events (death, life-threatening, disability, prolonged hospitalization, medically significant)	Diary Provider assessment	Short
Boge, 2009 RCT	AE nonspecific; Serious adverse events (death, life-threatening, disability, prolonged hospitalization, medically significant)	Diary	Short
Borgia, 1982 RCT	n/a	Provider assessment	Short
Bousvaros, 2005 RCT	n/a	Provider assessment	n/a
Bravo, 2008 RCT	AE nonspecific; Abdominal distension; Abdominal pain	Telephone interview Provider assessment	n/a
Brophy, 2008 RCT	Abdominal Pain; Painful spots; Dizzy spells; Stomach pain; Blood in stools	Questionnaire	n/a
Bruno, 1981 RCT	AE nonspecific; Blood chemistry parameters	Lab test	Short
Bruzzese, 2007 C-RCT	Vomiting	n/a	Short
Bu, 2007 RCT	Acute gastroenteritis	Diary	n/a
Chen, 2005 RCT	n/a	Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Chen, 2010 RCT	n/a	n/a	Short
Chou, 2010 RCT	Growth; Neurodevelopmental and sensory outcomes	Provider assessment	n/a
Chouraqui, 2004 RCT	Regurgitation; Vomiting	n/a	n/a
Chouraqui, 2008 RCT	AE nonspecific; Illnesses; Signs or symptoms of illnesses including abnormal lab values	Medical Dictionary for Regulatory Activities Diary Provider assessment	n/a
Chui, 2009 RCT	n/a	Provider assessment	Short
Coccorullo, 2010 RCT	n/a	n/a	Short
Connolly, 2005 RCT	n/a	Provider assessment Lab test	n/a
Cooper, 2006 RCT	n/a	n/a	n/a
Correa, 2005 RCT	n/a	Provider assessment	Short
Cui, 2004 RCT	Diarrhea; AE nonspecific	Lab test	n/a
Cunningham-Rundles, 2000 CCT	n/a	n/a	Short
Czaja, 2007 RCT	Abnormal vaginal discharge; External genital irritation; Vaginal candidiasis; Cystitis; Vaginal odor; Dysuria; Headache; Abdominal or pelvic cramps/pain; Low back pain	Diary Provider assessment	Short
Dadak, 2006 RCT	n/a	Provider assessment	n/a
De Preter, 2006 C-RCT	n/a	n/a	Short
de Roos, 1999 RCT	AE nonspecific	Diary	n/a
De Simone, 1992 RCT	n/a	Provider assessment Lab test	n/a
De Simone, 2001 CCT	AE nonspecific; Standard blood screening	Provider assessment Lab test	n/a
Dekker, 2009 RCT	Abdominal Pain; AE nonspecific; Reasons for hospitalizations; Vomiting; Morphometric measurements; Wheezing	Questionnaire	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Delia, 2002 RCT	AE nonspecific	Provider assessment	n/a
Delia, 2007 RCT	Death; Infections; Sepsis	Provider assessment	n/a
Dewan, 2007 RCT	n/a	Provider assessment	Short
Dolin, 2009 RCT	AE nonspecific	Diary	Short
Dubey, 2008 RCT	Abdominal Pain; Blood in stool; Fever; Vomiting; Abdominal distension; Lethargy; Irritability; Seizures; Rash	Provider assessment	n/a
Duman, 2005 RCT	n/a	Contact team	Short
Dupont, 2010 RCT	AE nonspecific	Diary	Short
Dylewski, 2010 RCT	AE nonspecific	MedDRA (version 10.1) Diary	Short
Ehrstrom, 2010 RCT	n/a	Provider assessment	Short
Eriksson, 2005 RCT	n/a	Questionnaire	n/a
Falck, 1999 RCT	AE nonspecific	Provider assessment Case report form	n/a
Felley, 2001 RCT	n/a	Diary Provider assessment	n/a
Feng, 1999 RCT	Diarrhea; AE nonspecific	n/a	Short
Folster-Holst, 2006 RCT	n/a	Provider assessment Parent report	Short
Forestier, 2008 RCT	n/a	Provider assessment	n/a
French, 2009 RCT	AE nonspecific	Questionnaire	Short
Frohmader, 2010 RCT	n/a	Provider assessment	Short
Fujimori, 2009 RCT	Blood variables	Lab test	n/a
Gade, 1989 RCT	AE nonspecific	Diary	Short
Galpin, 2005 RCT	AE nonspecific; Vomiting	Care taker questioned	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Gao, 2010 RCT	Diarrhea; n/a	Diary Provider assessment	n/a
Garcia Vilela, 2008 RCT	n/a	Provider assessment	n/a
Gerasimou, 2010 RCT	n/a	n/a	Short
Gibson, 2008 RCT	AE nonspecific; Digestive tolerance; Illnesses or signs or symptoms occurring or worsening; Abnormal lab findings	Provider assessment	Short
Gill, 2001 RCT	n/a	Provider assessment	Short
Gionchetti, 2000 RCT	AE nonspecific; Lab parameters; CBC; Blood chemistry	Provider assessment Lab test	n/a
Gionchetti, 2003 RCT	AE nonspecific; Laboratory studies (complete blood count and blood chemistry measurements	Diary Provider assessment	Short
Goossens, 2003 RCT	n/a;	Questionnaire	Short
Gracheva, 1999 CCT	Abdominal Pain;	Tests (no further information)	Short
Gruber, 2007 RCT	n/a;	Diary	n/a
Guillemard, 2010 RCT	n/a;	Provider assessment report	Short
Guyonnet, 2009 RCT	AE nonspecific; Adverse digestive comfort	Diary Questionnaire	n/a
Habermann, 2001 RCT	Hematologic, clinical chemistry results	Provider assessment	Short
Habermann, 2002 RCT	AE nonspecific; Blood count; Clinical chemistry	Provider assessment Lab test	Short
Haschke-Becher, 2008 RCT	D-lactate accumulation; Metabolic acidosis	Provider assessment	Short
Hatakka, 2008 C-RCT	AE nonspecific; Gastrointestinal complaints; Any signs of illness	Diary Provider assessment	Short
Heimburger, 1994 RCT	n/a;	Provider assessment	n/a
Hemmerling, 2009 RCT	AE nonspecific; Genital tract itching; Vaginal odor; Abnormal vaginal discharge; Nausea; Cramping; Headache; Constipation; Common cold symptoms	DAIDS Toxicity Table Addendum for Vaginal Microbicide Studies; WHO/CONRAD colposcopy manual 1994; DAIDS Adult Toxicity Table Diary Telephone interview Provider assessment	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Higashikawa, 2009 RCT	Diarrhea; AE nonspecific	Diary	Short
Hilton, 1997 RCT	Abdominal cramps	Diary Telephone interview Provider assessment	n/a
Hirata, 2002 CCT	Dry cough; Headache; Vertigo; Digestive symptoms; Itching	Provider assessment	Short
Hochter,1990 RCT	Diarrhea; n/a;	n/a	n/a
Honeycutt, 2007 RCT	Infections; AE nonspecific;	Provider assessment Medical record	Short
Hong, 2010 RCT	n/a	n/a	Short
Horvat, 2010 RCT	Constipation; Vomiting; Abdominal cramps; Distention; Nosocomial infections	Provider assessment	Short
Ishikawa, 2002 RCT	n/a	Diary Provider assessment	n/a
Ishikawa, 2003 RCT	n/a	n/a	Short
Ishikawa, 2005 RCT	n/a	Provider assessment	n/a
Isolauri, 1991 RCT	Diarrhea; n/a	Provider assessment	Short
Isolauri,1995 RCT	n/a	Lab test, parents' record	Short
Jirapinyo, 2002 RCT	Sepsis; Unexplained worsening of clinical condition	Provider assessment	n/a
Johansson, 1998 RCT	n/a	Recorded	Short
Kadooka, 2010 RCT	Abdominal Pain; Headache; Nausea	Diary Provider assessment	Short
Kajander, 2005 RCT	n/a	Diary	n/a
Kajander, 2008 RCT	n/a	Diary Lab test	n/a
Kajimoto, 2002 RCT	Dry cough; Digestive tract symptoms; Exanthema	Provider assessment	Short
Karvonen, 2001 RCT	Abdominal Pain; Abdominal discomfort; Stool consistency	Diary	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Kerac, 2009 RCT	Death; Sepsis; AE nonspecific	Provider assessment	Short
Kianifar, 2009 RCT	n/a	Provider assessment Lab test	Short
Kim, 2006 RCT	AE nonspecific; Lab tests; Physical exam; Blood count; Blood chemistry panel; Hepatic and renal function; Exacerbation of symptoms; Blood pressure; Weight; BMI	Telephone interview	Short
Kim, 2006 RCT	AE nonspecific; Lab tests; Physical exam; Blood count; Blood chemistry panel; Hepatic and renal function; Exacerbation of symptoms; Blood pressure; Weight; BMI	Telephone interview	Short
Kim, 2008 RCT	AE nonspecific	Provider assessment	n/a
Kirjavainen,2003 RCT	n/a	n/a	n/a
Klarin, 2008 RCT	AE nonspecific	Provider assessment	n/a
Klarin,2005 RCT	n/a	Provider assessment	n/a
Knight, 2007 RCT	Death	Provider assessment	n/a
Koning, 2008 RCT	Bloating; AE nonspecific; Nausea; Abdominal cramps; Flatulence	Questionnaire	n/a
Kopp, 2008 RCT	Infections	Questionnaire Provider assessment	Long-term
Kotzampassi, 2006 RCT	Infections	Provider assessment	n/a
Krasse, 2005 RCT	AE nonspecific	Provider assessment	n/a
Kuitunen, 2009 RCT	AE nonspecific; Hemoglobin (Anemia)	Questionnaire	Long-term
Kurugol, 2005 RCT	Diarrhea; n/a	Telephone interview	Short
La Rosa, 2003 RCT	Colic	Diary Provider assessment	n/a
Laitinen, 2008 RCT	n/a	Provider assessment	n/a
Langhendries, 1995 RCT	Vomiting; Spitting up; Skin problems	Provider assessment Mother recorded	n/a
Larsen, 2006 RCT	Bloating; Bowel habits; Bloating; Flatulence; Headache	Diary	Short
Larsson, 2008 RCT	AE nonspecific	Telephone interview	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Lata, 2009 RCT	n/a	Provider assessment	n/a
Lawrence, 2005 RCT	Diarrhea; n/a	n/a	n/a
Li, 2004 RCT	Infections	Provider assessment	n/a
Ligaarden, 2010 C-RCT	AE nonspecific	Diary	Short
Lighthouse, 2004 RCT	n/a	n/a	Short
Lin, 1989 C-RCT	Constipation; Flatulence; Stomach upset	Patient report	n/a
Lin, 2005 RCT	Sepsis; Sepsis due to Lactobacillus or Bifidobacterium	Provider assessment	n/a
Lin, 2008 RCT	Sepsis; Flatulence; Feeding intolerance (based on presence of gastric aspirate and abdominal distension)	Provider assessment	n/a
Ljungberg, 2006 RCT	Beta cell autoantibodies; Blood samples; Enterovirus infections	Provider assessment	Long-term
Loguercio, 1987 RCT	Constipation; Meteorism; Abdominal Pain	Provider assessment Lab test	Short
Lonnermark, 2010 RCT	n/a	Diary	Short
Lu, 2004 CCT	n/a	n/a	n/a
Luoto, 2010 RCT	n/a	Provider assessment	n/a
Mäkeläinen, 2003 RCT	AE nonspecific; Intestinal symptoms; Consistency and frequency of stools	Lab tests	Short
Malaguarnera, 2007 RCT	Abdominal Pain; Blood tests	Provider assessment	n/a
Malaguarnera, 2010 RCT	Blood tests (hemoglobin, hematocritus, white blood cell count and thrombocytes); Liver function tests (alanine amino transferase, aspartate amino transferase, gamma-glutamyl-transpeptidase, cholinesterase activity, serum bilirubin concentrations, prothrombin time and partial thromboplastin time)	Provider assessment	Short
Maldonado, 2009 RCT	AE nonspecific; Clinical examination (weight, length, head circumference); Spitting up; Vomiting; Night awakenings; Irritability; Severe crying; Respiratory infections; Sensitivity to antibiotics	Provider assessment	n/a
Mandel, 2010 RCT	AE nonspecific	Provider assessment	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Manley, 2007 C-RCT	n/a	Provider assessment	n/a
Manzoni, 2006 RCT	Sepsis	Provider assessment	n/a
Margreiter, 2006 RCT	Diarrhea; AE nonspecific; Physical examination; Tolerability	Diary Provider assessment	Short
Marotta, 2003 C-RCT	n/a	Lab test	n/a
Marrazzo, 2006 RCT	AE nonspecific; Abnormal vaginal discharge	Questionnaire Provider assessment	Short
Marseglia, 2007 RCT	AE nonspecific	Provider assessment	n/a
Marteau, 2004 RCT	AE nonspecific	Diary Provider assessment	n/a
Martiney, 2009 RCT	n/a	Lab, notebook	Short
Martinez, 2008 RCT	n/a	Provider assessment	n/a
Martinez, 2009 RCT	AE nonspecific	Provider assessment	n/a
Mayanagi, 2009 RCT	n/a	n/a	Short
McFarland, 1994 RCT	AE nonspecific	Diary Telephone interview Provider assessment	Short
McFarland, 1995 RCT	AE nonspecific; Physical symptoms; Fever; Rash; Changes in blood chemistries; Urinary indicators (protein, BUN, Glucose); Changes in liver enzymes	Provider assessment AE forms	n/a
McNaught, 2002 RCT	n/a	Provider assessment	Short
Merenstein, 2009 RCT	Death; AE nonspecific; Life threatening event; Hospitalization; Prolonged hospital stay; Permanent disability	Diary Telephone interview Provider assessment	Short
Merenstein, 2010 RCT	Death; AE nonspecific; Life-threatening event; Hospitalization; Prolongation of hospital stay; Permanent disability; Vomiting; Stomach pain; Constipation; Runny nose, Cough; Decreased appetite; Fever; Medication use; Rash	Parent report	Short
Metts, 2003 RCT	AE nonspecific	Provider assessment Patient report	n/a
Miele, 2009 RCT	AE nonspecific; Significant changes from baseline (lab) values	Diary Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Millar, 1993 RCT	Sepsis; General well being; Abdominal distension; Vomiting or regurgitation; Feed intolerance; Incidence of perineal rash; Frequency and consistency of stools; number of suppositories used; fluid intake; Weight; Duration of hospital stay	Provider assessment	n/a
Mimura, 2004 RCT	AE nonspecific;	Diary	n/a
Miyaji, 2006 RCT	n/a	n/a	Short
Morrow, 2010 RCT	AE nonspecific	Provider assessment	n/a
Mukerji, 2009 RCT	AE nonspecific	Questionnaire Telephone interview	Short
Naito, 2008 RCT	AE nonspecific	Common terminology criteria for adverse events v2.0 Provider assessment	Long-term
Newcomer, 1983 RCT	Intestinal symptoms; Pain; Gas; Borborygmi	Diary	n/a
Niers, 2009 RCT	AE nonspecific; Feeding difficulties	Diary Provider assessment	Long-term
Niv, 2005 RCT	Dyspepsia; Headache; Nausea	Diary	n/a
Nobuta, 2009 RCT	n/a	Questionnaire	Short
O'Mahony, 2005 RCT	n/a	Diary Provider assessment	Short
Ojetti, 2010 RCT	n/a	Diary	Short
Olah, 2005 RCT	Bloating	Provider assessment	n/a
Olivares, 2006 RCT	AE nonspecific	Provider assessment	Short
Osterlund, 2007 RCT	WHO performance status; Weight; Blood cell counts; Serum chemistry	Common Toxicity Criteria of the National Cancer Institute of Canada scale version 2 Provider assessment	n/a
Ouwehand, 2009 RCT	n/a	Diary	Short
Ozkinay, 2005 RCT	AE nonspecific	n/a	n/a
Panigrahi, 2008 RCT	Sepsis; AE nonspecific; Feeding and stooling patterns; Vital signs	Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Parent, 1996 RCT	n/a	Provider assessment	Short
Parfenov, 2005 CCT	Bloating	Provider assessment	n/a
Parfenov, 2005 CCT	AE nonspecific; Allergic reactions	Provider assessment	n/a
Parra, 2004 RCT	Modification in nutritional parameters; General health problems associated with product	Provider assessment	n/a
Passeron, 2005 RCT	AE nonspecific	Provider assessment	n/a
Peral, 2009 RCT	n/a	Provider assessment	Short
Pereg, 2010 RCT	n/a	n/a	n/a
Petschow, 2005 RCT	AE nonspecific; Stool characteristics; Tolerance symptoms; Fussiness; Gas	Diary	Short
Prantera, 2002 RCT	n/a	Provider assessment	n/a
Pregliasco, 2008 RCT	Bloating; AE nonspecific; Decreased bowel movement; Worsened intestinal function	Diary Telephone interview	n/a
Pregliasco, 2008 RCT	Bloating; AE nonspecific; Decreased bowel movement; Worsened intestinal functions	Diary Telephone interview	n/a
Pregliasco, 2008 RCT	Worsened intestinal functions (Increased bloating, Decreased bowel movement)	Telephone interview	n/a
Puccio, 2007 RCT	Cough; Constipation; Respiratory tract infection; Rhinitis; Wheezing; GI symptoms; Stool characteristics; Flatulence; Vomiting; Restlessness; Irritability; Colic	Diary	n/a
Rampengan, 2010 RCT	AE nonspecific	n/a	Short
Ranganathan C-RCT	AE nonspecific	n/a	Short
Rautava, 2008 RCT	AE nonspecific; Gastrointestinal symptoms; Vomiting	Diary	n/a
Rayes, 2002 RCT	AE nonspecific	Provider assessment	Short
Rayes, 2002 RCT	n/a	Provider assessment	Short
Rayes, 2005 RCT	Abdominal cramps; Abdominal distension	Provider assessment	n/a
Rayes, 2007 RCT	AE nonspecific	Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Reid, 1992 RCT	Rash; Vomiting; Nausea; Irritation; Discharge	n/a	n/a
Reid, 1995 RCT	n/a	Diary Provider assessment	n/a
Ren, 2010 RCT	Gastrointestinal side effects; Skin rash	Provider assessment	Short
Reuman, 1986 RCT	Death; AE nonspecific	Provider assessment	n/a
Richelsen, 1996 RCT	n/a	Telephone interview	n/a
Rio, 2002 RCT	n/a	Provider assessment	n/a
Roos, 1996 RCT	AE nonspecific	Diary Provider assessment	Short
Roos, 2001 RCT	AE nonspecific	n/a	n/a
Rose, 2010 RCT	Need for medical intervention; Pulmonary deterioration; Diaper rash; Deterioration of atopic eczema; Lactose intolerance	Diary Provider assessment	n/a
Rosenfeldt, 2002 RCT	Diarrhea; n/a	n/a	Short
Rosenfeldt, 2003 C-RCT	Abdominal Pain; AE nonspecific; Abdominal pain; Flatulence; Nausea; Medical treatment	n/a	n/a
Rouge, 2009 RCT	n/a	Provider assessment	n/a
Ruiz-Palacios, 1996 RCT	AE nonspecific	n/a	n/a
Saavedra, 2004 RCT	Loose stool; Discomfort with bowel movement; Vomiting; Colic or irritability; Day care absenteeism; Use of antibiotics; Healthcare attention for illness; Growth	Telephone interview	n/a
Safdar, 2008 RCT	AE nonspecific	Diary Provider assessment	n/a
Sahagun-flores, 2007 RCT	n/a	n/a	Short
Saint-Marc, 1995 RCT	n/a	n/a	Short
Salminen, 1988 RCT	Abdominal Pain; Tolerance; Flatulence; Meteorism; Vomiting	Provider assessment	n/a
Salminen, 2004 C-RCT	Infections; Diarrhea; CD4 cell counts; Plasma HIV viral load levels; serum C-reactive protein; Body temperature; Lactobacillus infections	Lab test	n/a
Samanta, 2008 RCT	Infections; Sepsis; Blood culture	Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Satokari, 2001 RCT	n/a	n/a	Short
Savino, 2006 RCT	Constipation; Vomiting	Diary Provider assessment	Short
Sazawal, 2010 RCT	n/a	n/a	n/a
Scalabrin, 2009 RCT	AE nonspecific	Provider assessment	Short
Schrezenmeir, 2004 RCT	Any symptoms of GI intolerance; Constipation; Nausea; Vomiting or regurgitation; Abdominal distension; Belching/Burping; Flatulence; Asthma; Bronchitis; Pneumonia; Severe anorexia; Weight loss; Asthenia	Diary Provider assessment	Short
Schultz, 2004 RCT	AE nonspecific	n/a	n/a
Seppo, 2003 RCT	n/a	Questionnaire	n/a
Sierra, 2010 RCT	Constipation; Fever; Dyspepsia; Headache; Flatulence; Muscular or bone ache; Maldigestion; Flu symptoms; Stomachache; Hematologic parameters (red cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean cell hemoglobin concentration, leucocytes, segmented neutrophils, eosinophils, basophils, lymphocytes, platelets)	Questionnaire	Short
Simons, 2006 RCT	AE nonspecific	Provider assessment	n/a
Simren, 2010 RCT	Biochemistry analysis; Hematology analysis	Telephone interview	Short
Song, 2010 RCT	n/a	Diary	Short
Songisepp, 2005 RCT	Infections; AE nonspecific	Daily questioned	n/a
Songisepp, 2005 CCT	Infections; AE nonspecific	Daily questioned	n/a
Sood, 2009 RCT	n/a	Provider assessment	Short
Spanhaak, 1998 RCT	Body weight; Blood pressure; Heart rate; Temperature; Hematology; Blood chemistry	Provider assessment	Short
Stockert, 2007 RCT	n/a	Diary	n/a
Stotzer, 1996 C-RCT	Bloating; Abdominal Pain; Flatulence	n/a	n/a
Stratiki, 2007 RCT	Feeding tolerance (vomiting, abdominal distension, tenderness and stool characteristics)	Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Sullivan, 2003 RCT	n/a	n/a	Short
Sykora, 2005 RCT	AE nonspecific	Side effect scoring system for H. pylori (de Boer, 1996) Questionnaire	Short
Tamura, 2007 RCT	n/a	n/a	Short
Taylor, 2007 RCT	n/a	Provider assessment	n/a
Tempe, 1985 RCT	n/a	n/a	Short
Teran, 2008 RCT	AE nonspecific; Fever; Vomiting	Provider assessment	n/a
Thomas, 2001 RCT	Bloating; Nausea; Abdominal cramps; Gas; Bloating	Diary Telephone interview	Short
Tomoda, 1991 CCT	AE nonspecific; Blood chemistry	Lab test	n/a
Tsuchiya, 2004 CCT	AE nonspecific	Diary Provider assessment Lab test; Specific form	n/a
Turchet, 2003 RCT	n/a	Provider assessment	Short
Tursi, 2004 RCT	AE nonspecific	Diary	n/a
Tursi, 2008 CCT	AE nonspecific	Provider assessment	n/a
Tursi, 2010 RCT	AE nonspecific	Provider assessment	Short
Underwood, 2009 RCT	n/a	Provider assessment	Short
Urban, 2008 RCT	Spitting up; Vomiting; Frequency of hard and loose stools; Flatulence; Restlessness; Hospital admissions	Provider assessment	n/a
Urbansek, 2001 RCT	Diarrhea; n/a	n/a	n/a
Van der Aa, 2010 RCT	AE nonspecific	Provider assessment	Short
Van Gossum, 2007 RCT	AE nonspecific	Provider assessment	n/a
Velaphi, 2008 RCT	Tolerance of feeds-stools pattern; Stool pattern; Spitting; Vomiting; Unrest morbidity; Changes in blood chemistry; Prolonged illness	Provider assessment	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Vendt, 2006 RCT	Defecation frequency; Stool consistency; Crying, Rash; Colic pain; Constipation; Excessive breast feeding	Diary	n/a
Vleggaar, 2008 C-RCT	n/a	Provider assessment	n/a
Vlieger, 2009 RCT	Vomiting; Constipation; Colic; Rash; Eczema	Diary Provider assessment	n/a
Wada, 2010 RCT	Infections; Blood culture / bacteremia due to administered strains	Provider assessment Daily records, lab	n/a
Wang, 2004 RCT	AE nonspecific	n/a	n/a
Wang, 2007 RCT	n/a	Provider assessment	n/a
Weizman, 2005 RCT	AE nonspecific	Questionnaire Telephone interview Provider assessment	Short
Weizman, 2006 RCT	Deviations of growth parameters; Regurgitation; Vomiting; Restlessness; Constipation	Questionnaire Telephone interview Provider assessment	n/a
Weston, 2005 RCT	Worsening of condition	Provider assessment	n/a
Wewalka, 2002 RCT	AE nonspecific; Thyroid parameters	Provider assessment	Short
Wheeler, 1997 C-RCT	n/a	n/a	n/a
Wildt, 2006 RCT	Abdominal Pain; AE nonspecific; Constipation	Diary Provider assessment	Short
Williams, 2008 RCT	n/a	n/a	n/a
Wind, 2010 RCT	AE nonspecific; Change in blood parameters; Nausea; Vomiting; Burping; Abdominal distension; Flatulence; Defecation frequency; Stool consistency	Gastrointestinal symptom rating scale; King's stool chart Diary Questionnaire Lab test	Short
Wolf, 1994 RCT	AE nonspecific	Questionnaire Provider assessment	n/a
Wolf, 1998 RCT	Nausea; Cramping; Distension; Flatulence; Vomiting; Constipation; Burping; Reflux; Bowel function	Daily questionnaire	Short
Worthley, 2009 C-RCT	General well-being; Gastrointestinal symptoms	Questionnaire Provider assessment	Short
Xia, 2010 RCT	AE nonspecific	Provider assessment	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Xiang, 2006 RCT	n/a	Provider assessment	n/a
Xiao, 2003 RCT	n/a	Lab test	n/a
Xiao, 2003 RCT	n/a	Diary	n/a
Yang, 2008 RCT	Lab changes (blood, urine, stool, liver, kidney function)	Lab test	Short
Yao-Zong, 2004 RCT	Diarrhea; AE nonspecific; Constipation	Diary Provider assessment	Short
Yonekura RCT	Bloating; Abdominal Pain; AE nonspecific; Irritability; Decreased motivation; Decreased appetite; Fatigue; Insomnia; Headache; Tinnitus; Vertigo; Itching (eczema); Vomiting; loose stools; Constipation; Changes in physical condition; History of present illness	Provider assessment	Short
Zhang, 2010 RCT	Gastrointestinal side effects	Provider assessment	Short
Ziegler, 2003 RCT	n/a	Diary	n/a
Zocco, 2003 RCT	AE nonspecific	n/a	n/a
An, 2010 Case series (uncontrolled)	Abdominal Pain; Vomiting	Questionnaire Provider assessment	Short
Barrett, 2008 Case series (uncontrolled)	n/a	Diary Questionnaire	n/a
Beck, 1961 Case series (uncontrolled)	n/a	n/a	n/a
Bekkali, 2007 Case series (uncontrolled)	AE nonspecific; Vomiting	Diary Provider assessment	n/a
Bellomo, 1979 Case series (uncontrolled)	Hematologic controls	n/a	Short
Benchimol, 2004 Case series (uncontrolled)	Diarrhea; n/a	Provider assessment	n/a
Berman, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Bibiloni, 2005 Case series (uncontrolled)	AE nonspecific; Biochemical adverse events	Provider assessment	n/a
Bruce, 1988 Case series (uncontrolled)	n/a	n/a	n/a
Bruni, 2008 Case series (uncontrolled)	Sensitization	Provider assessment	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Carlsson, 2009 Case series (uncontrolled)	n/a	n/a	n/a
Cobo Sanz, 2006 Case series (uncontrolled)	n/a	Questionnaire	n/a
Colecchia, 2006 Case series (uncontrolled)	AE nonspecific	Neri et al. (2000) IBS differentiation Questionnaire	Short
Di Pierro, 2009 Case series (uncontrolled)	n/a	n/a	Short
Dughera, 2007 Case series (uncontrolled)	AE nonspecific	Questionnaire	n/a
Elmer, 1995 Case series (uncontrolled)	Diarrhea; n/a	Telephone interview	n/a
Fukuda, 2008 Case series (uncontrolled)	AE nonspecific	Provider assessment	Short
Gabrielli, 2009 Case series (uncontrolled)	AE nonspecific; Clinical findings or patients' complaints not present 24h before enrollment	n/a	Short
Garrido, 2005 Case series (uncontrolled)	Gastrointestinal symptomatology	n/a	Short
Gionchetti, 2007 Case series (uncontrolled)	AE nonspecific; Blood count; Blood chemistry measurements	Diary	n/a
Glintborg, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Gniwotta, 1977 Case series (uncontrolled)	Diarrhea; n/a	n/a	n/a
Gotteland, 2003 Case series (uncontrolled)	n/a	n/a	n/a
Gruenwald, 2002 Case series (uncontrolled)	n/a	Questionnaire Provider assessment	n/a
Hensgens, 1976 Case series (uncontrolled)	n/a	Provider assessment	n/a
Huynh, 2009 Case series (uncontrolled)	AE nonspecific; Serum cytokine levels	Diary	n/a
Karimi, 2005 Case series (uncontrolled)	AE nonspecific	Telephone interview	Short
Kawamura,1981 Case series (uncontrolled)	AE nonspecific	n/a	n/a
Kirchhelle, 1996 Case series (uncontrolled)	AE nonspecific	Provider assessment	Short
Kitajima, 1997 Case series (uncontrolled)	n/a	Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Lamiki, 2010 Case series (uncontrolled)	AE nonspecific	Diary Provider assessment	n/a
Lee, 2010 Case series (uncontrolled)	AE nonspecific	Provider assessment	Short
Lombardo, 2009 Case series (uncontrolled)	n/a	Diary	Short
Luoto, 2010 Case series (uncontrolled)	Sepsis	Provider assessment	n/a
Malin, 1996 Case series (uncontrolled)	n/a	Provider assessment	Short
Malkov, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Mego, 2005 Case series (uncontrolled)	AE nonspecific	NCI-CTC (2.0) criteria n/a	n/a
Mego, 2006 Case series (uncontrolled)	AE nonspecific	NCI-CTC (2.0) criteria 2 Provider assessment	n/a
Michetti, 1999 Case series (uncontrolled)	n/a	n/a	Short
Muting, 1968 Case series (uncontrolled)	n/a	n/a	n/a
Nobuta, 2009 Case series (uncontrolled)	AE nonspecific	Questionnaire Interview	Short
Reid, 2001 Case series (uncontrolled)	AE nonspecific; Bladder or vaginal irritation; Discharge; Intestinal upset; Infections	Patient record	Short
Rosenfeldt, 2003 Case series (uncontrolled)	AE nonspecific; Gastrointestinal inconvenience (abdominal pain, flatulence, nausea); Medical treatment	n/a	n/a
Sakamoto, 2001 Case series (uncontrolled)	n/a	n/a	Short
Schneider, 2005 Case series (uncontrolled)	n/a	n/a	Short
Shen, 2005 Case series (uncontrolled)	Bloating; AE nonspecific; Intolerable constipation; Bleeding; Worsening abdominal pain	Provider assessment	n/a
Srinivasan, 2006 Case series (uncontrolled)	Cultures from stool, fluid, blood, urine, sputum, cerebrospinal fluid; Endotracheal secretions	Provider assessment	n/a
Tasli, 2006 Case series (uncontrolled)	Nausea; Vomiting; Abdominal fullness	Provider assessment	Short
van Bodegraven, 2004 Case series (uncontrolled)	n/a	n/a	n/a
Weiss, 2010 Case series (uncontrolled)	n/a	Provider assessment	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Yim, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Zahradnik, 2009 Case series (uncontrolled)	AE nonspecific	Diary Provider assessment	Short
Zahradnik, 2009 Case series (uncontrolled)	AE nonspecific	Diary Provider assessment	Short
An, 2010 Case series (uncontrolled)	Abdominal Pain; Vomiting	Questionnaire Provider assessment	Short
Barrett, 2008 Case series (uncontrolled)	n/a	Diary Questionnaire	n/a
Beck, 1961 Case series (uncontrolled)	n/a	n/a	n/a
Bekkali, 2007 Case series (uncontrolled)	AE nonspecific; Vomiting	Diary Provider assessment	n/a
Bellomo, 1979 Case series (uncontrolled)	Hematologic controls	n/a	Short
Benchimol, 2004 Case series (uncontrolled)	Diarrhea; n/a	Provider assessment	n/a
Berman, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Bibiloni, 2005 Case series (uncontrolled)	AE nonspecific; Biochemical adverse events	Provider assessment	n/a
Bruce, 1988 Case series (uncontrolled)	n/a	n/a	n/a
Bruni, 2008 Case series (uncontrolled)	Sensitization	Provider assessment	Short
Carlsson, 2009 Case series (uncontrolled)	n/a	n/a	n/a
Cobo Sanz, 2006 Case series (uncontrolled)	n/a	Questionnaire	n/a
Colecchia, 2006 Case series (uncontrolled)	AE nonspecific	Neri et al. (2000) IBS differentiation Questionnaire	Short
Di Pierro, 2009 Case series (uncontrolled)	n/a	n/a	Short
Dughera, 2007 Case series (uncontrolled)	AE nonspecific	Questionnaire	n/a
Elmer, 1995 Case series (uncontrolled)	Diarrhea; n/a	Telephone interview	n/a
Fukuda, 2008 Case series (uncontrolled)	AE nonspecific	Provider assessment	Short

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Gabrielli, 2009 Case series (uncontrolled)	AE nonspecific; Clinical findings or patients' complaints not present 24 hours before enrollment	n/a	Short
Garrido, 2005 Case series (uncontrolled)	Gastrointestinal symptomatology	n/a	Short
Gionchetti, 2007 Case series (uncontrolled)	AE nonspecific; Blood count; Blood chemistry measurements	Diary	n/a
Glintborg, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Gniwotta, 1977 Case series (uncontrolled)	Diarrhea; n/a	n/a	n/a
Gotteland, 2003 Case series (uncontrolled)	n/a	n/a	n/a
Gruenwald, 2002 Case series (uncontrolled)	n/a	Questionnaire Provider assessment	n/a
Hensgens, 1976 Case series (uncontrolled)	n/a	Provider assessment	n/a
Huynh, 2009 Case series (uncontrolled)	AE nonspecific; Serum cytokine levels	Diary	n/a
Karimi, 2005 Case series (uncontrolled)	AE nonspecific	Telephone interview	Short
Kawamura,1981 Case series (uncontrolled)	AE nonspecific	n/a	n/a
Kirchhelle, 1996 Case series (uncontrolled)	AE nonspecific	Provider assessment	Short
Kitajima, 1997 Case series (uncontrolled)	n/a	Provider assessment	n/a
Lamiki, 2010 Case series (uncontrolled)	AE nonspecific	Diary Provider assessment	n/a
Lee, 2010 Case series (uncontrolled)	AE nonspecific	Provider assessment	Short
Lombardo, 2009 Case series (uncontrolled)	n/a	Diary	Short
Luoto, 2010 Case series (uncontrolled)	Sepsis	Provider assessment	n/a
Malin, 1996 Case series (uncontrolled)	n/a	Provider assessment	Short
Malkov, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Mego, 2005 Case series (uncontrolled)	AE nonspecific	NCI-CTC (2.0) criteria n/a	n/a

Evidence Table C3. Assessment (continued)

Author, Year Study Design	Assessed Safety Parameters	Published Tool Method Used to Record Harms	Duration of Followup
Mego, 2006 Case series (uncontrolled)	AE nonspecific	NCI-CTC (2.0) criteria 2 Provider assessment	n/a
Michetti, 1999 Case series (uncontrolled)	n/a	n/a	Short
Muting, 1968 Case series (uncontrolled)	n/a	n/a	n/a
Nobuta, 2009 Case series (uncontrolled)	AE nonspecific	Questionnaire Interview	Short
Reid, 2001 Case series (uncontrolled)	AE nonspecific; Bladder or vaginal irritation; Discharge; Intestinal upset; Infections	Patient record	Short
Rosenfeldt, 2003 Case series (uncontrolled)	AE nonspecific; Gastrointestinal inconvenience (abdominal pain, flatulence, nausea); Medical treatment	n/a	n/a
Sakamoto, 2001 Case series (uncontrolled)	n/a	n/a	Short
Schneider, 2005 Case series (uncontrolled)	n/a	n/a	Short
Shen, 2005 Case series (uncontrolled)	Bloating; AE nonspecific; Intolerable constipation; Bleeding; Worsening abdominal pain	Provider assessment	n/a
Srinivasan, 2006 Case series (uncontrolled)	Cultures from stool, fluid, blood, urine, sputum, cerebrospinal fluid; Endotracheal secretions	Provider assessment	n/a
Tasli, 2006 Case series (uncontrolled)	Nausea; Vomiting; Abdominal fullness	Provider assessment	Short
van Bodegraven, 2004 Case series (uncontrolled)	n/a	n/a	n/a
Weiss, 2010 Case series (uncontrolled)	n/a	Provider assessment	n/a
Yim, 2006 Case series (uncontrolled)	n/a	Provider assessment	n/a
Zahradnik, 2009 Case series (uncontrolled)	AE nonspecific	Diary Provider assessment	Short
Zahradnik, 2009 Case series (uncontrolled)	AE nonspecific	Diary Provider assessment	Short

*Abbreviations
AE=Adverse Events
C-RCT=Cross-over Randomized Controlled Trial
CCT=Controlled Clinical Trials
n/a=not available or not applicable
RCT=Randomized Controlled Trial

Evidence Table C4. Results

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Abrahamsson, 2007 RCT Effectiveness unclear LTFU	1 La	117	VII Constipation n=4 VII Spitting up n=51 VII Colic n=11 XXII Episode of wheezing (withdrawal) n=1		n/a	22, 1		Antibiotics unclear	
Abrahamsson, 2007 RCT Effectiveness unclear LTFU	2	115	VII Constipation n=6 VII Spitting up n=43 VII Colic n=10 XXII Episode of wheezing n=0		n/a	22, 0		Antibiotics unclear	Placebo
Agerbaek, 1995 RCT Effective	1 En	29	VII Borborygmi n=n/a VII Loose stools n=n/a VII Obstipation n=n/a VII Lactose intolerance n=0		3	0, 0			
Agerbaek, 1995 RCT Effective	2	29	VII Borborygmi n=0 VII Loose stools n=0 VII Obstipation n=0 VII Lactose intolerance n=0			1, 0			Placebo
Aihara, 2005 RCT Effective	1 La	40	XXII Dry cough n=0 XXIII Exanthema n=0 XXIII Skin itching n=0 VII Dysgeusia n=0 XVII Headache n=0 VII Dizziness/drift n=0 VII Inappetence n=0 VII Diarrhea n=2 VII Constipation n=1 VII Flatulence n=0 VII Abdominal discomfort n=0		3	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Aihara, 2005 RCT Effective	2	40	XXII Dry cough n=0 XXIII Exanthema n=0 XXIII Skin itching n=0 VII Dysgeusia n=0 XVII Headache n=0 VII Dizziness/drift n=0 VII Inappetence n=0 VII Diarrhea n=4 VII Constipation n=2 VII Flatulence n=0 VII Abdominal discomfort n=0		6	n/a, 0			Placebo
Alberda, 2007 RCT Effectiveness unclear	1 St	10	VII Bowel obstruction (SAE) n=1 XI Lactobacillus-induced sepsis (SAE) n=0 XXII Respiratory failure - death n=0 II Congestive heart failure -death (5) n=1 II Myocardial infarction - death (5) n=0		2	n/a, 2			
Alberda, 2007 RCT Effectiveness unclear	2	9	VII Bowel obstruction (SAE) n=0 XI Lactobacillus-induced sepsis (SAE) n=0 XXII Respiratory failure - death (SAE) n=0 II Congestive heart failure -death (5) (SAE) n=0 II Myocardial infarction - death (5) (SAE) n=1		1	n/a, 1			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Alberda, 2007 RCT Effectiveness unclear	3 St	9	VII Bowel obstruction n=0 XI Sepsis due to lactobacilli (SAE) n=0 XXII Respiratory failure - death (5) (SAE) n=1 II Congestive heart failure -death (5) (SAE) n=0 II Myocardial infarct - death (5) (SAE) n=0		1	n/a, 1			
Allen, 2010 RCT Effective	1 Bi	220	XI Infectious and parasitic diseases (SAE) n=15 V Endocrine, nutritional and metabolic diseases n=0 VI Diseases of the eye and adnexa n=6 IV Diseases of the ear and mastoid process n=3 XI Diseases of the respiratory system n=24 VII Diseases of the digestive system n=8 XXIII Diseases of the skin and subcutaneous tissue n=12 XX Disease of genitourinary system n=0 XXVII Pregnancy, childbirth and puerperium n=4 XVIII Perinatal period conditions (e.g. jaundice) n=10 III Congenital malformations, deformations and chromosomal	The frequency of adverse events in the mothers was similar in the two groups	73	n/a, n/a	4	Antibiotics needed	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
			abnormalities (SAE) n=12 XIII Abnormal clinical and lab findings n=7 XII Injury, poisoning and other external causes n=2 XXVII External causes of morbidity and mortality (SAE) n=0 XI Infections due to L. or B. (SAE) n=0 XI Hospitalization with respiratory illness (SAE) n=4						
Allen, 2010 RCT Effective	2	234	XI Infectious and parasitic diseases (SAE) n=12 V Endocrine, nutritional and metabolic diseases n=1 VI Diseases of the eye and adnexa n=12 IV Diseases of the ear and mastoid process n=3 XI Diseases of the respiratory system n=16 VII Diseases of the digestive system n=12 XXIII Diseases of the skin and subcutaneous tissue n=1 XX Disease of genitourinary system n=5 XXVII Pregnancy, childbirth and puerperium n=18 XVIII Perinatal period conditions (e.g. jaundice) n=18		75	n/a, n/a	1	Antibiotics needed	Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
			III Congenital malformations, deformations and chromosomal abnormalities (SAE) n=12 XIII Abnormal clinical and lab findings n=4 XII Injury, poisoning and other external causes n=2 XXVII External causes of morbidity and mortality (SAE) n=2 XI Infections due to L. or B. (SAE) n=0 XI Hospitalization with respiratory illness (SAE) n=1						
Anderson, 2003 RCT Not effective	1 St	72	VII Diarrhea n=4 (states related to oligofructose)		4	n/a, 9			
Anderson, 2003 RCT Not effective	2	65	VII Diarrhea n=0		0	n/a, 5			Placebo
Andriulli, 2008 RCT Effective	1 La	132	VII Diarrhea (withdrew) n=3 VII Abdominal discomfort (withdrew) n=1 VII Vomiting (withdrew) n=1 VII Abdominal pain (withdrew) n=0 XXIII Skin rash n=0	States adverse events are not different between groups, no further data	5	25, 5			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Andriulli, 2008 RCT Effective	2	135	VII Diarrhea (withdrew) n=0 VII Abdominal discomfort (withdrew) n=0 VII Vomiting (withdrew) n=0 VII Abdominal pain (withdrew) n=3 XXIII Skin rash (withdrew) n=1		4	30, 4			Placebo
Anukam, 2006 RCT Effective	1 La	65	XVII Persistent headache n=2 XIV Increased appetite n=2		2	16, 0			
Anukam, 2006 RCT Effective	2	60	XVII Persistent headache n=0 XIV Increased appetite n=0		0	3, 0			Placebo
Anukam, 2008 RCT Effectiveness unclear	1 St	12	XI Bacteremia (SAE) n=0 XXVII Death (SAE) n=0 XXIII Skin rash n=0		0	2, 0			
Anukam, 2008 RCT Effectiveness unclear	2	12	XI Bacteremia (SAE) n=0 XXVII Death (SAE) n=0 XXIII Skin rash n=3		3	n/a, 0			Yogurt only
Anukam, 2009 RCT Effectiveness unclear	1 La	39	XVII Headache n=n/a VII Nausea n=n/a		n/a	20, n/a			
Anukam, 2009 RCT Effectiveness unclear	2	20	XVII Headache n=n/a VII Nausea n=n/a		n/a	13, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Arunachalam, 2000 RCT Effective	1 Bi	13	VII Digestive problems n=0 XIV Dietary sensitivities n=0 XXVII Adverse general health problems n=0		0	0, 0			
Arunachalam, 2000 RCT Effective	2	12	VII Digestive problems n=0 XIV Dietary sensitivities n=0 XXVII Adverse general health problems n=0		0	0, 0			Placebo
Aso, 1992 RCT Effective	1 La	29	XIII Abnormal lab findings n=0		0	6, 0			
Aso, 1992 RCT Effective	2	29	XIII Abnormal lab findings n=0		0	4, 0			No medication or placebo
Aso, 1995 RCT Effective	1 La	68	VII Diarrhea (1) n=1 VII Constipation (1) n=1 XIII Elevation of the hepatic transaminases (1) n=1 XIII Elevation of serum alanine aminotransferase and creatinine levels n=0		3	7, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Aso, 1995 RCT Effective	2	70	VII Diarrhea (1) n=2 VII Constipation (1) n=0 XIII Elevation of the hepatic transaminases n=0 XIII Elevation of serum alanine aminotransferase and creatinine levels n=1		3	6, n/a			Placebo
Awad, 2010 RCT Effective	1 La	60	XXVII Death (SAE) n=5 XI Probiotic bacteria in blood (SAE) n=0		5	n/a, n/a			
Awad, 2010 RCT Effective	2	30	XXVII Death (SAE) n=6 XI Probiotic bacteria in blood n=0		6	n/a, n/a			Placebo
Awad, 2010 RCT Effective	3 La	60	XXVII Death (SAE) n=14 XI Probiotic bacteria in blood (SAE) n=0		14	n/a, n/a			
Baerheim, 1994 RCT Not effective	1 La	25	XXI Messy discharge n=4		4	n/a, 0			
Baerheim, 1994 RCT Not effective	2	22	XXI Messy discharge n=1		1	n/a, 0			Placebo
Bajaj, 2008 RCT Effective	1 St	17	XI Sepsis -death (5) (SAE) n=1 (states unrelated)		1	3, 1			
Bajaj, 2008 RCT Effective	2	8	XI Sepsis -death (5) (SAE) n=0		0	0, 0			No treatment

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Banaszkiewicz, 2005 RCT Not effective	1 La	43	VII Abdominal pain n=3 VII Vomiting n=1 XVII Headache n=0		4	5, 1			
Banaszkiewicz, 2005 RCT Not effective	2	43	VII Abdominal pain n=5 VII Vomiting n=0 XVII Headache n=1		6	3, 0			Placebo
Barraud, 2010 RCT Not effective	1 Bi	87	VII Bowel ischemia (SAE) n=0 XI Bacteremia due to Lactobacillus (SAE) n=0	Non-severe sepsis patients in probiotics group had a higher mortality rate compared to control (p=0.08)	n/a	9, 0			
Barraud, 2010 RCT Not effective	2	80	VII Bowel ischemia (SAE) n=0 XI Bacteremia due to Lactobacillus (SAE) n=0		n/a	9, 0			Placebo
Barreto-Zuniga, 2001 RCT Effective	1 Bi	12	VII Bloating n=0 VII Loose stools n=0 XIII Routine blood chemistry changes n=0		0	n/a, 0			
Barreto-Zuniga, 2001 RCT Effective	2	12	VII Bloating n=0 VII Loose stools n=0 XIII Routine blood chemistry changes n=0		0	n/a, 0			Non-probiotic
Basu, 2007 RCT Not effective	1 La	330	XIII Electrolyte imbalance n=3 XI Septicemia (SAE) n=2 (states no LGG complications) XXVII Death (SAE) n=0		n/a	7, 5		Antibiotics unclear	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Basu, 2007 RCT Effective	1 La	125	XI Septicemia (SAE) n=1 XX Renal failure (SAE) n=1		n/a	8, 2			
Basu, 2007 RCT Not effective	2	332	XIII Electrolyte imbalance n=3 XI Septicemia (SAE) n=2 XXVII Death (SAE) n=1		n/a	9, 6			Placebo
Basu, 2007 RCT Effective	2	128	XI Septicemia (SAE) n=3 XX Renal failure (SAE) n=0		n/a	10, 3			ORS only
Basu, 2009 RCT Effective	1 La	196	XIII Electrolyte imbalance n=3 XI Septicemia (SAE) n=1 XXVII Death (SAE) n=0		n/a	8, 4			
Basu, 2009 RCT Effective	2	196	XIII Electrolyte imbalance n=4 XI Septicemia (SAE) n=3 XXVII Death (SAE) n=1		n/a	11, 8			Glucose-electrolyte rehydration solution only
Basu, 2009 RCT Effective	3 La	196	XIII Electrolyte imbalance n=5 XI Septicemia (SAE) n=3 XXVII Death (SAE) n=0		n/a	10, 8			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Beausoleil, 2007 RCT Effective	1 La	44	VII Softened stools n=8 XVII Taste disorder n=6 VII Abdominal cramps n=4 VII Bloating n=3 VII Gastroesophageal reflux n=2 VII Constipation n=2 VII Flatulence n=2 VII Modified stool colon n=1 (states not related) VII Nausea n=0 XXVII Death (SAE) n=3 (states unrelated to preparation) VII Vomiting n=0 VII Foul-smelling stools n=0 XIX Hallucination n=0 XXIII Rash n=0 XXIII Pruritus n=1		21	n/a, n/a			
Beausoleil, 2007 RCT Effective	2	45	VII Softened stools n=9 XVII Taste disorder n=7 VII Abdominal cramps n=5 VII Bloating n=3 VII Gastroesophageal reflux n=2 VII Constipation n=1 VII Flatulence n=1 VII Modified stool colon n=2 VII Nausea n=4 XXVII Death (SAE) n=0 VII Vomiting n=1 VII Foul-smelling stools n=1 XIX Hallucination n=1 XXIII Rash n=1 XXIII Pruritus n=0		20	n/a, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Bellomo, 1979 RCT Effective	1 En	29	I Significant hematologic change n=0		0	0, 0			
Bellomo, 1979 RCT Effective	2	30	I Significant hematologic change n=0		0	0, 0			Placebo
Bertolami, 1999 C-RCT Effectiveness unclear	1 En	17	VII Nausea n=0		n/a	0, 0			
Bertolami, 1999 C-RCT Effectiveness unclear	2	15	VII Nausea n=2			0, 0			Placebo
Besselink, 2008 RCT Not effective	1 Bi	153	VII Bowel ischemia (SAE) n=9 XXVII Death (SAE) n=24 VII Nausea n=20 VII Abdominal fullness n=36 VII Diarrhea n=25 XI Infections caused by administered probiotics n=0		n/a	3, 0			
Besselink, 2008 RCT Not effective	2	145	VII Bowel ischemia (SAE) n=0 XXVII Death (SAE) n=9 VII Nausea n=23 VII Abdominal fullness n=43 VII Diarrhea n=28 XI Infections caused by administered probiotics n=0			7, 5			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Bin-Nun, 2005 RCT Effective	1 St	72	XI Sepsis due to administered probiotics (SAE) n=0	No differences in feeding intolerance (diarrhea, abdominal distension, vomiting), no increased susceptibility to infections	n/a	n/a, n/a			
Bin-Nun, 2005 RCT Effective	2	73	XI Sepsis due to administered probiotics (SAE) n=0		n/a	n/a, n/a			Feeding supplement only
Black, 1997 CCT Effectiveness unclear	1 Bi	10	XXVII Feeling sick n=0 XXI Candida vaginitis n=0 VII Diarrhea (severe) n=0 VII Diarrhea n=0		n/a	0, 0			
Black, 1997 CCT Effectiveness unclear	2	10	XXVII Feeling sick n=1 XXI Candida vaginitis n=1 VII Diarrhea (severe) n=1 VII Diarrhea n=0			1, 1			Placebo
Boge, 2009 RCT Effective	1 St	44	XI Common infectious diseases n=n/a		28	3, 2			
Boge, 2009 RCT Effective	1 St	113	XI Common infectious diseases n=n/a		59	n/a, 4			
Boge, 2009 RCT Effective	2	42	XI Common infectious diseases n=n/a		31	8, 7			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Boge, 2009 RCT Effective	2	109	XXVII Common infectious diseases n=n/a		61	n/a, 12			Placebo
Borgia, 1982 RCT Effective	1 St	40		2 patients died (age>=85, cardiovascular cause) but group unclear	n/a	1, n/a			
Borgia, 1982 RCT Effective	2	40			n/a	2, n/a			Antibiotics only
Borgia, 1982 RCT Effective	3 St	40				2, n/a			
Borgia, 1982 RCT Effective	4 St	40				3, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Bousvaros, 2005 RCT Not effective	1 La	39	VII Perianal abscess (SAE) n=1 (states not related to probiotics) XXVII Perirectal abscess (SAE) n=1 (states not related to probiotics) VII Vomiting/unable to tolerate n=3 VII Diarrhea (1) n=1 (states unrelated) XXVII Acute swelling n=1 (states not related) VII Nausea n=1 (states not related) XXII Sore throat n=0 (states not related) VII Abdominal pain n=1 (states not related) XIX Diagnosis of eating disorder n=1 (states not related) XXVII Cervical lymph nodes n=0 XXVII Headache dizziness n=0 (states not related) XXVII Fatigue n=0 (states not related)		7	14, 2	2	Antibiotics needed surgical drainage	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Bousvaros, 2005 RCT Not effective	2	36	VII Perianal abscess (SAE) n=0 VII Perirectal abscess (SAE) n=0 VII Vomiting/unable to tolerate n=0 VII Mild diarrhea n=1 XXVII Acute swelling n=0 VII Nausea n=1 XXII Sore throat n=1 VII Abdominal pain n=2 XIX Diagnosis of eating disorder n=1 XXVII Cervical lymph nodes n=1 XXVII Headache dizziness n=1 XXVII Fatigue n=1		8	n/a, n/a	0		Placebo
Bravo, 2008 RCT Not effective	1 Sa	41	VII Abdominal distension or abdominal pain n=2		3	2, n/a			
Bravo, 2008 RCT Not effective	2	45	VII Abdominal distension or abdominal pain n=n/a		4	2, n/a			Placebo
Brophy, 2008 RCT Not effective	1 Bi	71	VII Stomach cramps n=3 VII Indigestion n=1 XXVII Painful spots n=1 XVII Dizzy spells n=1 XXVII General decline in well-being n=0		6	20, 3			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Brophy, 2008 RCT Not effective	2	76	VII Stomach cramps n=3 VII Indigestion n=1 XXVII Painful spots n=0 XVII Dizzy spells n=0 XXVII General decline in well-being n=1		5	19, 3			Placebo
Bruno, 1981 RCT Effective	1 En	25	I Blood chemistry changes n=0		0	n/a, n/a			
Bruno, 1981 RCT Effective	2	24	I Blood chemistry changes n=0		0	n/a, n/a			Placebo
Bruzzese, 2007 C-RCT Effective	1 La	19	VII Vomiting n=1		n/a	n/a, n/a			
Bruzzese, 2007 C-RCT Effective	2	19	VII Vomiting n=0		n/a	n/a, n/a			Non-probiotic
Bu, 2007 RCT Effective	1 La	18	VII Acute gastroenteritis n=n/a VII Mild diarrhea n=0		n/a	1, n/a			
Bu, 2007 RCT Effective	2	9	VII Acute gastroenteritis n=n/a VII Mild diarrhea n=0		n/a	1, n/a			Placebo
Chen, 2005 RCT Effective	1 La	65	XXVII Nostril erosion n=0 XXII Pneumonia n=0 XI Urinary tract infection n=1 (states unrelated) XXII Aspiration pneumonia n=1 (states unrelated) XXII n=		n/a	n/a, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Chen, 2005 RCT Effective	2	63	XXVII Nostril erosion n=1 (states unrelated) XXII Pneumonia n=1 (states unrelated) XI Urinary tract infection n=0 XXII Aspiration pneumonia n=0		n/a	n/a, n/a			Non-probiotic
Chen, 2010 RCT Effective	1 La	55	XI Upper respiratory tract infection n=4		4	6, 4			
Chen, 2010 RCT Effective	2	63	XI Upper respiratory tract infection n=5		5	7, 5			Placebo
Chou, 2010 RCT Effective	1 Bi	153	XXVII Growth adverse effects n=0 XVII Neurodevelopmental adverse effects n=0 XVII Sensory adverse effects n=0		n/a	n/a, n/a			
Chou, 2010 RCT Effective	2	148	XXVII Growth adverse effects n=0 XVII Neurodevelopmental adverse effects n=0 XVII Sensory adverse effects n=0		n/a	n/a, n/a			Placebo
Chouraqui, 2004 RCT Effectiveness unclear	1 St	46	VII Regurgitation and spitting n=5 VII Vomiting n=0 XV Growth (suppression) n=0		5	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Chouraqui, 2004 RCT Effectiveness unclear	2	44	VII Regurgitation and Spitting n=6 VII Vomiting n=0 XV Growth (suppression) n=0		6	n/a, 0			Placebo
Chouraqui, 2008 RCT Effective	1 Bi	70	VII Gastroenteritis (SAE per author) (SAE) n=1 VII Gastroesophageal reflux disease (SAE per author) (SAE) n=0 VII Diarrhea (SAE per author) n=2 XXVII Milk allergy (SAE per author) n=2 VII Vomiting (SAE per author) n=0 XI Febrile infection (SAE per author) (SAE) n=1 XXV Surgery (SAE per author) (SAE) n=0 VIII Pyrexia (SAE per author) n=0 VII Rectal hemorrhage (SAE per author) (SAE) n=1 XX Pyelonephritis (SAE per author) (SAE) n=1 XXII Bronchiolitis (SAE per author) (SAE) n=2 XXII Cough (SAE per author) n=1 XXVII Drug toxicity (SAE per author) (SAE) n=0 XII Inguinal hernia (SAE per author) (SAE) n=0		n/a	10, 1	1	Antibiotics unclear	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Chouraqui, 2008 RCT Effective	2	70	VII Gastroenteritis (SAE per author) (SAE) n=0 VII Gastroesophageal reflux disease (SAE per author) (SAE) n=1 VII Diarrhea (SAE per author) n=1 XXVII Milk allergy (SAE per author) n=0 VII Vomiting (SAE per author) n=1 XI Febrile infection (SAE per author) (SAE) n=1 XXV Surgery (SAE per author) (SAE) n=0 VIII Pyrexia (SAE per author) n=2 VII Rectal hemorrhage (SAE per author) (SAE) n=0 XX Pyelonephritis (SAE per author) (SAE) n=0 XXII Bronchiolitis (SAE per author) (SAE) n=0 XXII Cough (SAE per author) n=0 XXVII Drug toxicity (SAE per author) (SAE) n=1 XII Inguinal hernia (SAE per author) (SAE) n=0		n/a	17, 2	1	Antibiotics unclear	Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Chouraqui, 2008 RCT Effective	3 Bi	70	VII Gastroenteritis (SAE per author) (SAE) n=0 VII Gastroesophageal reflux disease (SAE per author) (SAE) n=0 VII Diarrhea (SAE per author) n=1 XXVII Milk allergy (SAE per author) n=0 VII Vomiting (SAE per author) n=0 XI Febrile infection (SAE per author) (SAE) n=0 XXV Surgery (SAE per author) (SAE) n=1 VIII Pyrexia (SAE per author) n=0 VII Rectal hemorrhage (SAE per author) (SAE) n=0 XX Pyelonephritis (SAE per author) (SAE) n=0 XXI Bronchiolitis (SAE per author) (SAE) n=3 XXI Cough (SAE per author) n=0 XXVII Drug toxicity (SAE per author) (SAE) n=0 XII Inguinal hernia (SAE per author) (SAE) n=2		n/a	16, 1	2	Antibiotics unclear	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Chouraqui, 2008 RCT Effective	4 Bi	74	VII Gastroenteritis (SAE per author) (SAE) n=0 VII Gastroesophageal reflux disease (SAE per author) (SAE) n=0 VII Diarrhea (SAE per author) n=0 XXVII Milk allergy (SAE per author) n=0 VII Vomiting (SAE per author) n=2 XI Febrile infection (SAE per author) (SAE) n=0 XXV Surgery (SAE per author) (SAE) n=0 VIII Pyrexia (SAE per author) n=0 VII Rectal hemorrhage (SAE per author) (SAE) n=0 XX Pyelonephritis (SAE per author) (SAE) n=1 XXI Bronchiolitis (SAE per author) (SAE) n=1 XXI Cough (SAE per author) n=0 XXVII Drug toxicity (SAE per author) (SAE) n=0 XII Inguinal hernia (SAE per author) (SAE) n=0		n/a	14, 1	0	Antibiotics unclear	
Chui, 2009 RCT Effectiveness unclear	1 En	20	XXVII Death (SAE) n=1		n/a	0, 0			
Chui, 2009 RCT Effectiveness unclear	2	25	XXVII Death (SAE) n=2		n/a	0, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Coccorullo, 2010 RCT Effectiveness unclear	1 La	22	VII Vomiting n=0 VII Bloating n=0 VII Increased flatulence n=0		0	0, 0			
Coccorullo, 2010 RCT Effectiveness unclear	2	22	VII Vomiting n=0 VII Bloating n=0 VII Increased flatulence n=0		0	0, 0			Placebo
Connolly, 2005 RCT Effective	1 La	14	XIV D-lactic acidosis n=0		0	0, 0			
Connolly, 2005 RCT Effective	2	10	XIV D-lactic acidosis n=0		0	0, 0			Placebo
Cooper, 2006 RCT Effective	1 Bi	98		No difference in gastrointestinal or respiratory problems between groups	n/a	n/a, n/a			
Cooper, 2006 RCT Effective	2	173				n/a, n/a			Formula only
Correa, 2005 RCT Effective	1 St	87	XI Pneumonia -death (5) (SAE) n=1 (states infection not due to supplemented bacteria)		n/a	7, 1			
Correa, 2005 RCT Effective	2	82	XI Pneumonia -death (5) (SAE) n=0		n/a	5, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Cui, 2004 RCT Effective	1 Ba	103	XIII Body weight changes n=0 VIII Temperature changes n=0 XXII Respiratory rate changes n=0 II Heart rate changes n=0 II Blood pressure changes n=0 XIII Blood routine changes n=0 IX Liver function changes n=0 XX Renal function changes n=0		0	n/a, 0			
Cui, 2004 RCT Effective	2 Bi	101	XIII Body weight changes n=0 VIII Temperature changes n=0 XXII Respiratory rate changes n=0 II Heart rate changes n=0 II Blood pressure changes n=0 XIII Blood routine changes n=0 IX Liver function changes n=0 XX Renal function changes n=0		0	n/a, 0			Other Probiotic
Cunningham-Rundles, 2000 CCT Effectiveness unclear	1 La		VII Flatulence n=0		0	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Cunningham-Rundles, 2000 CCT Effectiveness unclear	2		VII Flatulence n=0		0	n/a, 0			Placebo
Czaja, 2007 RCT Effective	1 La	15	XXI Abnormal vaginal discharge n=6 XXI External genital irritation n=1 XI Vaginal candidiasis n=4 XXI Vaginal odor n=1 VII Abdominal or pelvic cramps / abdominal pain n=0 XX Dysuria n=0		n/a	0, 0			
Czaja, 2007 RCT Effective	2	15	XXI Abnormal vaginal discharge n=7 XXI External genital irritation n=5 XI Vaginal candidiasis n=2 XXI Vaginal odor n=0 VII Abdominal or pelvic cramps / abdominal pain n=1 XX Dysuria n=1			0, 0			Placebo
Dadak, 2006 RCT Not effective	1 La	6		1 death, group unclear	n/a	n/a, n/a			
Dadak, 2006 RCT Not effective	2	6				1, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
De Preter, 2006 C-RCT Effectiveness unclear	1 Sa	45	VII Flatulence n=0		n/a	,		Antibiotics unclear	
De Preter, 2006 C-RCT Effectiveness unclear	2	45	VII Flatulence n=0		n/a	,		Antibiotics needed	Placebo
de Roos, 1999 RCT Not effective	1 St	39		1 gastrointestinal complaint, group unclear	n/a	n/a, n/a			
de Roos, 1999 RCT Not effective	2	39				n/a, n/a			Yogurt only
De Simone, 1992 RCT Effective	1 Bi	15	VII Intestinal rumbling and flatulence (1) n=2 VII Variation in stool consistency and diarrhea n=0		2	0, 0			
De Simone, 1992 RCT Effective	2	10	VII Intestinal rumbling and flatulence n=0 VII Variation in stool consistency and diarrhea n=0		1	0, 0			Placebo
De Simone, 2001 CCT Effective	1 St	130	XIII Blood count changes n=0 XIII Blood chemistry changes n=0		n/a	n/a, n/a			
De Simone, 2001 CCT Effective	2 En	121	XIII Blood count changes n=0 XIII Blood chemistry changes n=0			n/a, n/a			Other Probiotic

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Dekker, 2009 RCT Effective	1 La	170	III Congenital malformation hospitalization (SAE) n=3 XXIII Dermatological hospitalization (SAE) n=3 VII Gastrointestinal hospitalization (SAE) n=7 XX Genito-urinary hospitalization (SAE) n=1 XI Infectious diseases hospitalization (SAE) n=6 XXVII Neurology hospitalization (SAE) n=0 VI Ophthalmology & otology hospitalization (SAE) n=4 XXVII Orthopedics & rheumatoid hospitalization (SAE) n=0 XXII Respiratory hospitalization (SAE) n=9 XI Trauma and injury hospitalization (SAE) n=1 VII Diarrhea or vomiting (SAE) n=3 XXVII Other hospitalizations (SAE) n=11	No statistically significant differences between groups for diarrhea after antibiotics, other diarrhea, reflux or spilling, abdominal pain or vomiting. Hospitalizations of mothers 6.4, 6.9 and 3.2% in the 3 arms	n/a	26, n/a	39		

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Dekker, 2009 RCT Effective	2	171	III Congenital malformation hospitalization (SAE) n=2 XXIII Dermatological hospitalization (SAE) n=1 VII Gastrointestinal hospitalization (SAE) n=7 XX Genito-urinary hospitalization (SAE) n=3 XI Infectious diseases hospitalization (SAE) n=3 XXVII Neurology hospitalization (SAE) n=0 VI Ophthalmology & otology hospitalization (SAE) n=6 XXVII Orthopedics & rheumatoid hospitalization (SAE) n=1 XXII Respiratory hospitalization (SAE) n=16 XI Trauma and injury hospitalization (SAE) n=1 VII Diarrhea or vomiting (SAE) n=2 XXVII Other hospitalizations (SAE) n=4		n/a	21, n/a	39		Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Dekker, 2009 RCT Effective	3 Bi	171	III Congenital malformation hospitalization (SAE) n=3 XXIII Dermatological hospitalization (SAE) n=4 VII Gastrointestinal hospitalization (SAE) n=0 XX Genito-urinary hospitalization (SAE) n=1 XI Infectious diseases hospitalization (SAE) n=7 XXVII Neurology hospitalization (SAE) n=1 VI Ophthalmology & otology hospitalization (SAE) n=5 XXVII Orthopedics & rheumatoid hospitalization (SAE) n=0 XXII Respiratory hospitalization (SAE) n=6 XI Trauma and injury hospitalization (SAE) n=4 VII Diarrhea or vomiting (SAE) n=2 XXVII Other hospitalizations (SAE) n=6			19, n/a	36		
Delia, 2002 RCT Effective	1 St	95	VII Gastrointestinal toxicity n=0 XXVII Death (SAE) n=0		0	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Delia, 2002 RCT Effective	2	95	VII Gastrointestinal toxicity n=2 XXVII Death (SAE) n=0		2	2, 2			Placebo
Delia, 2007 RCT Effective	1 St	245	XXVI Septic shock (SAE) n=0 XI Bacteremia (SAE) n=0 XI Sepsis (SAE) n=0	1 myocardial infarction death, group unclear	n/a	2, 1			
Delia, 2007 RCT Effective	2	245	XXVI Septic shock (SAE) n=0 XI Bacteremia (SAE) n=0 XI Sepsis (SAE) n=0		n/a	6, 0			Placebo
Dewan, 2007 RCT Effectiveness unclear	1 St	39	XI Bronchopneumonia - death (5) (SAE) n=1		1	7, 1			
Dewan, 2007 RCT Effectiveness unclear	2	41	XI Bronchopneumonia - death (5) (SAE) n=1		1	5, 1			Non-probiotic
Dolin, 2009 RCT Effective	1 Ba	26	XVII Headache n=n/a		5	0, 0			
Dolin, 2009 RCT Effective	2	29	XVII Headache n=1		6	3, 0			Placebo
Dubey, 2008 RCT Effective	1 St	113	XXIII Rash n=0	No side effects were noticed that required treatment discontinuation	n/a	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Dubey, 2008 RCT Effective	2	111	XXIII Rash n=0			n/a, 0			Placebo
Duman, 2005 RCT Effective	1 Sa	204	XXIII Skin reaction n=1 II Palpitation n=0 VII Dry mouth n=1 XVII Metallic taste n=1 VII Apthons lesion in mouth n=0 VI Blurred vision n=0		3	8, 1			
Duman, 2005 RCT Effective	2	185	XXIII Skin reaction n=n/a II Palpitation n=1 VII Dry mouth n=0 XVII Metallic taste n=0 VII Apthons lesion in mouth n=1 VI Blurred vision n=n/a		3	13, 1			Triple therapy only
Dupont, 2010 RCT Effective	1 Bi	30	VII Vomiting n=1 (feeding-related per author) VII Colitis n=1 (feeding-related per author) VII Constipation n=0 (feeding-related per author) VII Regurgitations n=0 (feeding-related per author) VII Flatulence n=0 (feeding-related per author)		n/a	10, 4			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Dupont, 2010 RCT Effective	2	32	VII Vomiting n=4 (feeding-related per author) VII Colitis n=1 (feeding-related per author) VII Constipation n=5 (feeding-related per author) VII Regurgitations n=3 (feeding-related per author) VII Flatulence n=1 (feeding-related per author)		n/a	6, 5			Formula only
Dylewski, 2010 RCT Effective	1 La	233	XXVII Death (SAE) n=3 VII Eructation n=0 VII Constipation n=12 VII Flatulence n=7 VII Nausea n=7 VII Vomiting n=5 VII Dyspepsia n=0 VII Dysphagia n=1 VII Fecal incontinence n=1 XXII Dyspnea n=0 VII Gastro esophageal adverse events n=1 VII Reflux gastritis n=1 XI Vulvovaginal mycotic infection n=0 XV Muscle spasms n=0 XXVII Hyperthermia n=0 XIII Pyrexia n=0 XV Arthralgia n=1 XVII Headache n=1		72	17, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Dylewski, 2010 RCT Effective	2	239	XXVII Death (SAE) n=4 VII Eructation n=1 VII Constipation n=8 VII Flatulence n=13 VII Nausea n=5 VII Vomiting n=0 VII Dyspepsia n=2 VII Dysphagia n=0 VII Fecal incontinence n=0 XXII Dyspnea n=1 VII Gastro esophageal adverse events n=0 VII Reflux gastritis n=1 XI Vulvovaginal mycotic infection n=2 XV Muscle spasms n=2 XXVII Hyperthermia n=1 XIII Pyrexia n=1 XV Arthralgia n=0 XVII Headache n=0	Presence of at least 1 treatment-emergent non serious adverse event: 76	76	18, 0			Placebo
Ehrstrom, 2010 RCT Effectiveness unclear	1 La	60	XXI Vulvovaginal pruritus n=1 XXI Vaginal bleeding n=1 XXI Swollen and vulva n=0 XVII Headache n=0 XXI Vulvar itching n=0		n/a	n/a, n/a			
Ehrstrom, 2010 RCT Effectiveness unclear	2	35	XXI Vulvovaginal pruritus n=5 XXI Vaginal bleeding n=0 XXI Swollen and vulva n=1 XVII Headache n=1 XXI Vulvar itching n=1		n/a	n/a, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Eriksson, 2005 RCT Not effective	1 La	127	XI Candida infection n=n/a (14.2%) XXI Itching and burning n=4		n/a	36, n/a			
Eriksson, 2005 RCT Not effective	2	128	XI Candida infection n=n/a (13.5%) XXI Itching and burning n=8		n/a	32, n/a			Placebo
Falck, 1999 RCT Effective	1 St	228	XXII Respiratory related to common cold n=34 (16%)		77	15, 4			
Falck, 1999 RCT Effective	2	114	XXII Respiratory related to common cold n=14 (13%)		36	6, 3			Placebo
Felley, 2001 RCT Effective	1 La	26	VII Diarrhea (profuse; withdrew) n=1 (while taking clarithromycin)		n/a	1, 1			
Felley, 2001 RCT Effective	2	27	VII Diarrhea (profuse) n=0			0, 0			Placebo
Feng, 1999 RCT Effective	1 St	36	VII Nausea (1) n=2		2	0, 0			
Feng, 1999 RCT Effective	2	36	VII Nausea (1) n=3		3	0, 0			Other Probiotic
Folster-Holst, 2006 RCT Not effective	1 La	26	VII Diarrhea (mild) n=4 VII Nausea/vomiting n=3 VIII Fever n=1 XXIII Urticaria n=0		n/a	5, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Folster-Holst, 2006 RCT Not effective	2	28	VII Diarrhea n=4 VII Nausea/vomiting n=4 VIII Fever n=1 XXIII Urticaria n=1		n/a	7, 1			Placebo
Forestier, 2008 RCT Effective	1 La	118	XI Lactobacillus-related sepsis (SAE) n=0		n/a	16, 0			
Forestier, 2008 RCT Effective	2	118	XI Lactobacillus-related sepsis (SAE) n=0			12, 0			Placebo
French, 2009 RCT Effective	1 La	21	XII Injection site temporary pain or redness n=n/a XXVII Febrile illness n=0		n/a	3, 0			
French, 2009 RCT Effective	2	26	XII Injection site temporary pain or redness n=n/a XXVII Febrile illness n=0		n/a	4, 0			Placebo
Frohmader, 2010 RCT Effective	1 St	20	XXVII Death (SAE) n=5 XI Infections due to probiotic strains (SAE) n=0		n/a	0, 0			
Frohmader, 2010 RCT Effective	2	25	XXVII Death (SAE) n=3 XI Infections due to probiotic strains n=0		n/a	0, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Fujimori, 2009 RCT Effective	1 Bi	40	XIII Blood count changes n=0 XIII Liver enzyme changes n=0 XIII Serum urea nitrogen changes n=0 XIII Creatinine changes n=0 XIII Electrolytes changes n=0 XIII Total protein / cholesterol changes n=0 XIII Albumin changes n=0		0	11, 0			
Fujimori, 2009 RCT Effective	2	40	XIII Blood count changes n=0 XIII Liver enzyme changes n=0 XIII Serum urea nitrogen changes n=0 XIII Creatinine changes n=0 XIII Electrolytes changes n=0 XIII Total protein / cholesterol changes n=0 XIII Albumin changes n=0		0	15, 0			Prebiotics

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Fujimori, 2009 RCT Effective	3 Bi	40	XIII Blood counts n=0 XIII Liver enzyme changes n=0 XIII Serum urea nitrogen changes n=0 XIII Creatinine changes n=0 XIII Electrolytes changes n=0 XIII Total protein / total cholesterol changes n=0 XIII Albumin changes n=0		0	11, 0			
Gade, 1989 RCT Effective	1 St	32		1 polyneuritis hospitalization (withdrawal), group unclear	n/a	n/a, 0			
Gade, 1989 RCT Effective	2	22			n/a	n/a, 0			Placebo
Galpin, 2005 RCT Not effective	1 La	81	VII Vomiting n=0		0	1, 1			
Galpin, 2005 RCT Not effective	2	83	VII Vomiting n=0		0	2, 0			Placebo
Gao, 2010 RCT Effective	1 La	85	VIII Fever n=0 VII Hematochezia n=0		0	7, 0			
Gao, 2010 RCT Effective	2	84	VIII Fever n=1 (not study related per author) VII Hematochezia n=1 (not study related per author)		2	8, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Gao, 2010 RCT Effective	3 La	86	XIII Fever n=1(not study related per author) VII Hematochezia n=0		1	4, 0			
Garcia Vilela, 2008 RCT Effectiveness unclear	1 Sa	18	VII Abdominal pain, vomiting and diarrhea n=0		0	1, 0			
Garcia Vilela, 2008 RCT Effectiveness unclear	2	16	VII Abdominal pain, vomiting and diarrhea n=2			2, 2			Placebo
Gerasimou, 2010 RCT Effective	1 Bi	48	XI Upper respiratory infections n=11 XI Lower respiratory infection n=4 XXIII Herpetic stomatitis n=7 VII Diarrhea n=3 VII Constipation n=6 VII Abdominal colic n=5 XXVII Burn (SAE) n=1 (states unrelated) XXII Croup (SAE) n=1 (states unrelated) XXVII Head injury (SAE) n=0 XXVII Food poisoning n=0		26	5, 2		Antibiotics needed	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Gerasimou, 2010 RCT Effective	2	48	XI Upper respiratory infections n=10 XI Lower respiratory infection n=5 XXIII Herpetic stomatitis n=5 VII Diarrhea n=2 VII Constipation n=6 VII Abdominal colic n=4 XXVII Burn (SAE) n=0 XXII Croup (SAE) n=0 XXVII Head injury (SAE) n=1 (states unrelated) XXVII Food poisoning n=2 (states unrelated)		24	1, 1			Placebo
Gibson, 2008 RCT Not effective	1 Bi	72	XI Intestinal infections disease n=21 VII Symptoms and signs involving the digestive system n=11 VII Feeding problems n=11 XI Respiratory infections n=47 XI Candidiasis n=6 XXIII Dermatitis n=13 VII Parent perception of constipation/irritability (n=1 (drop out) XXVII Death (SAE) n=0		61	17, 1	18		

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Gibson, 2008 RCT Not effective	2	70	XI Intestinal infections disease n=29 VII Symptoms and signs involving the digestive system n=8 VII Feeding problems n=22 XI Respiratory infections n=49 XI Candidiasis n=9 XXIII Dermatitis n=11 VII Parent perception of constipation/irritability n=1 (drop out) XXVII Death (SAE) n=0		65	27, 1	11		Formula only
Gill, 2001 RCT Effective	1 Bi	15	VII Digestive discomfort n=0		0	0, 0			
Gill, 2001 RCT Effective	2 Bi	15	VII Digestive discomfort n=1		1	1, 1			Other Probiotic
Gionchetti, 2000 RCT Effective	1 St	20	XIII CBC n=0 XIII Blood chemistry changes n=0		0	0, 0			
Gionchetti, 2000 RCT Effective	2	20	XIII CBC n=0 XIII Blood chemistry changes n=0		0	0, 0			Placebo
Gionchetti, 2003 RCT Effective	1 St	20	XIII Blood count changes n=0 XIII Blood chemistry changes n=0		0	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Gionchetti, 2003 RCT Effective	2	20	XIII Blood count changes n=0 XIII Blood chemistry changes n=0		0	0, 0			Placebo
Goossens, 2003 RCT Effective	1 La	11	VII 5 liquid stools per day n=0		n/a	0, 0			
Goossens, 2003 RCT Effective	2	11	5 liquid stools per day1			2, 1			Placebo
Gracheva, 1999 CCT Effective	1 Bi	30	VII Abdominal pain (treatment discontinued) n=1		1	n/a, n/a			
Gracheva, 1999 CCT Effective	2 Bi	20	VII Abdominal pain n=0		0	n/a, n/a			Other Probiotic

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Gruber, 2007 RCT Not effective	1 La	56	XI Lower respiratory tract infections n=24 XI Ear nose and throat infections n=8 VII Gastrointestinal complaints n=18 XI Other infections n=22 XXIII Skin disorders n=9 XXVII Conjunctivitis, dental problems or unrest n=9 VII Acute enteritis n=1 (states not related to study medication) XXIII Eczema herpeticatum n=1 (states not related to study medication) XXII Spasmodic croup n=1 (states not related to study medication) VII Inguinal hernia n=1 (states not related to study medication) XI Pneumonia n=1 (states not related to study medication)		46	n/a, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Gruber, 2007 RCT Not effective	2	50	XI Lower respiratory tract infections n=18 XI Ear nose and throat infections n=15 VII Gastrointestinal complaints n=10 XI Other infections n=16 XXIII Skin disorders n=5 XXVII Conjunctivitis, dental problems or unrest n=7 VII Acute enteritis n=0 XXIII Eczema herpeticatum n=0 XXII Spasmodic croup n=0 VII Inguinal hernia n=0 XI Pneumonia n=0		38	n/a, n/a			Placebo
Guillemard, 2010 RCT Effective	1 St	537	XV Muscular-bone adverse events n=n/a VII Gastrointestinal adverse events n=n/a XI Infections other than common infectious diseases n=n/a		137	n/a, n/a			
Guillemard, 2010 RCT Effective	2	535	XV Muscular-bone adverse events n=n/a VII Gastrointestinal adverse events n=n/a XI Infections other than common infectious diseases n=n/a		139	n/a, n/a			Placebo
Guyonnet, 2009 RCT Effective	1 St	144	VII Adverse digestive comfort n=0		0	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Guyonnet, 2009 RCT Effective	2	69	VII Adverse digestive comfort n=0		0	n/a, 0			No intervention
Guyonnet, 2009 RCT Effective	3 St	147	VII Adverse digestive comfort n=0			n/a, 0			
Habermann, 2001 RCT Effective	1 En	70	VII Various gastrointestinal complaints n=4	No difference in blood and clinical lab panels between groups	4	n/a, n/a			
Habermann, 2001 RCT Effective	2	66	VII Various gastrointestinal complaints n=3		3	n/a, n/a			Placebo
Habermann, 2002 RCT Effective	1 En	78	VII Disgust n=n/a VII Nausea n=n/a VII Vomiting n=n/a VII Meteorism n=n/a I Blood count changes n=0 XXVII Clinical chemical panel changes n=0		12	n/a, n/a			
Habermann, 2002 RCT Effective	2	79	VII Disgust n=n/a VII Nausea n=n/a VII Vomiting n=n/a VII Meteorism n=n/a I Blood count changes n=0 XXVII Clinical chemical panel changes n=0		13	n/a, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Haschke-Becher, 2008 RCT Effective	1 La	19	XI Bronchopneumonia n=0 VII Vomiting n=0 XI Otitis n=0 XVII Neuropathy n=0	Increased D-lactate excretion in probiotic group compared to breastfed group	n/a	2, 0		Antibiotics unclear	
Haschke-Becher, 2008 RCT Effective	2	26	XI Bronchopneumonia n=1 VII Vomiting n=1 XI Otitis n=1 XVII Neuropathy n=1		n/a	8, 4		Antibiotics unclear	Placebo
Hatakka, 2008 C-RCT Not effective	1 La	19	VII Gastrointestinal complaints n=n/a XXVII Any signs of illness n=n/a		n/a	0, 0			
Hatakka, 2008 C-RCT Not effective	2	19	VII Gastrointestinal complaints n=n/a XXVII Any signs of illness n=n/a			0, 0			Placebo
Heimburger, 1994 RCT Not effective	1 La	31		Discontinuation due to gastric retention of feeding, patient removal of feeding tube, death, number and group unclear	n/a	13, n/a			
Heimburger, 1994 RCT Not effective	2	31				8, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Hemmerling, 2009 RCT Effective	1 La	3	XXI Vaginal discharge n=1 VII Abdominal pain n=1 XXI Metrorrhagia n=0 XXI Vulvovaginitis n=0 XVII Headache n=1 XXI Vaginal candidiasis n=0 XXI Vaginal odor n=1 XXI Erythema n=0 XXI Petechiae n=0 XXI Edema n=0 XXI Abrasion n=0 XXI Laceration n=0 XX Urinary tract infection n=0	1 Gastroenteritis, 1 ear pain, 1 upper respiratory tract infection, treatment group unclear	3	0, 0			
Hemmerling, 2009 RCT Effective	2	3	XXI Vaginal discharge n=0 VII Abdominal pain n=1 XXI Metrorrhagia n=2 XXI Vulvovaginitis n=1 XVII Headache n=1 XXI Vaginal candidiasis n=1 XXI Vaginal odor n=0 XXI Erythema n=1 XXI Petechiae n=0 XXI Edema n=1 XXI Abrasion n=0 XXI Laceration n=1 XXI Urinary tract infection n=1		3	0, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Hemmerling, 2009 RCT Effective	3 La	3	XXI Vaginal discharge n=2 VII Abdominal pain n=2 XXI Metrorrhagia n=0 XXI Vulvovaginitis n=1 XVII Headache n=1 XXI Vaginal candidiasis n=1 XXI Vaginal odor n=2 XXI Erythema n=0 XXI Petechiae n=1 XXI Edema n=0 XXI Abrasion n=1 XXI Urinary tract infection n=0		3	0, 0			
Hemmerling, 2009 RCT Effective	4 La	3	XXI Vaginal discharge n=2 VII Abdominal pain n=0 XXI Metrorrhagia n=2 XXI Vulvovaginitis n=2 XVII Headache n=0 XXI Vaginal candidiasis n=1 XXI Vaginal odor n=0 XXI Erythema n=1 XXI Petechiae n=0 XXI Edema n=0 XXI Abrasion n=0 XXI Urinary tract infection n=0		3	0, 0			
Higashikawa, 2009 RCT Effective	1 La	24	XX Abnormal changes in urinalysis n=0 XIII Abnormal changes in serum biochemical parameters n=0		n/a	0, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Higashikawa, 2009 RCT Effective	2 La	22	XX Abnormal changes in urinalysis n=0 XIII Abnormal changes in serum biochemical parameters n=0		n/a	3, n/a			Other Probiotic
Higashikawa, 2009 RCT Effective	3 St	22	XX Abnormal changes in urine analysis n=0 XIII Abnormal changes in serum biochemical parameters n=0			1, n/a			
Hilton, 1997 RCT Effective	1 La	200	VII Abdominal cramps n=2		2	74, 0			
Hilton, 1997 RCT Effective	2	200	VII Abdominal cramps n=2		n/a	81, 0			Placebo
Hirata, 2002 CCT Effective	1 Sa	18	VII Constipation (1) n=1 XVII Exacerbation of headaches n=0 VIII Dry cough n=0 XVII Dizziness n=0 XVII Other neurological symptoms n=0 VII Gastrointestinal symptoms n=0 XXIII Skin symptoms n=0		n/a	2, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Hirata, 2002 CCT Effective	2	18	VII Constipation (mild) n=0 XVII Exacerbation of headaches n=0 VIII Dry cough n=0 XVII Dizziness n=0 XVII Other neurological symptoms n=0 VII Gastrointestinal symptoms n=0 XXIII Skin symptoms n=0		n/a	2, 0			Placebo
Hochter,1990 RCT Effective	1 Sa	43	VII Constipation n=1		1	n/a, n/a			
Hochter,1990 RCT Effective	2	49	VII Vomiting n=1		1	n/a, n/a			Placebo
Honeycutt, 2007 RCT Not effective	1 La	31	XXVII Death (SAE) n=2 VII Nausea n=1 XI Lactobacillus bacteremia (SAE) n=0		3	4, 3			
Honeycutt, 2007 RCT Not effective	2	30	XXVII Death (SAE) n=4 VII Nausea n=1 XI Lactobacillus bacteremia (SAE) n=0		5	5, 5			Placebo
Hong, 2010 RCT Effective	1 Bi	36	XXVII Common cold, headache, cystitis, and / or low back pain n=8	12 patients reported common cold, headache, cystitis, low back pain, exacerbation of abdominal pain, exacerbation of constipation but group unclear. 8 AEs in each group	n/a	1, 1			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Hong, 2010 RCT Effective	2	34	XXVII Common cold, headache, cystitis, and / or low back pain n=8		n/a	1, 1			Placebo
Horvat, 2010 RCT Effective	1 La	20	XI Mild wound infection with secretion n=0		n/a	n/a, n/a			
Horvat, 2010 RCT Effective	2 La	20	XI Mild worsened infection with secretion n=1		n/a	n/a, n/a			Other Probiotic
Horvat, 2010 RCT Effective	3	28	XI Mild infection with secretion n=1		1	n/a, n/a			
Ishikawa, 2002 RCT Effective	1 Sa	11	XI Coryza-like illness n=1 VII Abdominal pain n=1 VII Diarrhea n=0 VII Vomiting n=0		1	0, 0			
Ishikawa, 2002 RCT Effective	2	10	XI Coryza-like illness n=0 VII Abdominal pain n=0 VII Diarrhea n=0 VII Vomiting n=0		0	0, 0			No treatment
Ishikawa, 2003 RCT Effectiveness unclear	1 La	28		2 patients with soft stools and abdominal discomfort, probiotics group but unclear which one	n/a	n/a, n/a			
Ishikawa, 2003 RCT Effectiveness unclear	2	21	VII Abdominal discomfort n=0 VII Loose stools n=0		0	n/a, n/a			No treatment

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Ishikawa, 2003 RCT Effectiveness unclear	3 La	29		2 patients taking LS 1 experienced abdominal discomfort and loose stools but unclear which treatment group		n/a, n/a			
Ishikawa, 2005 RCT Effective	1 La	99	XVI Colorectal cancer (2) (SAE) n=2 XVII Cerebral hemorrhage -death (SAE) n=0 VII Peritonitis (3, surgery) (SAE) n=0 XVI Lung cancer -death (SAE) n=0		n/a	3, n/a	0	0	
Ishikawa, 2005 RCT Effective	2	97	XVI Colorectal cancer (2) (SAE) n=1 XVII Cerebral hemorrhage -death (SAE) n=0 VII Peritonitis (3, surgery) (SAE) n=0 XVI Lung cancer -death (SAE) n=0		n/a	4, n/a	0		Dietary instructions only
Ishikawa, 2005 RCT Effective	3 La	103	XVI Colorectal cancer (SAE) n=1 XVII Cerebral hemorrhage -death (SAE) n=1 XVI Lung cancer -death (SAE) n=0 VII Peritonitis (SAE) n=1		n/a	7, n/a	1		

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Isolauri, 1991 RCT Effective	1 La	24	VII Vomiting on day 1 n=14 VII Vomiting on day 2 n=5 VII Vomiting on day 3 n=0 VII Vomiting on day 4 + 5 n=0		n/a	0, 0			
Isolauri, 1991 RCT Effective	2	24	VII Vomiting on day 1 n=13 VII Vomiting on day 2 n=9 VII Vomiting on day 3 n=4 VII Vomiting on day 4 + 5 n=0			0, 0			Non-probiotic
Isolauri, 1991 RCT Effective	3 La	23	VII Vomiting on day 1 n=10 VII Vomiting on day 2 n=5 VII Vomiting on day 3 n=2 VII Vomiting on day 4 + 5 n=0			0, 0			
Isolauri,1995 RCT Effective	1 La	30	VIII Fever (>38C) n=n/a VII Vomiting n=2 VII Loose stool n=n/a		n/a	n/a, n/a			
Isolauri,1995 RCT Effective	2	30	VIII Fever (>38C) n=n/a VII Vomiting n=0 VII Loose stool n=n/a			n/a, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Jirapinyo, 2002 RCT Effectiveness unclear	1 Bi	8	XXVII Worsening of clinical condition n=0 XI Sepsis due to Lactobacillus or Bifidobacterium (SAE) n=0		n/a	0, 0			
Jirapinyo, 2002 RCT Effectiveness unclear	2	10	XXVII Worsening of clinical condition n=0 XI Sepsis due to Lactobacillus or Bifidobacterium (SAE) n=0		n/a	0, 0			Placebo
Johansson, 1998 RCT Effective	1 La	26	XXVII Transient nausea, abdominal discomfort and flu-like symptoms n=5		5	0, 0			
Johansson, 1998 RCT Effective	2	22	XXVII Transient nausea, abdominal discomfort and flu-like symptoms n=5		5	0, 0			Placebo
Kadooka, 2010 RCT Effective	1 St	43	VII Nausea n=0 XVII Headache n=0 VII Abdominal pain n=0		0	0, 0			
Kadooka, 2010 RCT Effective	2	44	VII Nausea n=0 XVII Headache n=0 VII Abdominal pain n=0		0	0, 0			Fermented milk only
Kajander, 2005 RCT Effective	1 Bi	52	XXVII Illness or hospitalization, not IBS related n=1		n/a	8, 4			
Kajander, 2005 RCT Effective	2	51	XXVII Illness or hospitalization, not IBS related n=3		n/a	9, 4			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Kajander, 2008 RCT Effective	1 Bi	43	VII GI symptoms n=n/a XXII Respiratory tract n=n/a VI Eye operation n=n/a XXVI Atherosclerotic finding in the carotid artery n=n/a XXIII Inflamed mole n=n/a XX Cystitis n=n/a XV Tenosynovitis n=n/a XI Oral herpes n=0 V Hyperthyroidism n=0 XXII Breathing difficulties n=0 V Hyperthyroidism n=0 XXVII Backache n=0 XXV Foot operation n=0 XXI Vaginitis n=0 XXVII Intestinal warms n=0		10	5, 2			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Kajander, 2008 RCT Effective	2	43	VII GI symptoms n=n/a XXII Respiratory tract n=n/a VI Eye operation n=0 XXVI Atherosclerotic finding in the carotid artery n=0 XXIII Inflamed mole n=0 XX Cystitis n=0 XV Tenosynovitis n=0 XI Oral herpes n=0 V Hyperthyroidism n=n/a Breathing difficultiesn/a V Hyperthyroidism n=n/a XXVII Backache n=n/a XXV Foot operation n=n/a XXI Vaginitis n=n/a XXVII Intestinal warms n=n/a		15	10, 6			Placebo
Kajimoto, 2002 RCT Effective	1 St	33	XXII Dry cough n=0 VII Gastrointestinal symptoms n=0 XXIII Skin symptoms n=0		0	n/a, 0			
Kajimoto, 2002 RCT Effective	2	33	XXII Dry cough n=0 VII Gastrointestinal symptoms n=0 XXIII Skin symptoms n=0		0	n/a, 0			Yogurt only
Karvonen, 2001 RCT Effective	1 La	12	VII Abdominal symptoms n=n/a (states similar between groups)		n/a	n/a, n/a			
Karvonen, 2001 RCT Effective	2	28	VII Abdominal symptoms n=n/a		n/a	n/a, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Karvonen, 2001 RCT Effective	3 La	25	VII Abdominal symptoms n=n/a		n/a	n/a, n/a			
Karvonen, 2001 RCT Effective	4 La	25	VII Abdominal symptoms n=n/a		n/a	n/a, n/a			
Kerac, 2009 RCT Not effective	1 La	399	XXVII Death (SAE) n=108 XXVII Not tolerating/clinically worsening n=6 XI Probiotics-related sepsis (SAE) n=0 XXVII Medical visits with problem n=26 XXVII Readmission episodes (SAE) n=87	17/68 (probiotic group) versus 23/69 (control group) taken blood cultures positive	n/a	n/a, n/a	27		
Kerac, 2009 RCT Not effective	2	396	XXVII Death (SAE) n=119 XXVII Not tolerating/clinically worsening n=5 XI Probiotics-related sepsis (SAE) n=0 XXVII Medical visits with problem n=48 XXVII Readmission episodes (SAE) n=71		n/a	n/a, n/a	16		Placebo
Kianifar, 2009 RCT Effective	1 Bi	34	XIII Bacteremia (SAE) n=0 XIII Fungemia (SAE) n=0		n/a	2, 0			
Kianifar, 2009 RCT Effective	2	34	XIII Bacteremia (SAE) n=0 XIII Fungemia (SAE) n=0		n/a	4, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Kim, 2006 RCT Effectiveness unclear	1 Ba	12	VII Loose stool, diarrhea or worsening of GI symptoms n=0 VII Dehydration n=0 IX Elevated blood pressure n=0	No abnormal changes in blood chemistry	0	3, 0			
Kim, 2006 RCT Effectiveness unclear	1 Ba	12	VII Loose stool, diarrhea w/ or w/out worsening of GI symptoms n=1 (states not related) VII Dehydration n=1 (states not related) IX Elevated blood pressure n=1 (states not related)		1	2, 1			
Kim, 2006 RCT Effectiveness unclear	2	12	VII Loose stool, diarrhea or worsening of G1 symptoms n=0 VII Dehydration n=0 IX Elevated blood pressure n=0		0	3, 0			Placebo
Kim, 2006 RCT Effectiveness unclear	2 Ba	12	VII Loose stool, diarrhea w/ or w/out worsening of GI symptoms n=1 (states not related) VII Dehydration n=0 (states not related) IX Elevated blood pressure n=0 (states not related)		1	3, 1			Other Probiotic
Kim, 2006 RCT Effectiveness unclear	3 Ba	12	VII Loose stool, diarrhea or worsening of GI symptoms n=1 VII Dehydration n=0 IX Elevated blood pressure n=0		1	2, 1			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Kim, 2008 RCT Effectiveness unclear	1 St	168	XXVII Metallic taste n=28 VII Diarrhea n=16 VII Epigastric soreness n=7 VII Epigastric pain n=4 VII Bloating n=4 VII Epigastric discomfort n=1 VII Nausea n=3 VII Acid regurgitation n=2 VIII Headache n=1 VII Constipation n=1 XIV Weight gain n=1 XXIII Pruritus n=1		69	6, 2			
Kim, 2008 RCT Effectiveness unclear	2	179	XXVII Metallic taste n=13 VII Diarrhea n=14 VII Epigastric soreness n=6 VII Epigastric pain n=5 VII Bloating n=2 VII Epigastric discomfort n=4 VII Nausea n=n/a VII Acid regurgitation n=1 VIII Headache n=1 VII Constipation n=1 XIV Weight gain n=1 XXIII Pruritus n=n/a		47	15, 1			Triple therapy only
Kirjavainen,2003 RCT Effectiveness unclear	1 La	17	VII Diarrhea n=0		0	3, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Kirjavainen,2003 RCT Effectiveness unclear	2	10	VII Diarrhea n=0		0	2, 0			Placebo
Kirjavainen,2003 RCT Effectiveness unclear	3 La	16	VII Diarrhea n=5		5	3, 0			
Klarin, 2008 RCT Not effective	1 La	23	XXVII Death (SAE) n=5		n/a	n/a, n/a			
Klarin, 2008 RCT Not effective	2	21	XXVII Death (in-hospital mortality) (SAE) n=6			n/a, n/a			Non-probiotic
Klarin,2005 RCT Effective	1 La	9	XXVII Death (SAE) n=2 VII Diarrhea n=n/a (states no difference between groups) VII Gas bloating n=n/a		n/a	1, 0			
Klarin,2005 RCT Effective	2	8	XXVII Death (SAE) n=2 VII Diarrhea n=n/a VII Gas bloating n=n/a		n/a	1, 0			Placebo
Knight, 2007 RCT Not effective	1 La	150	XXVII Death attributable to probiotics (SAE) n=0 VII Diarrhea n=7 XXVII Colonization (Leuconostoc, in tracheal aspirate) n=1		n/a	20, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Knight, 2007 RCT Not effective	2	150	XXVII Death attributable to probiotics (SAE) n=0 VII Diarrhea n=9 XXVII Colonization (Leuconostoc, in tracheal aspirate) n=0		n/a	21, 0			Placebo
Koning, 2008 RCT Effectiveness unclear	1 En	20	VII Nausea n=n/a VII Abdominal cramps n=n/a VII Bloating n=n/a VII Flatulence n=n/a		n/a	1, 0			
Koning, 2008 RCT Effectiveness unclear	2	21	VII Nausea n=n/a VII Abdominal cramps n=n/a VII Bloating n=n/a VII Flatulence n=n/a	90% mild-mod symptoms in placebo	n/a	2, 0			Placebo
Kopp, 2008 RCT Not effective LTFU	1 La	54	XXII Wheezing bronchitis (5 or more episodes) n=13		n/a	4, 0			
Kopp, 2008 RCT Not effective LTFU	2	51	XXII Wheezing bronchitis (5 or more episodes) n=4		n/a	7, 0			Placebo
Kotzampassi, 2006 RCT Effective	1 La	41	VII Severe constipation n=4 VII Diarrhea n=5 VII Increased gastric residuals n=7 XI Infection due to species contained in formula (SAE) n=0	White blood cell count, c-reactive protein levels and endotoxin levels decreased compared to placebo	n/a	6, 6			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Kotzampassi, 2006 RCT Effective	2	36	VII Severe constipation n=6 VII Diarrhea n=10 VII Increased gastric residuals n=15 XI Infection due to species contained in formula (SAE) n=0		n/a	6, 6			Placebo
Krasse, 2005 RCT Effective	1 La	20	VII Increased bowel movements n=0		0	n/a, 0		Antibiotics unclear	
Krasse, 2005 RCT Effective	2	18	VII Increased bowel movements n=0		0	n/a, 0		Antibiotics needed	Placebo
Krasse, 2005 RCT Effective	3 La	21	VII Increased bowel movements n=1		1	n/a, 0		Antibiotics unclear	
Kuitunen, 2009 RCT Not effective LTFU	1 Bi	610	XIII Anemia n=16 (1 at 6 months) XXVII Excessive crying n=13 VII Abdominal discomfort n=35 VII Vomiting n=7		n/a	n/a, n/a			
Kuitunen, 2009 RCT Not effective LTFU	2	613	XIII Anemia n=10 (0 at 6 mons; 10 at 2yrs) XXVII Excessive crying n=9 VII Abdominal discomfort n=37 VII Vomiting n=12		n/a	n/a, n/a			Placebo
Kurugol, 2005 RCT Effective	1 Sa	115	VII Meteorism n=1		1	15, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Kurugol, 2005 RCT Effective	2	117	VII Meteorism n=0		0	17, 0			Placebo
La Rosa, 2003 RCT Effective	1 Ba	60	XXVII Abdominal colic n=0		0	n/a, n/a			
La Rosa, 2003 RCT Effective	2	60	VII Abdominal colic n=1		1	n/a, 1			Placebo
Laitinen, 2008 RCT Effective	1 Bi	85	VII Flatulence, loose stools or constipation n=5		5	12, 9			
Laitinen, 2008 RCT Effective	2	86	VII Flatulence, loose stools or constipation n=6		6	17, 7			Placebo
Langhendries, 1995 RCT Effective	1 St	20		Well accepted (both groups)	n/a	n/a, n/a			
Langhendries, 1995 RCT Effective	2	20			n/a	n/a, n/a			Formula only
Larsen, 2006 RCT Effectiveness unclear	1 Bi	15	X Hay fever n=n/a VII Diarrhea n=n/a (1 pat dropped out before treatment)	68% in all groups complained of flatulence, 37% abdominal bloating, 22% headache	n/a	1, 1			
Larsen, 2006 RCT Effectiveness unclear	2	15	X Hay fever n=n/a VII Diarrhea n=n/a		n/a	1, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Larsen, 2006 RCT Effectiveness unclear	3 Bi	15	X Hay fever n=n/a VII Diarrhea n=n/a		n/a	0, 0			
Larsen, 2006 RCT Effectiveness unclear	4 Bi	15	X Hay fever n=1 VII Diarrhea n=n/a			0, 0			
Larsson, 2008 RCT Effectiveness unclear	1 La	50	X Suspected allergy (vaginal discomfort) n=1 XXIII Itching n=0 XI Candida infection n=5	Headache, menorrhagia, hemorrhoids, influenza, bronchitis, whiplash, asthma, urinary tract infection occurred, number and group unclear	14	n/a, 1		Antibiotics needed	
Larsson, 2008 RCT Effectiveness unclear	2	50	X Suspected allergy (vaginal discomfort) n=0 XXIII Itching n=0 XI Candida infection n=4		12	n/a, 1			Placebo
Lata, 2009 RCT Effectiveness unclear	1 Bi	7	XXVII Death (SAE) n=0		n/a	n/a, n/a			
Lata, 2009 RCT Effectiveness unclear	2	15	XXVII Death (SAE) n=0		n/a	n/a, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Lawrence, 2005 RCT Not effective	1 La	8	VII Bloating n=2 VII Excessive flatulence n=3 VII Nausea n=0 VII Vomiting n=0 VII Abdominal pain n=0 VII Constipation n=0 XI Lactobacillus infections (SAE) n=0	Concomitant antibiotics may have caused side effects	5	0, 0			
Lawrence, 2005 RCT Not effective	2	7	VII Bloating n=1 VII Excessive flatulence n=0 VII Nausea n=0 VII Vomiting n=0 VII Abdominal pain n=0 VII Constipation n=0 XI Lactobacillus infections (SAE) n=0		1	0, 0			Placebo
Li, 2004 RCT Effective	1 Bi	10	VII Flatulence n=0 VII Increased residual gastric content n=0 VII Diarrhea n=0 VII Constipation n=0 XI Septicemia due to Bifidobacterium (SAE) n=0		0	n/a, n/a			
Li, 2004 RCT Effective	2	10	VII Flatulence n=0 VII Increased residual gastric content n=0 VII Diarrhea n=0 VII Constipation n=0 XI Septicemia due to Bifidobacterium (SAE) n=0		0	n/a, n/a			No supplement

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Ligaarden, 2010 C-RCT Not effective	1 La	10		1 pts was hospitalized for cervicobrachialgia during washout and there were 3 minor adverse events, group unclear	n/a	1, 0		hospital stay	
Ligaarden, 2010 C-RCT Not effective	2	9				2, 0			Placebo
Lighthouse, 2004 RCT Effectiveness unclear	1 Bi	10	VII Bowel abnormalities n=0 VIII Feverish episode n=2 VIII Diarrheal syndrome n=0		n/a	2, 2			
Lighthouse, 2004 RCT Effectiveness unclear	2	10	VII Bowel abnormalities n=0 VIII Feverish episode n=0 VIII Diarrheal syndrome n=0			0, 0			Non-probiotic
Lin, 1989 C-RCT Not effective	1 La	460	VII Constipation n=6 VII Flatulence n=15 VII Diarrhea n=9 VII Stomach upset n=3		n/a	126, n/a			
Lin, 1989 C-RCT Not effective	2	460	VII Constipation n=5 VII Flatulence n=11 VII Diarrhea n=10 VII Stomach upset n=1			126, n/a			Placebo
Lin, 2005 RCT Effective	1 Bi	180	XI Sepsis due to Lactobacillus a Bifidobacterium (SAE) n=0		n/a	n/a, 7			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Lin, 2005 RCT Effective	2	187	XI Sepsis due to Lactobacillus or Bifidobacterium (SAE) n=0		n/a	n/a, 20			Breast milk only
Lin, 2008 RCT Effective	1 Bi	222	XI Sepsis due to probiotics (SAE) n=0 VII Flatulence n=0 VII Diarrhea n=0		n/a	5, 2			
Lin, 2008 RCT Effective	2	221	XI Sepsis due to probiotics (SAE) n=0 VII Flatulence n=0 VII Diarrhea n=0		n/a	4, 3			Placebo
Ljungberg, 2006 RCT Effective LTFU	1 Bi			3 samples positive for beta cell autoantibodies, group not stated	n/a	n/a, n/a			
Ljungberg, 2006 RCT Effective LTFU	2					n/a, n/a			Placebo
Loguercio, 1987 RCT Effective	1 En	20	VII Constipation (switched treatment) n=1 VII Meteorism n=0 VII Abdominal pain n=0 VII Diarrhea n=0		1	1, 1		Lactulose	
Loguercio, 1987 RCT Effective	2	20	VII Constipation (switched treatment) n=0 VII Meteorism n=5 VII Abdominal pain n=6 VII Diarrhea n=1		6	2, 2			Non-probiotic
Lonnermark, 2010 RCT Effective	1 La	118	VII Constipation n=3		3	38, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Lonnermark, 2010 RCT Effective	2	121	VII Constipation n=3		3	38, n/a			Placebo
Lu, 2004 CCT Effective	1 La		VII Vomiting n=0 VII Diarrhea n=0 VII Obstipation n=0 XXI Abdominal pain n=0 X Allergic reactions n=0		0	n/a, 0			
Lu, 2004 CCT Effective	2		VII Vomiting n=0 VII Diarrhea n=0 VII Obstipation n=0 XXI Abdominal pain n=0 X Allergic reactions n=0		0	n/a, n/a			Placebo
Lu, 2004 CCT Effective	3 La		VII Vomiting n=0 VII Diarrhea n=0 VII Constipation n=0 VII Abdominal pain n=0 XXI Cough n=0 X Allergic reaction n=0		0	n/a, n/a			
Lu, 2004 CCT Effective	4 La		VII Vomiting n=0 VII Diarrhea n=0 VII Constipation n=0 VII Abdominal pain n=0 XXI Cough n=0 X Allergic reaction n=0		0	n/a, n/a			
Luoto, 2010 RCT Effective	1 Bi	85	XXVII Death (SAE) n=0 XI Sepsis (SAE) n=0 XXVII Illness in child n=3	Discontinued to illness in mother (treatment = 3, control = 3); miscarriage 2 in both groups	n/a	18, n/a			
Luoto, 2010 RCT Effective	2	86	XXVII Death (SAE) n=0 XI Sepsis (SAE) n=0 XXVII Illness in child n=1		n/a	23, n/a			Dietary counseling only

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Mдkelдinen, 2003 RCT Effective	1 Bi	19	VII Intestinal complaints n=0		0	n/a, n/a			
Mдkelдinen, 2003 RCT Effective	2	20	VII Intestinal complaints n=0		0	n/a, n/a			Placebo
Malaguarnera, 2007 RCT Effectiveness unclear	1 Bi	30	VII Nausea n=1 XVII Headache (1) n=1 VII Abdominal pain n=2 VII Diarrhea n=0 XVII Headache moderate n=0		n/a	0, 0			
Malaguarnera, 2007 RCT Effectiveness unclear	2	30	VII Nausea n=0 XVII Headache slight n=0 VII Abdominal pain n=0 VII Diarrhea n=2 XVII Headache moderate n=1			0, 0			Placebo
Malaguarnera, 2010 RCT Effective	1 Bi	63	VII Abdominal pain n=0 VII Cramping n=0 VII Diarrhea n=0 VII Flatulence n=0		0	n/a, n/a			
Malaguarnera, 2010 RCT Effective	2	62	VII Abdominal pain n=n/a VII Cramping n=n/a VII Diarrhea n=n/a VII Flatulence n=n/a		n/a	n/a, n/a			Non-probiotic

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Maldonado, 2009 RCT Effective	1 La	40	VII Spitting up n=1 XXVII Night awakenings n=1 XXVII Irritability n=0 XXVII Severe crying n=0 VII Constipation n=4		n/a	0, 0			
Maldonado, 2009 RCT Effective	2	40	VII Spitting up n=2 XXVII Night awakenings n=3 XXVII Irritability n=1 XXVII Severe crying n=0 VII Constipation n=6		n/a	0, 0			Placebo
Mandel, 2010 RCT Effective	1 Ba	22	XXIII Shingles n=1 XXIII Poison ivy n=1 XXII A cold n=1 I Leg edema n=1 VII Gastrointestinal reflux n=0 XI Upper respiratory infection n=0 XI Urinary tract infection n=0		4	n/a, n/a			
Mandel, 2010 RCT Effective	2	22	XXIII Shingles n=0 XXIII Poison ivy n=0 XXII A cold n=0 I Leg edema n=0 VII Gastrointestinal reflux n=1 XI Upper respiratory infection n=1 XI Urinary tract infection n=1		3	n/a, n/a			Placebo
Manley, 2007 C-RCT Effective	1 La	14	XXVII Death (SAE) n=3 (2 after cross-over to treatment)		n/a	3, 1			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Manley, 2007 C-RCT Effective	2	13	XXVII Death (SAE) n=0			5, 2			Yogurt only
Manzoni, 2006 RCT Effective	1 La	39	XI Sepsis due to LGG (SAE) n=0		0	0, 0			
Manzoni, 2006 RCT Effective	2	41	XI Sepsis due to LGG (SAE) n=0		0	0, 0			Milk only
Margreiter, 2006 RCT Effective	1 Bi	81	XIII Lab abnormalities n=0		0	10, 0			
Margreiter, 2006 RCT Effective	2 En	85	XIII Lab abnormalities n=0		0	8, 0			Other Probiotic
Marotta, 2003 C-RCT Effective	1 Bi	26	XXVII Significant dietary change n=0 XXVII Significant pharmacological change n=0 XIII Significant weight change n=0 VII Abdominal complaints n=0 VII Changes in bowel habit n=0		0	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Marotta, 2003 C-RCT Effective	2	15	XXVII Significant dietary change n=0 XXVII Significant pharmacological change n=0 XIII Significant weight change n=0 VII Abdominal complaints n=0 VII Changes in bowel habit n=0		0	0, 0			Non-probiotic
Marrazzo, 2006 RCT Effective	1 La		XXVII Stickiness n=n/a XXI Abnormal vaginal discharge n=n/a	Between 3.6% and 7.8% reported SE's	n/a	n/a, n/a			
Marrazzo, 2006 RCT Effective	2		XXVII Stickiness n=n/a XXI Abnormal vaginal discharge n=n/a		n/a	n/a, n/a			Placebo
Marseglia, 2007 RCT Effective	1 Ba	40		3 cases of diarrhea, group unclear	n/a	0, 0			
Marseglia, 2007 RCT Effective	2	40				0, 0			No treatment
Marteau, 2004 RCT Not effective	1 La	48	VII Digestive disorder n=n/a XXIII Edema n=1 XXIII Cutaneous nevus n=0		6	13, 0			
Marteau, 2004 RCT Not effective	2	50	VII Digestive disorder n=n/a XXIII Edema n=1 XXIII Cutaneous nevus n=0		6	7, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Martiney, 2009 RCT Effective	1 St	24	XIII Abdominal hematological parameters n=0		0	3, 0			
Martiney, 2009 RCT Effective	2	25	XIII Abdominal hematological parameters n=0		0	2, 0			Yogurt only
Martinez, 2008 RCT Effective	1 La	29	XIV Increased appetite n=2 (states not due to probiotics) XVII Headache n=1 VII Light stool n=1		n/a	n/a, n/a			
Martinez, 2008 RCT Effective	2	26	XIV Increased appetite n=0 XVII Headache n=0 VII Light stool n=0		n/a	n/a, n/a			Placebo
Martinez, 2009 RCT Effective	1 La	32	XVII Persistent headache n=1 (states not due to probiotics)		n/a	n/a, n/a			
Martinez, 2009 RCT Effective	2	32	XVII Persistent headache episode n=0			n/a, n/a			Placebo
Mayanagi, 2009 RCT Effectiveness unclear	1 La	34	XI Respiratory infection n=0		0	0, 0			
Mayanagi, 2009 RCT Effectiveness unclear	2	33	XI Respiratory infection n=1		1	1, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
McFarland, 1994 RCT Effectiveness unclear	1 Sa	57	VII Constipation n=8 XI Pneumonia -death (5) (SAE) n=1 XI Staphylococcus sepsis -death (5) (SAE) n=0 XXVII Increased thirst n=5	1 rash occurred (withdrew), group unclear	n/a	n/a, n/a			
McFarland, 1994 RCT Effectiveness unclear	2	67	VII Constipation n=2 XI Pneumonia -death (5) (SAE) n=0 XI Staphylococcus sepsis -death (5) (SAE) n=4 XXVII Increased thirst n=0		n/a	n/a, n/a			Placebo
McFarland, 1995 RCT Effective	1 Sa	97	VII Intestinal gas n=0 VIII Fever n=0	3 deaths, 4 nausea or constipation, group unclear	n/a	n/a, n/a			
McFarland, 1995 RCT Effective	2	96	VII Intestinal gas n=7 VIII Fever n=5		n/a	n/a, n/a			Placebo
McNaught, 2002 RCT Not effective	1 La	64	VII Nausea n=16 VII Paralytic ileus n=12		n/a	n/a, n/a			
McNaught, 2002 RCT Not effective	2	65	VII Nausea n=0 (or not reported) VII Paralytic ileus n=0 (or not reported)		n/a	n/a, n/a			No treatment

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Merenstein, 2009 RCT Not effective	1 Sa	61	XXVII Emesis n=1 VII Constipation n=0 XXVII Death (SAE) n=0 XXVII Permanent disability (SAE) n=0 XXVII Life-threatening event (SAE) n=0 XXVII Hospitalization (SAE) n=0 XXVII Prolonged hospital stay (SAE) n=0		1	n/a, n/a	0		
Merenstein, 2009 RCT Not effective	2 Sa	64	XXVII Emesis n=0 VII Constipation n=1 XXVII Death (SAE) n=0 XXVII Permanent disability (SAE) n=0 XXVII Life-threatening event (SAE) n=0 XXVII Hospitalization (SAE) n=0 XXVII Prolonged hospital stay (SAE) n=0		1	n/a, n/a	0		Other Probiotic

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Merenstein, 2010 RCT Effectiveness unclear	1 St	314	VII Diarrhea n=6 VII Gas n=1 VII Vomiting n=0 VII Lack of appetite n=0 VII Constipation n=2 XXIII Hives n=1 XXIII Rash n=7 XI Gastro-intestinal virus (SAE) n=1 XI Pneumonia leading to asthma attack (SAE) n=0 XI Viral infection causing fever (SAE) n=0 XXVII Death (SAE) n=0 XXVII Life-threatening event (SAE) n=0 XXVII Hospitalization (SAE) n=1 (unrelated to study product per author) XXVII Prolonged hospital stay (SAE) n=0 XXVII Permanent disability (SAE) n=0		18	1, n/a	1		

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Merenstein, 2010 RCT Effectiveness unclear	2	342	VII Diarrhea n=3 VII Gas n=0 VII Vomiting n=3 VII Lack of appetite n=3 VII Constipation n=2 XXIII Hives n=0 XXIII Rash n=10 XI Gastro-intestinal virus (SAE) n=0 XI Pneumonia leading to asthma attack (SAE) n=1 XI Viral infection causing fever (SAE) n=1 XXVII Death (SAE) n=0 XXVII Life-threatening event (SAE) n=0 XXVII Hospitalization (SAE) n=2 (unrelated to study product per author) XXVII Prolonged hospital stay (SAE) n=0 XXVII Permanent disability (SAE) n=0		22	1, n/a	2		Placebo
Metts, 2003 RCT Effective	1 La	9	XXI Vaginal discharge n=0		0	n/a, n/a			
Metts, 2003 RCT Effective	2	10	XXI Vaginal discharge n=1		1	n/a, n/a			Placebo
Metts, 2003 RCT Effective	3 Bi	8	XXI Vaginal discharge n=1		1	n/a, n/a			
Miele, 2009 RCT Effective	1 St	14	XIII Lab value changes n=0		0	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Miele, 2009 RCT Effective	2	15	XIII Lab value changes n=0		0	0, 0			Placebo
Millar, 1993 RCT Effectiveness unclear	1 La	10	XI Sepsis (SAE) n=0 XI Perineal Candida infection n=1 XI Infection attributable to LGG n=0		1	0, 0		Antibiotics unclear	
Millar, 1993 RCT Effectiveness unclear	2	10	XI Sepsis (SAE) n=0 XI Perineal Candida infection n=1 XI Infection attributable to LGG n=0		1	0, 0		Antibiotics needed	Milk only
Mimura, 2004 RCT Effective	1 St	20	VII Abdominal cramps n=1 VII Vomiting n=1 VII Diarrhea n=1		1	1, 1		Antibiotics needed	
Mimura, 2004 RCT Effective	2	16	VII Abdominal cramps n=0 VII Vomiting n=0 VII Diarrhea n=0		0	0, 0			Placebo
Miyaji, 2006 RCT Effective	1 La	21	VII New gastrointestinal symptoms n=0		n/a	n/a, n/a			
Miyaji, 2006 RCT Effective	2	18	VII New gastrointestinal symptoms n=0			n/a, n/a			Placebo
Morrow, 2010 RCT Effective	1 La	73	XI Lactobacillus bacteremia (SAE) n=0 XI Lactobacillus pneumonia (SAE) n=0		n/a	5, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Morrow, 2010 RCT Effective	2	73	XI Lactobacillus bacteremia (SAE) n=0 XI Lactobacillus pneumonia (SAE) n=0		n/a	3, 0			Placebo
Mukerji, 2009 RCT Not effective	1 La	39	VII Bloating n=7 VII Diarrhea n=8 VII Abdominal pain n=7 VII Loose stools n=9		14	2, n/a			
Mukerji, 2009 RCT Not effective	2	38	VII Bloating n=9 VII Diarrhea n=10 VII Abdominal pain n=7 VII Loose stools n=8		17	3, n/a			Placebo
Naito, 2008 RCT Effective LTFU	1 La	100	XX Pain on micturition n=31 XX Urinary frequency adverse events n=25 XX Gross hematuria n=16 VII Constipation n=6 VII Diarrhea n=2 XXVII Death (SAE) n=4		n/a	24, 0			
Naito, 2008 RCT Effective LTFU	2	102	XX Pain on micturition n=42 XX Urinary frequency adverse events n=31 XX Gross hematuria n=19 VII Constipation n=4 VII Diarrhea n=0 XXVII Death (SAE) n=3		n/a	7, 0			Chemotherapy only
Newcomer, 1983 RCT Not effective	1 La	10	VII Diarrhea n=n/a VII Abdominal pain n=n/a VII Gas n=n/a VII Borborygmi n=n/a		n/a	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Newcomer, 1983 RCT Not effective	2	10	VII Diarrhea n=n/a VII Abdominal pain n=n/a VII Gas n=n/a VII Borborygmi n=n/a			0, 0			Placebo
Niers, 2009 RCT Effective LTFU	1 Bi	78	XXVII Health problems n=4 XXVII Feeding difficulties n=9 VII Gastrointestinal colic n=1	Health problems - mother (4 versus 2 in treatment and control); use of antibiotics by mother or child (both 3)	n/a	28, 19		Antibiotics unclear	
Niers, 2009 RCT Effective LTFU	2	78	XXVII Health problems n=3 XXVII Feeding difficulties n=7 VII Gastrointestinal colic n=1 VII n=			30, 17		Antibiotics unclear	Placebo
Niv, 2005 RCT Not effective	1 La	27	VII Dyspepsia n=1 XVII Headache n=1 VII Nausea n=0		13	6, 0			
Niv, 2005 RCT Not effective	2	27	VII Dyspepsia n=3 XVII Headache n=0 VII Nausea n=1		13	9, 1			Placebo
Nobuta, 2009 RCT Effective	1 La	16	VII Abdominal pain n=1 XI Cold n=0 VII Abdominal pain and diarrhea n=0		n/a	2, 1			
Nobuta, 2009 RCT Effective	2	16	VII Abdominal pain n=0 XI Cold n=0 VII Abdominal pain and diarrhea n=0		n/a	0, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Nobuta, 2009 RCT Effective	3 La	16	VII Abdominal pain n=0 XI Cold n=1 VII Abdominal pain and diarrhea n=0		n/a	1, 1			
Nobuta, 2009 RCT Effective	4 La	16	VII Abdominal pain n=0 XI Cold n=0 VII Abdominal pain and diarrhea n=1		n/a	2, 1			
O'Mahony, 2005 RCT Effective	1 La		XIII Blood count changes n=0 XIII Serum chemistry changes n=0 XIII Serum immunoglobulin changes n=0	1 epistaxis, 1 unstable angina, 1 chest pain due to anxiety, 1 hospitalized with abdominal pain, group unclear	n/a	n/a, n/a			
O'Mahony, 2005 RCT Effective	2		XIII Blood count changes n=0 XIII Serum chemistry changes n=0 XIII Serum immunoglobulin changes n=0		n/a	n/a, n/a			Placebo
O'Mahony, 2005 RCT Effective	3 Bi		XIII Blood count changes n=0 XIII Serum chemistry changes n=0 XII Serum immunoglobulin changes n=0		n/a	n/a, n/a			
Ojetti, 2010 RCT Effectiveness unclear	1 La	20	VII Constipation n=1		n/a	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Ojetti, 2010 RCT Effectiveness unclear	2	20	VII Constipation n=0		n/a	0, 0			Placebo
Ojetti, 2010 RCT Effectiveness unclear	3	20	VII Diarrhea n=n/a VII Constipation n=n/a VII Flatulence n=n/a VII Bloating n=n/a VII Abdominal pain n=n/a		n/a	0, 0			
Olah, 2005 RCT Effective	1 La	33	VII Diarrhea n=n/a VII Bloating n=n/a		5	n/a, n/a			
Olah, 2005 RCT Effective	2	29	VII Diarrhea n=n/a VII Bloating n=n/a		4	n/a, n/a			Prebiotics
Olivares, 2006 RCT Effective	1 St	15	I Hematological changes n=0 XXVII Health disturbances n=0	Gastrointestinal discomfort was very low in both groups	n/a	n/a, 0			
Olivares, 2006 RCT Effective	2	15	I Hematological changes n=0 XXVII Health disturbances n=0		n/a	n/a, 0			Yogurt only
Osterlund, 2007 RCT Effective	1 La	98	XI Lactobacillus growth in blood n=0		n/a	n/a, 0			
Osterlund, 2007 RCT Effective	2	52	I Lactobacillus growth in blood n=0		n/a	n/a, 7			Chemotherapy only

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Ouwehand, 2009 RCT Effectiveness unclear	1 Bi	24	XXII Asthma n=2		n/a	4, 2			
Ouwehand, 2009 RCT Effectiveness unclear	2	23	XXII Asthma n=1		n/a	2, 1			Placebo
Ozkinay, 2005 RCT Effective	1 La	240	VII Diarrhea n=1 VII Nausea n=0		1	4, 0			
Ozkinay, 2005 RCT Effective	2	120	VII Diarrhea n=1 VII Nausea n=1			2, 0			Placebo
Panigrahi, 2008 RCT Effectiveness unclear	1 La	19	XI Sepsis (SAE) n=0 VII Diarrhea (hospitalized) n=0		0	n/a, 0	0		
Panigrahi, 2008 RCT Effectiveness unclear	2	12	XI Sepsis (SAE) n=0 VII Diarrhea (hospitalized) n=4		4	n/a, 0	4		Placebo
Parent, 1996 RCT Effective	1 La	17	XXI Disagreeable sensations and burning n=1		1	9, 0			
Parent, 1996 RCT Effective	2	15	XXI Disagreeable sensations and burning n=0		0	6, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Parfenov, 2005 CCT Effective	1 St	30	VII Bloating n=5		5	,			
Parfenov, 2005 CCT Effective	1 St	20	XXVII Allergic reactions n=0		0	n/a, n/a			
Parfenov, 2005 CCT Effective	2	30	VII Bloating n=0		0	,			No treatment
Parfenov, 2005 CCT Effective	2	10	XXVII Allergic reactions n=0		0	n/a, n/a			
Parra, 2004 RCT Effective	1 La	23	XXVII Modification in nutritional parameters n=0 XXVII General Health problem associated with consumption of the product n=0		n/a	0, 0			
Parra, 2004 RCT Effective	2	22	XXVII Modification in nutritional parameters n=0 XXVII General Health problem associated with consumption of the product n=0		n/a	0, 0			Milk only
Passeron, 2005 RCT Effective	1 La	24	VII Abdominal pain (1) n=2		2	7, 0			
Passeron, 2005 RCT Effective	2	24	VII Abdominal pain (1) n=1		1	2, 0			Prebiotics

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Peral, 2009 RCT Effectiveness unclear	1 La	38	X Local or systemic allergic symptoms n=0 XIII Pain (tolerable) n=5 XI Administered organism in peripheral blood or wound samples (SAE) n=0		5	0, 0			
Peral, 2009 RCT Effectiveness unclear	2	42	X Local or systemic allergic symptoms n=0 XIII Pain (tolerable) n=0 XI Administered organism in peripheral blood or wound samples (SAE) n=0		0	0, 0			Non-probiotic
Pereg, 2010 RCT Effectiveness unclear	1 St	20	XXVII Acute illnesses not related to liver disease requiring hospitalization (SAE) n=2		n/a	2, 0	3	Paracentesis	
Pereg, 2010 RCT Effectiveness unclear	2	20	XXVII Acute illnesses not related to liver disease requiring hospitalization n=2		n/a	2, 0	3		Placebo
Petschow, 2005 RCT Effective	1 La	15	XXVII Increased fussiness n=n/a VII Increased gas n=n/a XI Thrush n=n/a XXII Nasal congestion n=n/a XXIII Diaper rash n=n/a XXII Upper respiratory events n=n/a		n/a	3, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Petschow, 2005 RCT Effective	2	15	XXVII Increased fussiness n=n/a VII Increased gas n=n/a XI Thrush n=n/a XXII Nasal congestion n=n/a XXIII Diaper rash n=n/a XXII Upper respiratory events n=n/a		n/a	0, 0			Formula only
Petschow, 2005 RCT Effective	3 La	14	XXVII Increased fussiness n=n/a VII Increased gas n=n/a XI Thrush n=n/a XXII Nasal congestion n=n/a XXIII Diaper rash n=n/a XXII Upper respiratory events n=n/a			0, 0			
Petschow, 2005 RCT Effective	4 La	15	XXVII Increased fussiness n=n/a VII Increased gas n=n/a XI Thrush n=n/a XXII Nasal congestion n=n/a XXIII Diaper rash n=n/a XXII Upper respiratory events n=n/a			2, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Prantera, 2002 RCT Not effective	1 La	23	XI Suture stitch suppuration n=1 (states not treatment related) XIII Mild increased alanine aminotransferase n=1 (not treatment related per author) XXIII Acne n=0 VII Nausea n=0 XX Hematuria n=0 XIX Depressive state n=0	Diarrhea, bloating, and meteorism did not differ between groups	2	5, 0			
Prantera, 2002 RCT Not effective	2	22	XI Suture stitch suppuration n=1 (not treatment related per author) XIII Mild increased alanine aminotransferase n=1 (not treatment related per author) XXIII Acne n=1 (not treatment related per author) VII Nausea n=1 (not treatment related per author) XX Hematuria n=1 (not treatment related per author) XIX Depressive state n=1 (not treatment related per author)		6	3, 0			Placebo
Pregliasco, 2008 RCT Effective	1 Bi	122	VII Worsened bowel function n=9		9	8, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Pregliasco, 2008 RCT Effective	2	115	VII Worsened bowel function n=9		9	10, 0			Placebo
Pregliasco, 2008 RCT Effective	1 Bi	79	VII Worsened bowel function n=6		6	5, 0			
Pregliasco, 2008 RCT Effective	2	76	VII Worsened bowel function n=10		10	8, 0			Placebo
Pregliasco, 2008 RCT Effective	3 Bi	79	VII Worsened bowel function n=9		9	9, 0			
Pregliasco, 2008 RCT Effective	1 Bi	84	VII Worsened bowel function n=13		13	8, 0			
Pregliasco, 2008 RCT Effective	2	82	VII Worsened bowel function n=5		5	7, 0			Placebo
Pregliasco, 2008 RCT Effective	3 Bi	84	VII Worsened bowel function n=9		9	6, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Puccio, 2007 RCT Effective	1 Bi	42	XI Respiratory tract infections n=17 XXVII Sudden infant death (SAE) n=1 XXVII Congenital disorder (SAE) n=0 XXVII Adverse event (illnesses and symptoms) n=30 XXVII Life-threatening event (permanent harm, in-patient treatment) (SAE) n=12 XXVII Serious adverse event (fatal, life-thretening, in-patient treatment) (SAE) n=12	No significant difference in dropout rates (reasons: life-threatening events, hospitalizations, spitting and crying, other adverse events or other reasons; group unclear), crying, restlessness, colic, spitting and vomiting	n/a	23, n/a			
Puccio, 2007 RCT Effective	2	55	XI Respiratory tract infections n=27 XXVII Sudden infant death (SAE) n=0 XXVII Congenital disorder (SAE) n=1 XXVII Adverse event (illnesses and symptoms) (SAE) n=12 XXVII Life-threatening event (permanent harm, in-patient treatment) (SAE) n=10 XXVII Serious adverse event (fatal, life-thretening, in-patient treatment) (SAE) n=10		n/a	14, n/a			Placebo
Rampengan, 2010 RCT Effective	1 La	43	XXVII Respiratory or bowel symptoms n=4		n/a	4, 4			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Rampengan, 2010 RCT Effective	2 La	43	XXVII Respiratory or bowel symptoms n=3		n/a	3, 3			Other Probiotic
Ranganathan C-RCT Effective	1 St	16		Death due to a myocardial infarction and minor event such as bloating or gastrointestinal of temporary nature, lasting only a few days, group / phase unclear	n/a	n/a, n/a			
Ranganathan C-RCT Effective	2	16				n/a, n/a			Placebo
Rautava, 2008 RCT Effective	1 Bi	38	VII Vomiting n=1 VII Flatulence n=0 XXVII Increased fussing n=0		1	6, 2			
Rautava, 2008 RCT Effective	2	43	VII Vomiting n=n/a VII Flatulence n=n/a XXVII Increased fussing n=n/a		3	2, 1			Placebo
Rayes, 2002 RCT Effective	1 La	35	VII Abdominal side effects (distension, cramps or diarrhea) n=6		6	4, 0			
Rayes, 2002 RCT Effective	2	36	VII Abdominal side effects (distension, cramps or diarrhea) n=8		8	4, 0			Parenteral or enteral nutrition only

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Rayes, 2002 RCT Effective	3 La	34	VII Abdominal side effects (distension, cramps or diarrhea) n=11		11	2, 0			
Rayes, 2002 RCT Effectiveness unclear	1 La	30	VII Abdominal distension n=3 VII Abdominal cramps n=4 VII Diarrhea n=0		n/a	0, 0			
Rayes, 2002 RCT Effectiveness unclear	2	30	VII Abdominal distension n=4 VII Abdominal cramps n=6 VII Diarrhea n=0			0, 0			Standard crystalloid solution only
Rayes, 2002 RCT Effectiveness unclear	3 La	30	VII Abdominal distension n=6 VII Abdominal cramps n=5 VII Diarrhea n=0			0, 0			
Rayes, 2005 RCT Effective	1 La	33	VII Diarrhea (disappeared with temporary treatment reduction) n=3 VII Abdominal cramps (disappeared with temporary treatment reduction) n=5 VII Abdominal distension n=0		n/a	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Rayes, 2005 RCT Effective	2	33	VII Diarrhea (disappeared with temporary treatment reduction) n=4 VII Abdominal cramps (disappeared with temporary treatment reduction) n=6 VII Abdominal distension (disappeared with temporary treatment reduction) n=6		n/a	0, 0			Placebo
Rayes, 2007 RCT Effective	1 La	45	VII Diarrhea n=2 VII Abdominal cramps n=3 VII Abdominal distension and cramps n=0		n/a	5, 0			
Rayes, 2007 RCT Effective	2		VII Diarrhea n=2 VII Abdominal cramps n=0 VII Abdominal distension and cramps n=6			,			Placebo
Reid, 1992 RCT Effectiveness unclear	1 La	19	XXIII Rash n=0 VII Vomiting n=0 VII Diarrhea n=0 VII Nausea n=0 XX Irritation n=0 XX Discharge n=0 XI Superinfection (SAE) n=0	1 pneumonia, group unclear	n/a	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Reid, 1992 RCT Effectiveness unclear	2	21	XXIII Rash n=o VII Vomiting n=0 VII Diarrhea n=0 VII Nausea n=0 XX Irritation n=0 XX Discharge n=0 XI Superinfection (SAE) n=n			n/a, 0			Placebo
Reid, 1995 RCT Effective	1 La	25	XXVII Emergence of uncommon uropathogens n=0 XXVII Adverse alteration of urogenital flora n=0		0	8, 0			
Reid, 1995 RCT Effective	2	24	XXVII emergence of uncommon uropathogens n=0 XXVII Adverse alteration of urogenital flora n=0		0	3, 0			Prebiotics
Ren, 2010 RCT Effective	1 Bi	35	XXIII Skin rash n=0 VII Gastrointestinal side effects n=0		0	n/a, n/a			
Ren, 2010 RCT Effective	2	35	XXIII Skin rash n=0 VII Gastrointestinal side effects n=0		0	n/a, n/a			Non-probiotic
Reuman, 1986 RCT Not effective	1 La	15	XXVII Death (SAE) n=1	No statistically significant difference between groups in duration of hospitalization, days not fed orally, antibiotics use, weight gain, formula volume, or other morbidity scores	n/a	1, 1			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Reuman, 1986 RCT Not effective	2	15	XXVII Death (SAE) n=3		n/a	3, 3			Placebo
Richelsen, 1996 RCT Effectiveness unclear	1 En	44		1 abdominal symptoms, 1 weight gain, 1 hypertriglyceridemia but unclear which group	n/a	n/a, n/a			
Richelsen, 1996 RCT Effectiveness unclear	2	43			n/a	n/a, n/a			Placebo
Rio, 2002 RCT Effective	1 La	50	XXVII Death (SAE) n=0		n/a	28, n/a			
Rio, 2002 RCT Effective	2	50	XXVII Death (SAE) n=0		n/a	14, n/a			Placebo
Roos, 1996 RCT Effective	1 St	51	XXII Throat pain n=1 XVII Headache n=0 XXII Coughing n=1 XXII Running nose n=1 VIII Fever n=2 XXII Common cold n=1		13	n/a, n/a			
Roos, 1996 RCT Effective	2	61	XXII Throat pain n=3 XVII Headache n=3 XXII Coughing n=3 XXII Running nose n=2 VIII Fever n=2 XXII Common cold n=2		18	n/a, n/a			Placebo
Roos, 2001 RCT Effective	1 St	53	XI Pneumonia n=0		22	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Roos, 2001 RCT Effective	2	55	XI Pneumonia n=1		25	n/a, 2			Placebo
Rose, 2010 RCT Not effective	1 La	65	XXIII Diaper rash n=2 XXVII Lactose intolerance (withdrawn) n=0	LGG recipients with allergic sensitization even tended to need more medical intervention.	n/a	9, 3			
Rose, 2010 RCT Not effective	2	66	XXIII Diaper rash n=0 XXVII Lactose intolerance (withdrawn) n=1 0		n/a	20, 6			Placebo
Rosenfeldt, 2002 RCT Effective	1 La	27	VII Constipation n=1		1	3, 3			
Rosenfeldt, 2002 RCT Effective	2	23	VII Constipation n=n/a		n/a	4, 2			Placebo
Rosenfeldt, 2003 C-RCT Effective	1 La	13	VII Abdominal pain (mild, transitory) n=2 VII Loose stools n=0		2	1, 0			
Rosenfeldt, 2003 C-RCT Effective	2	13	VII Abdominal pain (1) n=1 VII Loose stools n=1		1	1, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Rouge, 2009 RCT Effectiveness unclear	1 Bi	45	XI Sepsis (SAE) n=15 XI Sepsis due to Bifidobacterium and Lactobacillus (SAE) n=0 XI Nosocomial infection in infants <=1000g (SAE) n=12		n/a	2, 2			
Rouge, 2009 RCT Effectiveness unclear	2	49	XI Sepsis (SAE) n=13 XI Sepsis due to Bifidobacterium and Lactobacillus (SAE) n=0 XI Nosocomial infection in infants <=1000g (SAE) n=14		n/a	4, 4			Placebo
Ruiz-Palacios, 1996 RCT Effective	1 Bi			Intake, incidences of vomiting, abdominal discomfort, gas and stool characteristics were not statistically different across groups	n/a	n/a, n/a			
Ruiz-Palacios, 1996 RCT Effective	2				n/a	n/a, n/a			Placebo
Ruiz-Palacios, 1996 RCT Effective	3 Bi				n/a	n/a, n/a			
Ruiz-Palacios, 1996 RCT Effective	4 Bi				n/a	n/a, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Saavedra, 2004 RCT Effective	1 St	44	XXIII Viral rash (dropout) n=1 VII Loose stools (dropout) n=1 VII Vomiting (dropout) n=1	No difference in growth; other data presented as mean values per 100 subject days.	n/a	5, 3			
Saavedra, 2004 RCT Effective	2	44	XXIII Viral rash n=0 VII Loose stools n=0 VII Vomiting n=0		n/a	5, 1			Placebo
Saavedra, 2004 RCT Effective	3 St	43	XXIII Viral rash n=0 VII Loose stools n=0 VII Vomiting n=0			4, 1			
Safdar, 2008 RCT Effectiveness unclear	1 La	23	VIII Fever n=2 VII Nausea n=0		2	0, 0			
Safdar, 2008 RCT Effectiveness unclear	2	17	VIII Fever n=2 VII Nausea n=3		5	1, 0			Placebo
Sahagun-flores, 2007 RCT Effective	1 La	35	VII Diarrhea, metallic taste, abdominal upset (withdrawal) n=1 XXVII Allergy n=0		n/a	4, 1			
Sahagun-flores, 2007 RCT Effective	2	36	VII Diarrhea, metallic taste, abdominal upset (withdrawal) n=0 XXVII Allergy n=1		n/a	3, 1			Antibiotics only

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Saint-Marc, 1995 RCT Effective	1 Sa	18	XI Infection (SAE) n=0	Potassium and hemoglobin levels were slightly but significantly increased in the treated group compared to control	n/a	0, 0			
Saint-Marc, 1995 RCT Effective	2	17	XI Infection (SAE) n=0		n/a	0, 0			Placebo
Salminen, 1988 RCT Effective	1 La	12	VII Flatulence n=6 (states due to lactulose)		n/a	1, 0			
Salminen, 1988 RCT Effective	2	12	VII Flatulence n=7			2, 0			Dietary counseling only
Salminen, 2004 C-RCT Effectiveness unclear	1 La	20	XIII Change in CD4 counts / no effect on counts n=0 XIII Change in HIV R copies (SAE) n=0 (no HIV R copies) XI Infections due to Lactobacillus n=0		0	3, 0			
Salminen, 2004 C-RCT Effectiveness unclear	2	20	XIII Change in CD4 counts / no effect on counts n=0 XIII Change in HIV R copies (SAE) n=0 XI infections due to Lactobacillus n=0		0	3, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Samanta, 2008 RCT Effective	1 Bi	91	XI Blood culture grew Lactobacillus or Bifidobacterium (monitored for sepsis) (SAE) n=0		n/a	n/a, n/a			
Samanta, 2008 RCT Effective	2	95	XI Blood culture grew Lactobacillus or Bifidobacterium (monitored for sepsis) (SAE) n=0		n/a	n/a, n/a			Placebo
Satokari, 2001 RCT Not effective	1 Bi	10	VII Abdominal discomfort n=0		0	n/a, 0			
Satokari, 2001 RCT Not effective	2	9	VII Abdominal discomfort n=1	1 participant was treated with antibiotics, timing unclear	n/a	n/a, 0		Antibiotics unclear	Prebiotics
Savino, 2006 RCT Effective	1 La	45		2 gastroesophageal reflux, group unclear	n/a	4, 0			
Savino, 2006 RCT Effective	2	45				3, 0			Non-probiotic
Sazawal, 2010 RCT Effective	1 Bi	312	XXVII Death (SAE) n=0		0	16, 0			
Sazawal, 2010 RCT Effective	2	312	XXVII Death (SAE) n=2		2	27, 2			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Scalabrin, 2009 RCT Effective	1 La	95	XXVII Excessive crying n=0 XXVII Intolerant to formula (SAE) n=0 (SAE per author) VII Gastroesophageal reflux (SAE) n=1 (SAE per author) VII Vomiting n=n/a	Upper respiratory infection (27%), nasal congestion (21%), gas (17%), otitis media (16%), diaper rash (15%), group unclear; 5 serious adverse events per author in study group, 3 in control group, 8 in additional group	n/a	32, 23			
Scalabrin, 2009 RCT Effective	2	95	XXVII Excessive crying n=0 XXVII Intolerant to formula (SAE) n=0 (SAE per author) VII Gastroesophageal reflux (SAE) n=0 (SAE per author) VII Vomiting n=n/a		n/a	25, 14			Formula only
Scalabrin, 2009 RCT Effective	3 La	99	XXVII Excessive crying n=0 XXVII Intolerant (SAE) n=1(SAE per author) VII Gastroesophageal reflux (SAE) n=0(SAE per author) VII Vomiting n=n/a		n/a	22, 10			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Schrezenmeir, 2004 RCT Effectiveness unclear	1 Bi	50	VII Diarrhea n=2 (states unrelated to treatment in 1 patient) VII Vomiting (moderate) n=1 VII Postprandial abdominal pain n=0 XXII Asthma, bronchitis and pneumonia n=1 (states unrelated) XXVII Anorexia (severe) and weight loss n=0 XXVII Asthenia n=0		4	24, n/a			
Schrezenmeir, 2004 RCT Effectiveness unclear	2	43	VII Diarrhea n=0 VII Vomiting (moderate) n=1 VII Postprandial abdominal pain (moderate) n=0 XXII Asthma, bronchitis and pneumonia n=0 XXVII Anorexia (severe) and weight loss n=0 XXVII Asthenia n=0		1	17, n/a			Pediasure only
Schultz, 2004 RCT Not effective	1 La	5	VII Bloating (mild) n=n/a		n/a	n/a, 0			
Schultz, 2004 RCT Not effective	2	6	VII Bloating n=n/a		n/a	n/a, 0			Placebo
Seppo, 2003 RCT Effective	1 La	22	XXVII Feeling ill (withdrew) n=n/a VII Bloating n=0 VII Flatulence n=0		n/a	n/a, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Seppo, 2003 RCT Effective	2	17	XXVII Feeling ill n=n/a VII Bloating n=1 VII Flatulence n=1			n/a, n/a			Milk only
Sierra, 2010 RCT Effective	1 La	20	VII Diarrhea n=0 VII Constipation n=0 VII Dyspepsia n=0 VII Flatulence n=0 VII Stomach ache n=0 VII Maldigestion n=0 VIII Fever n=0 XVII Headache n=0 XV Muscular or bone ache n=0 XI Flu symptoms n=0 I Hematological abnormalities n=0		0	0, 0			
Sierra, 2010 RCT Effective	2	20	VII Diarrhea n=0 VII Constipation n=0 VII Dyspepsia n=0 VII Flatulence n=0 VII Stomach ache n=0 VII Maldigestion n=0 VIII Fever n=0 XVII Headache n=0 XV Muscular or bone ache n=0 XI Flu symptoms n=0 I Hematological abnormalities n=0		0	0, 0			Placebo
Simons, 2006 RCT Not effective	1 La	24	VII Constipation and flatulence n=2		2	1, 1			
Simons, 2006 RCT Not effective	2	22	VII Constipation and flatulence n=1		1	1, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Simren, 2010 RCT Effectiveness unclear	1 St	37	XIII Effects on biochemistry n=0 XIII Effects on hematology n=0		0	4, 0			
Simren, 2010 RCT Effectiveness unclear	2	37	XIII Effects on biochemistry n=0 XIII Effects on hematology n=0		0	3, 0			Placebo
Song, 2010 RCT Effective	1 Sa	330	XI Fungemia due to Saccharomyces boulardii (SAE) n=0		0	21, 0			
Song, 2010 RCT Effective	2	331	XI Fungemia due to Saccharomyces boulardii (SAE) n=0		0	35, 0			Triple therapy only
Song, 2010 RCT Effective	3 Sa	330	XI Fungemia due to Saccharomyces boulardii (SAE) n=0		0	11, 0			
Songisepp, 2005 CCT Effective	1 La	16	XI Acute infections n=0 VII Changes in GI function n=0 XXVII Adverse affects in general welfare n=0		0	0, 0			
Songisepp, 2005 RCT Effective	1 La	12	VII Change in GI function n=0 XXVII Adverse effects in general welfare n=0	1 acute respiratory viral infection, group unclear	n/a	n/a, n/a			
Songisepp, 2005 CCT Effective	2	5	XI Acute infections n=0 VII Changes in GI function n=0 XXVII Adverse affects in general welfare n=0		0	0, 0			Goat's milk only

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Songisepp, 2005 RCT Effective	2	12	VII Change in GI function n=0 XXVII Adverse effects in general welfare n=0		n/a	n/a, n/a			Placebo
Sood, 2009 RCT Effective	1 St	77	VII Abdominal bloating and discomfort n=14 XVII Unpleasant taste feeling n=7		n/a	22, n/a			
Sood, 2009 RCT Effective	2	70	VII Abdominal bloating and discomfort n=0 XVII Unpleasant taste feeling n=0		n/a	41, n/a			Placebo
Spanhaak, 1998 RCT Effective	1 La	10	XIII Body weight changes n=0 XIII Blood pressure n=0 II Heart rate n=0 XIII Temperature n=0 XIII Hematology n=0 XIII Blood chemistry changes n=0		0	n/a, 0			
Spanhaak, 1998 RCT Effective	2	10	XIII Body weight changes n=0 XIII Blood pressure n=0 II Heart rate n=0 XIII Temperature n=0 XIII Hematology n=0 XIII Blood chemistry changes n=0		0	n/a, 0			Placebo
Stockert, 2007 RCT Effectiveness unclear	1 En	9	VII Mild flatulence and diarrhea n=2		n/a	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Stockert, 2007 RCT Effectiveness unclear	2	8	VII Mild flatulence and diarrhea n=4		n/a	1, 0			Placebo
Stotzer, 1996 C-RCT Not effective	1 La	17	XXVII Deteriorated general condition n=1 (states due to underlying disease during run-in) XXVII Side effects unspecified n=1		n/a	3, 2			
Stotzer, 1996 C-RCT Not effective	2	17				3, 2			Placebo
Stratiki, 2007 RCT Effective	1 Bi	43	VII Feeding intolerance (Vomiting; Abdominal distension; Tenderness; Stool characteristics) n=0	2 intervention, 3 control infants excluded due to NEC, severe infection, need for parenteral nutrition or inadequate urine collection	n/a	2, n/a			
Stratiki, 2007 RCT Effective	2	37	VII Feeding intolerance (Vomiting; Abdominal distension; Tenderness; Stool characteristics) n=n/a		0	3, n/a			Placebo
Sullivan, 2003 RCT Effective	1 Bi	12	VII Diarrhea n=1 VII Looser stools n=1		2	n/a, n/a		Antibiotics needed	
Sullivan, 2003 RCT Effective	2	12	VII Diarrhea n=0 VII Looser stools n=0		0	n/a, n/a			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Sykora, 2005 RCT Effective	1 La	39	VII Nausea n=n/a XVII Headache n=n/a VII Recurrent vomiting n=n/a VII Diarrhea n=n/a VII Abdominal pain n=n/a VII Heart burn n=n/a XIV Anorexia n=n/a XVII Metallic taste n=n/a VII Flatulence n=n/a VII Borborygmi n=n/a	13 adverse events	7	3, 2			
Sykora, 2005 RCT Effective	2	47	VII Nausea n=n/a XVII Headache n=n/a VII Recurrent vomiting n=n/a VII Diarrhea n=n/a VII Abdominal pain n=n/a VII Heart burn n=n/a XIV Anorexia n=n/a XVII Metallic taste n=n/a VII Flatulence n=n/a VII Borborygmi n=n/a	15 adverse events	9	3, 1			Placebo
Tamura, 2007 RCT Effectiveness unclear	1 La	60	XXVII Cold n=10 (states not related to probiotic) VII diarrhea n=3 (states not related to probiotic) VII Vomiting n=1 (not related to diarrhea)		n/a	5, 0			
Tamura, 2007 RCT Effectiveness unclear	2	60				6, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Taylor, 2007 RCT Not effective	1 La	115	VII Colic / abdominal discomfort n=3 XIX Postnatal depression n=1 XXVII Unrelated infant health problem n=1 XXVII Infant refused supplement n=1 X Allergy sensitization (skin prick test) n=35		n/a	26, 5			
Taylor, 2007 RCT Not effective	2	111	VII Colic / abdominal discomfort n=1 XIX Postnatal depression n=1 XXVII Unrelated infant health problem n=3 XXVII Infant refused supplement n=0 X Allergy sensitization (skin prick test) n=21		n/a	22, 5			Placebo
Tempe, 1985 RCT Effective	1 Sa	20	XXVII Death (SAE) n=3 (states not attributable to intervention)		3	n/a, 3			
Tempe, 1985 RCT Effective	2	20	XXVII Death (SAE) n=3		3	n/a, 3			Placebo
Teran, 2008 RCT Effective	1 Sa	30	XXVII Staining of physiologic fluids n=0	No significant difference between groups for fever, vomiting and number of stools per day	n/a	5, 0			
Teran, 2008 RCT Effective	2	29	XXVII Staining of physiologic fluids n=0		n/a	4, 0			Rehydration solution only

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Thomas, 2001 RCT Not effective	1 La	152	VII Nausea n=n/a VII Abdominal cramps n=n/a VII Gas or bloating n=n/a	no statistically significant difference in proportion of participants experiencing adverse events	n/a	19, 0			
Thomas, 2001 RCT Not effective	2	150	VII Nausea n=n/a VII Abdominal cramps n=n/a VII Gas or bloating n=n/a		n/a	16, 0			Placebo
Tomoda, 1991 CCT Effective	1 St	10	I Changes in blood chemistry n=0		0	,		2	
Tomoda, 1991 CCT Effective	2	10	I Changes in blood chemistry n=0		0	,	0		Yogurt only
Tsuchiya, 2004 CCT Effective	1 Bi	34	VII Diarrhea n=n/a (a few) XXVII Overt clinical adverse side-effects n=0 XXVII Biochemical adverse events n=0		n/a	n/a, 0			
Tsuchiya, 2004 CCT Effective	2 Bi	34	VII Diarrhea n=n/a XXVII Overt clinical adverse side-effects n=0 XXVII Biochemical adverse events n=0		n/a	n/a, 0			Synbiotics
Turchet, 2003 RCT Effectiveness unclear	1 La	180	VII Dyspepsia n=45 XI Bronchopneumonia (SAE) n=1 (states not related)		n/a	n/a, 2			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Turchet, 2003 RCT Effectiveness unclear	2	180	VII Dyspepsia n=0 (or not reported) XI Bronchopneumonia (SAE) n=0		n/a	n/a, n/a			No study product
Tursi, 2004 RCT Effectiveness unclear	1 St	30	XXIII Cutaneous rash n=0 VII Diarrhea and abdominal pain n=0 XXVII Cephalea, epigastric pain, or fatigue n=1		1	2, 0			
Tursi, 2004 RCT Effectiveness unclear	2	30	XXIII Cutaneous rash n=0 VII Diarrhea and abdominal pain n=0 XXVII Cephalea, epigastric pain, or fatigue n=3		3	4, 0			Balsalazide only
Tursi, 2008 CCT Effective	1 La	29	XI Acute bronchial pneumonia (SAE) n=0	2 epigastric pain, 1 nausea, 1 diarrhea, group unclear	n/a	n/a, 0			
Tursi, 2008 CCT Effective	2	27	XI Acute bronchial pneumonia (SAE) n=0		n/a	n/a, 0			Mesalazine only
Tursi, 2008 CCT Effective	3 La	29	XI Acute bronchial pneumonia (SAE) n=1		n/a	n/a, 0	1		

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Tursi, 2010 RCT Effective	1 St	71	XVII Dizziness n=1 XI Flue-like syndrome n=1 VII Abdominal bloating w/ or w/out discomfort n=6 VIII Fever n=0 XX Cystitis n=0 XVII Unpleasant taste in mouth n=0		8	6, 0			
Tursi, 2010 RCT Effective	2	73	XVII Dizziness n=0 XI Flue-like syndrome n=0 VII Abdominal bloating w/ or w/out discomfort n=3 VIII Fever n=1 XX Cystitis n=1 XVII Unpleasant taste in mouth n=4		9	7, 5			Placebo
Underwood, 2009 RCT Effectiveness unclear	1 La	30	VII Feeding intolerance (emesis, gastric distention, excessive gastric residuals; transient) n=3		3	n/a, 0			
Underwood, 2009 RCT Effectiveness unclear	2	29	VII Feeding intolerance (emesis, gastric distention, excessive gastric residuals; transient) n=1		1	n/a, 0			Placebo
Underwood, 2009 RCT Effectiveness unclear	3 Bi	31	VII Feeding intolerance (emesis, gastric distention, excessive gastric residuals; transient) n=0		0	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Urban, 2008 RCT Effective	1 Bi	45	XXVII Serious illness (SAE) n=7	Spitting up, vomiting, hard stools, loose stools, flatulence, restlessness: no difference between groups; 17 hospital admissions including 5 cases of septicemia, group unclear	n/a	13, 0			
Urban, 2008 RCT Effective	2	43	XXVII Serious illness (SAE) n=4		n/a	9, 0			Formula only
Urbansek, 2001 RCT Effective	1 La	102	VII Gastrointestinal problems n=3 XXVII Labial edema n=0		3	n/a, n/a		Antibiotics unclear	
Urbansek, 2001 RCT Effective	2	103	VII Gastrointestinal problems n=2 XXVII Labial edema n=1		3	n/a, n/a			Placebo
Van der Aa, 2010 RCT Not effective	1 Bi	46	XXII Respiratory syncytial virus bronchiolitis (hospitalized) (SAE) n=1 XXVII Cow's milk allergy (hospitalized) (SAE) n=0		n/a	6, 2	2		
Van der Aa, 2010 RCT Not effective	2	44	XXII Respiratory syncytial virus bronchiolitis (hospitalized) (SAE) n=0 XXVII Cow's milk allergy (hospitalized) (SAE) n=1		n/a	2, 1	0		Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Van Gossum, 2007 RCT Not effective	1 La	34		Feeding intolerance and treatment related complications occurred, number and group unclear	n/a	7, n/a			
Van Gossum, 2007 RCT Not effective	2	36			n/a	14, n/a			Maltodextrin only
Velaphi, 2008 RCT Not effective	1 Bi	53	XI Bronchopneumonia n=3 VII Gastroenteritis n=1	5 withdrawals due to prolonged illness, group unclear; No statistically significant difference in number of stools, spitting, vomiting, flatulence, doctor visits or hospital admissions; congenital syphilis, ophthalmia neonatorum, jaundice, and diabetes insipidus occurred, group unclear	n/a	16, n/a			
Velaphi, 2008 RCT Not effective	2	51	XI Bronchopneumonia n=6 VII Gastroenteritis n=0		n/a	15, n/a			Formula only
Vendt, 2006 RCT Effective	1 La	60	VII Colic pain n=1 VII Constipation n=1 VII diarrhea n=2		4	9, 4			
Vendt, 2006 RCT Effective	2	60	VII Colic pain n=3 VII Constipation n=1 VII Diarrhea n=0		4	6, 4			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Vleggaar, 2008 C-RCT Not effective	1 Bi	14	XI Submandibular abscess n=1 VII Ulcerative colitis exacerbation n=0		1	2, 2			
Vleggaar, 2008 C-RCT Not effective	2	12	XI Submandibular abscess n=0 VII Ulcerative colitis exacerbation n=		1	0, 0			Placebo
Vlieger, 2009 RCT Effective	1 Bi	69	VII Vomiting n=10 VII Diarrhea n=2 VII Constipation n=4 VII Colic n=17 XI Rash n=15		n/a	28, n/a			
Vlieger, 2009 RCT Effective	2	64	VII Vomiting n=15 VII Diarrhea n=1 VII Constipation n=7 VII Colic n=13 XI Rash n=19			26, n/a			Prebiotics
Wada, 2010 RCT Effective	1 Bi	19	XI Bacteremia (SAE) n=0		0	1, 0			
Wada, 2010 RCT Effective	2	23	XI Bacteremia (SAE) n=0		0	1, 0			Placebo
Wang, 2004 RCT Effective	1 St	60	VIII Fever n=0 VII Abdominal pain n=0 VII Diarrhea n=0		n/a	0, 0			
Wang, 2004 RCT Effective	2	20	VIII Fever n=0 VII Abdominal pain n=0 VII Diarrhea n=0		n/a	0, 0			Fermented milk only

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Wang, 2007 RCT Effective	1 Bi	33	XI Serious infections n=0 XI Positive blood culture n=0 XIII Elevated c-reactive protein level n=0		n/a	n/a, n/a			
Wang, 2007 RCT Effective	2	33	XI Serious infections n=0 XI Positive blood culture n=0 XIII Elevated c-reactive protein level n=0			n/a, n/a			No supplement
Weizman, 2005 RCT Effective	1 Bi	73	VII Bloody stools n=0 XXVII Hospitalization (SAE) n=0	No differences in growth parameters, behavior or stooling parameter	n/a	2, 0	0	Antibiotics unclear	
Weizman, 2005 RCT Effective	2	60	VII Bloody stools n=0 XXVII Hospitalization (SAE) n=0		n/a	2, 0	0	Antibiotics unclear	Placebo
Weizman, 2005 RCT Effective	3	68	VII Bloody stools n=0 XXVII Hospitalization (SAE) n=0		n/a	3, 0	0	Antibiotics unclear	
Weizman, 2006 RCT Effective	1 Bi	20	IV Otitis media n=0 XI Upper respiratory infection n=1		1	4, 0			
Weizman, 2006 RCT Effective	2	19	IV Otitis media n=0 XI Upper respiratory infection n=1		1	3, 0			Placebo
Weston, 2005 RCT Effective	1 La	28	VII Vomiting n=0		n/a	2, 0			
Weston, 2005 RCT Effective	2	28	VII Vomiting n=1		n/a	1, 1			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Wewalka, 2002 RCT Effective	1 La	35	XX Pollakiuria (reversible) n=0 V Increased thyroid-stimulating hormone (TSH) n=0		0	n/a, n/a			
Wewalka, 2002 RCT Effective	2	35	XX Pollakiuria n=1 V Increased thyroid-stimulating hormone (TSH) n=2		3	n/a, n/a			Non-probiotic
Wheeler, 1997 C-RCT Not effective	1 St	16	VII Gastrointestinal complications n=0		0	1, 0			
Wheeler, 1997 C-RCT Not effective	2	16	VII Gastrointestinal complication n=0		0	1, 0			Yogurt only
Wildt, 2006 RCT Not effective	1 Bi	21	VII Gastrointestinal symptoms n=6 XV Musculoskeletal pain n=2 XXVII Tiredness, dizziness, malaise, and hot flush n=1 XVII Headache n=3 XXVII Cold, flu, gastroenteritis, and cystitis n=5 VII Blood in stool n=2		21	n/a, n/a			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Wildt, 2006 RCT Not effective	2	8	VII Gastrointestinal symptoms n=4 XV Musculoskeletal pain n=1 XXVII Tiredness, dizziness, malaise, and hot flush n=5 XVII Headache n=2 XXVII Cold, flu, gastroenteritis, and cystitis n=2 VII Blood in stool n=2		8	n/a, n/a			Placebo
Williams, 2008 RCT Effective	1 Bi	28	VII Increased flatulence n=1		1	0, 0			
Williams, 2008 RCT Effective	2	28	VII Increased Flatulence n=0		0	4, 1			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Wind, 2010 RCT Effective	1 La	18	VII Increased flatulence n=2 (possibly related to intervention per author) VII Intermittent abdominal cramps n=1 (possibly related to intervention per author) VII More loose stools n=1 (possibly related to intervention per author) VII Pain in the lower abdomen n=2 (possibly related to intervention per author) I Clinically relevant changes in blood parameters n=0	No difference between groups regarding heartburn, acid regurgitation, sucking sensations in the epigastrium, nausea and vomiting, borborygmi, abdominal distension, eructation, hard stools, urgent need for defecation, feeling of incomplete evacuation, dyspeptic syndrome, indigestion syndrome, bowel dysfunction syndrome; 16 adverse events in treatment, 27 in control group	n/a	1, 0			
Wind, 2010 RCT Effective	2	18	VII Increased flatulence n=0 VII Intermitted abdominal cramps n=0 VII More loose stools n=4 (possibly related to intervention per author) VII Pain in the lower abdomen n=1 (possibly related to intervention per author) I Clinically relevant changes in blood parameters n=0		n/a	1, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Wolf, 1994 RCT Effectiveness unclear	1 La	15	VII Flatulence n=n/a VII Diarrhea n=1 VII Cramping n=0		n/a	n/a, 0			
Wolf, 1994 RCT Effectiveness unclear	2	15	VII Flatulence n=n/a VII Diarrhea n=n/a VII Cramping n=n/a			n/a, 0			Placebo
Wolf, 1998 RCT Effective	1 La	18	XI Bacteria in blood samples (SAE) n=0 VII Diarrhea (severe) n=n/a VII Vomiting (severe) n=0 VII Flatulence (severe) n=n/a VII Burping (sever) n=n/a VII Reflux (severe) n=0 VII Nausea (severe) n=n/a VII Cramping (severe) n=n/a VII Distension (severe) n=n/a VII Constipation (severe) n=0	Bacteria in urine samples not different across groups	n/a	3, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Wolf, 1998 RCT Effective	2	21	XI Bacteria in blood samples (SAE) n=0 VII Diarrhea (severe) n=n/a VII Vomiting (severe) n=0 VII Flatulence 9severe) n=n/a VII Burping (severe) n=n/a VII Reflux (severe) n=n/a VII Nausea (severe) n=n/a VII Cramping (severe) n=n/a VII Distension (severe) n=n/a VII Constipation (severe) n=n/a		n/a	1, 0			Placebo
Worthley, 2009 C-RCT Effectiveness unclear	1 Bi	19	VII Excessive flatus n=5 VII Abdominal pain n=1 VII Abdominal bloating n=4 VII Frequent or loose bowel movements n=7 VII Excessive abdominal gurgling noises n=2		n/a	n/a, n/a			
Worthley, 2009 C-RCT Effectiveness unclear	2	20	VII Excessive flatus n=n/a VII Abdominal pain n=n/a VII Abdominal bloating n=n/a VII Frequent or loose bowel movements n=n/a VII Excessive abdominal gurgling noises n=n/a		n/a	n/a, n/a			Prebiotics

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Xia, 2010 RCT Effective	1 La	30	XI Systemic inflammatory response syndrome (SAE) n=26 VII Anastomotic leakage (SAE) n=2		n/a	0, 0			
Xia, 2010 RCT Effective	2	30	XI Systemic inflammatory response syndrome (SAE) n=24 VII Anastomotic leakage (SAE) n=2		n/a	0, 0			Placebo
Xiang, 2006 RCT Effective	1 Ba	22	VII Nausea (1) n=1 VIII Headache (1) n=0 VII Vomiting (1) n=0		1	0, 0			
Xiang, 2006 RCT Effective	2	24	VII Nausea (1) n=1 VIII Headache (1) n=1 VII Vomiting (1) n=1		2	0, 0			Sulfasalazine only
Xiao, 2003 RCT Effectiveness unclear	1 St	16	VII Increased fecal frequency n=5		5	0, 0			
Xiao, 2003 RCT Effective	1 La	70	VII Vomiting (excessive, withdrew) n=3 XXVII Insomnia n=0 VII Constipation n=0		3	1, 1			
Xiao, 2003 RCT Effectiveness unclear	2	16	VII Increased fecal frequency n=1		1	0, 0			Yogurt only
Xiao, 2003 RCT Effective	2 La	67	VII Vomiting (excessive, withdrew) n=1 XXVII Insomnia n=1 VII Constipation n=1		3	3, 3			Other Probiotic

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Yang, 2008 RCT Effective	1 St	67	XIII Blood assay changes n=0 XIII Change in stool assays n=0 XIII Change in liver function n=0 XIII Change in urine assays n=0		0	4, 0			
Yang, 2008 RCT Effective	2	68	XIII Blood assay changes n=0 XIII Change in stool assays n=0 XIII Change in liver function n=0 XIII Change in urine assays n=0		0	5, 0			Placebo
Yao-Zong, 2004 RCT Effectiveness unclear	1 En	202	VII Cessation of bowel movement for 2 days n=5	Adverse events reported were minor and nonspecific and their frequency was not different in the two groups.	5	9, 5			
Yao-Zong, 2004 RCT Effectiveness unclear	2	208	VII Cessation of bowel movement for 2 days n=8		8	12, 8			Dioctahedral smectite
Yonekura RCT Effectiveness unclear	1 La	69	VII Loose stools and diarrhea n=n/a 15%	No significant difference in adverse events between groups.	n/a	11, 0			
Yonekura RCT Effectiveness unclear	2	69	VII Loose stools and diarrhea n=n/a (10%)		n/a	11, 0			Placebo

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Zhang, 2010 RCT Effective	1 Bi	30	VII Gastrointestinal discomfort n=3		n/a	0, 0			
Zhang, 2010 RCT Effective	2	30	VII Gastrointestinal discomfort n=6		n/a	0, 0			Non-probiotic
Ziegler, 2003 RCT Effective	1 Bi	40	VII Constipation n=n/a VII Flatulence n=n/a XI Upper respiratory infections n=n/a		7	12, 0			
Ziegler, 2003 RCT Effective	2	42	VII Constipation n=n/a VII Flatulence n=n/a XI Upper respiratory infections n=n/a		5	9, 0			Formula only
Zocco, 2003 RCT Effective	1 La	65		Most frequent side effects were nausea, epigastric pain, and constipation, group unclear; side effects determining drop out was observed only in patients with Crohn's disease consuming LGG (group unclear)	n/a	n/a, 0			
Zocco, 2003 RCT Effective	2	62			n/a	n/a, 0			Mesalazine only
Zocco, 2003 RCT Effective	3 La				n/a	n/a, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
An, 2010 Case Series Effective	1 Bi	19	VII Vomiting n=0 VII Abdominal pain n=0 VII Diarrhea n=0		0	n/a, n/a			
Barrett, 2008 Case Series Effective	1 La	18	VII Increased nausea n=3		3	2, 2			
Beck, 1961 Case Series Effective	1 La	59	VII Constipation (1) n=1 VII Gassy n=1 VII Large amounts of gas n=1 VII Liquid stool n=1		n/a	0, 0			
Bekkali, 2007 Case Series Effective	1 Bi	20	VII Vomiting n=0 VII Bloating n=0 VII Flatulence n=0		0	0, 0			
Bellomo, 1979 Case Series Effective	1 En	45	I Significant hematologic changes n=0		0	0, 0			
Benchimol, 2004 Case Series Effective	1 Bi	2	XXIII Erythema around the anus (1) n=1		1	0, 0			
Berman, 2006 Case Series Effective	1 Bi	10	VII Gastrointestinal gas n=1 VII Increased constipation n=1		1	0, 0			
Bibiloni, 2005 Case Series Effectiveness unclear	1 St	32	XIII Biochemical adverse events n=0 VII Bloating n=10		10	2, 0			
Bruce, 1988 Case Series Effectiveness unclear	1 La	5	VII Gastroenteritis n=1		1	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Bruni, 2008 Case Series Not effective	1 La	85	XXVII Sensitization (skin prick test) n=n/a XXVII Sensitization (cow's milk) n=n/a		n/a	0, 0			
Carlsson, 2009 Case Series Effectiveness unclear	1 La	15	XXVII Death (SAE) n=2 VII Diarrhea n=1		3	2, 2		reduced probiotics by half	
Cobo Sanz, 2006 Case Series Effective	1 St	381	XI Otorhinolaryngological infections n=16 VII Abdominal pain n=11 VII Diarrhea n=7		n/a	n/a, n/a			
Colecchia, 2006 Case Series Effective	1 Bi	645	VII Diarrhea (1) n=6		6	9, 0			
Di Pierro, 2009 Case Series Effective	1 La	165	XXI Irritation (mild) n=12		12	0, 0			
Dughera, 2007 Case Series Effective	1 Bi	129	VII Dyspepsia (1) n=1		1	n/a, n/a			
Elmer, 1995 Case Series Effectiveness unclear	1 Sa	7	XXVII Thirst n=3 XXVII Dry month n=2 VII Gas n=1 XXIII Itching n=1		3	0, 0			
Fukuda, 2008 Case Series Effective	1 Bi	117	VII Diarrhea n=1		1	15, 0			
Gabrielli, 2009 Case Series Effective	1 Ba	40	VII Constipation n=1		1	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Garrido, 2005 Case Series Effective	1 Ba	8	VII Mild increases of borborygmi n=n/a (only with 500 ml/day)		n/a	0, 0			
Gionchetti, 2007 Case Series Effective	1 St	23	VII Transient bloating (1) n=1		1	0, 0			
Glintborg, 2006 Case Series Not effective	1 La	8	VII Constipation worsened n=1		n/a	1, 1			
Gniwotta, 1977 Case Series Effective	1 Sa	145	XXVII Allergic reactions n=0		0	29,			
Gotteland, 2003 Case Series Effective	1 La	12	VII Diarrhea n=1		1	1, 1			
Gruenwald, 2002 Case Series Effectiveness unclear	1 Bi	42	VII Nausea n=n/a XXIII Pruritus n=n/a XXII Dyspnea n=n/a IX Cholecystitis n=n/a XXVII Depression n=n/a VII Uneasiness n=n/a VII Gastralgia n=n/a VII Fullness n=n/a VII Eructation n=n/a		n/a	4, 4			
Hensgens, 1976 Case Series Not effective	1 La	5	VII Gastrointestinal intolerance n=0 VII Change in stools n=0		0	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Huynh, 2009 Case Series Effective	1 St	19	VII Increased nausea n=7 XIII Biochemical adverse events n=0 VII Flatulence n=12 VII Vomiting (3) n=1 VII Diarrhea (3) n=1 VII Increased bloating n=12		n/a	1, n/a	1	IV fluids	
Karimi, 2005 Case Series Effectiveness unclear	1 St	29	XXVII Rhinitis (withdrew, was present before study strted) n=1 VII Nausea (1/3 withdrew) n=3 VII Mild to moderate bloating (withdrew) n=1 VII Nonspecific gastrointestinal symptoms (withdrew) n=1 XXVII Non-IBD deterioration of well-being n=1		n/a	13, 7			
Kawamura,1981 Case Series Effective	1 La	30	VII GI symptoms n=0 VIII Fever n=0		0	0, 0			
Kirchhelle, 1996 Case Series Effective	1 Sa	98	X Allergic reactions (medium intensity) n=2 (states unlikely related to probiotics or link could not be established)		2	4, 0			
Kitajima, 1997 Case Series Effective	1 Bi	66	VII Functional ileus n=2		2	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Lamiki, 2010 Case Series Effective	1 Bi	46	VII Diarrhea n=0 VII Abdominal pain n=0 VII Nausea n=0 XIII Biochemical adverse effects n=0		0	1, 0			
Lee, 2010 Case Series Not effective	1 St	12	VII Gastrointestinal disturbances n=3 XV Flare of rheumatoid arthritis n=1		4	0, 0			
Lombardo, 2009 Case Series Effective	1 La	100	VII Nausea (slight) n=1		1	n/a, 0			
Luoto, 2010 Case Series Effective	1 La	644	XI LGG Septicemia (SAE) n=0		n/a	n/a, n/a			
Malin, 1996 Case Series Effective	1 La	16	VII Watery stools n=1		n/a	n/a, n/a			
Malkov, 2006 Case Series Effective	1 Ba	10	VII Sicchasia n=1 XXVII Slight blood n=n/a XVII Intracranial pressure gain (SAE) n=n/a XVII Stroke -death (5) (SAE) n=1 XXVII Death (SAE) n=7 IX Liver failure -death (5) (SAE) n=1 XXVII Death due to pulmonary edema and stroke (SAE) n=1		n/a	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Mego, 2005 Case Series Effective	1 En	11	VIII Febrile episode n=0 XI Infection caused by tested probiotics n=0 XXVII Significant mucositis n=0 VII Diarrhea n=0 XI Bacteremia (SAE) n=5 VII Enterocolitis n=2 XI Candidemia (SAE) n=1 XI Pneumonia n=1 VII Meteorism (mild) n=1		5	0, 0			
Mego, 2006 Case Series Not effective	1 En	14	XI Bacteremia caused by probiotic strain (SAE) n=0 XI Infection caused by probiotic strain (SAE) n=0 VII Diarrhea (1) n=2 XXVII Treatment related death (SAE) n=0		n/a	0, 0		Antibiotics needed	
Michetti, 1999 Case Series Effectiveness unclear	1 La	10	VII Diarrhea (1) n=0 VII Abdominal pain n=0 VII Loss of appetite n=0 VII Constipation n=2 VII Pyrosis n=2 VII Nausea n=1		5	0, 0			
Muting, 1968 Case Series Effective	1 Bi	20	XIII Increased blood sugar n=n/a VII Stomach pains n=1 XI Severe tooth infection n=1		n/a	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Nobuta, 2009 Case Series Effective	1 La	42	VII Acute enterocolitis n=1 VII Tenesmus n=n/a VII Abdominal pain n=n/a VII Diarrhea n=n/a		n/a	3, 1			
Reid, 2001 Case Series Effective	1 La	10	XX Bladder irritation n=0 XXI Vaginal irritation n=0 XXI Discharge n=0 VII Intestinal upset n=0 XXII Bronchitis n=1		n/a	7, 0		Antibiotics needed	
Rosenfeldt, 2003 Case Series Effective	1 La	11	VII Abdominal pain n=0 VII Loose stools n=0		0	n/a, 0			
Sakamoto, 2001 Case Series Effective	1 La	31	VII Gastrointestinal n=0		0	2, 0			
Schneider, 2005 Case Series Effectiveness unclear	1 Sa	10	VII Changes in the number of bowel movements n=0 VII Changes in stool consistency n=0 VIII Fever n=0 XI Fungemia (SAE) n=0 VII Diarrhea (1) n=1		1	0, 0			
Shen, 2005 Case Series Not effective	1 St	31	VII Bloody bowel movements n=1 VII Severe constipation n=n/a VII Bloating n=n/a VII Gas n=n/a		n/a	25, 2			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Srinivasan, 2006 Case Series Effective	1 La	28	XIII Pathologic growth of lactobacilli n=0		0	0, 0			
Tasli, 2006 Case Series Effective	1 La	25	VII Nausea n=n/a 1 withdrew VII Abdominal fullness (withdrew) n=1		n/a	2, 1			
van Bodegraven, 2004 Case Series Effectiveness unclear	1 St	29	VIII Deterioration of general well-being n=2 (not IBD related) VII Gastrointestinal symptoms n=5		7	12, 9			
Weiss, 2010 Case Series Effective	1 St	10	VII Mild flatulence n=3		n/a	0, 0			
Yim, 2006 Case Series Effective	1 Bi	64	VII Constipation n=1		n/a	14, 3			
Zahradnik, 2009 Case Series Effective	1 St	8	XXVII Tingle in the throat (1) n=2 (states unrelated) XXVII Sore throat (1) n=2 (unrelated per author) XXVII Cold sore/ulcer (1) n=2 (unrelated per author) XVII Headache (1) n=1 (unrelated per author) VII Stomach ache (1) n=1 (unrelated per author)		n/a	0, 0			

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Zahradnik, 2009 Case Series Effective	1 St	12	XXVII Sore throat n=2 XXVII Mouth sore/fever blister n=4 XVII Headache n=1 XXII Cough n=2 XXVII Congestion n=1		n/a	1, 0			
Barton, 2001 Case Study Not effective	1 En	1	XI Bacteremia (SAE) n=1 XI Meningitis (SAE) n=1		1	0, 0		Antibiotics needed	
Bassetti, 1998 Case Study Not effective	1 Sa	1	XI Fungemia (SAE) n=1		1	0, 0		Antibiotics needed	
Burkhardt, 2005 Case Study Not effective	1 Sa	1	XI Sepsis (4) (SAE) n=1		1	0, 0		Antibiotics needed	
Cesaro, 2000 Case Study Not effective LTFU	1 Sa	1	XI Fungemia (4) (SAE) n=1		1	0, 0		Antibiotics needed	
Cherifi, 2004 Case Study Effectiveness unclear	1 Sa	1	XI Fungemia (SAE) n=1 XXVII Death (SAE) n=1 (states anorexia nervosa complications)		1	0, 0		Antibiotics needed	
Conen, 2009 Case Study Not effective	1 La	1	XI Abscess (SAE) n=1		1	0, 0	1	Antibiotics needed Antifungal treatment	
De Groote, 2005 Case Study Not effective	1 La	1	XI Bacteremia (SAE) n=1		1	0, 0		Antibiotics needed	
Force, 1995 Case Study Not effective	1 Sa	2	XI Fungemia (SAE) n=2		2	0, 0		Antibiotics needed	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Fredenucci, 1998 Case Study Not effective	1 Sa	1	XI Fungemia (SAE) n=1		1	0, 0		Antibiotics needed	
Hennequin, 2000 Case Study Not effective	1 Sa	4	XI Fungemia (4) (SAE) n=4 XI Septic shock (SAE) n=1 XXVI Hypotension n=1 VIII Fever n=2		4	0, 0		Antibiotics unclear	
Henry, 2004 Case Study Not effective	1 Sa	1	XI Fungemia (SAE) n=1		1	0, 0		Antibiotics needed	
Hwang, 2009 Case Study Not effective	1 Sa	1	XXVII Food protein-induced enterocolitis syndrome (SAE) n=1		1	0, 0	1	IV fluid	
Jensen, 1974 Case Study Not effective	1 Sa	1	VIII Fever n=1		1	0, 0	1		
Kniehl, 2003 Case Study Effectiveness unclear	1 Ba	3	VII Diarrhea n=3		3	0, 0			
Ku, 2006 Case Study Not effective	1 Bi	1	XIV D-lactic acidosis (4) (SAE) n=1		1	0, 0		Antibiotics needed supportive care, magnesium, IV bicarbonate	
Kunz, 2004 Case Study Not effective	1 La	2	XI Sepsis (4) (SAE) n=2		2	0, 0		Antibiotics needed	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Land, 2005 Case Study Not effective	1 La	2	XI Bacteremia (4) (SAE) n=2 XI Sepsis (4) (SAE) n=2		2	0, 0		Antibiotics needed 2	
LeDoux, 2006 Case Study Not effective	1 La	1	XI Bacteremia (SAE) n=1		1	0, 0	1	Antibiotics needed	
Lestin, 2003 Case Study Not effective	1 Sa	1	XI Sepsis (SAE) n=1 VII Toxic megacolon (SAE) n=1 XXVII Death (SAE) n=1 (organ failure after bypass)		1	0, 0		Antibiotics needed	
Lherm, 2002 Case Study Not effective	1 Sa	6	XI Fungemia (SAE) n=6 XXVII Death (SAE) n=3		6	0, 0		Antibiotics needed	
Lolis, 2008 Case Study Not effective	1 Sa	1	XI Fungemia (4) (SAE) n=1		1	0, 0		Antibiotics needed	
Lungarotti, 2003 Case Study Not effective	1 Sa	1	XI Fungemia (SAE) n=1 I Methemoglobinemia (SAE) n=1		1	0, 0		Antibiotics needed	
Mackay, 1999 Case Study Not effective	1 St	1	XI Endocarditis (4) (SAE) n=1		1	0, 0	1	Antibiotics needed	
Munakata, 2010 Case Study Not effective	1 St	1	XXVII D-lactic acidosis (4) (SAE) n=1		1	0, 0	1	Antibiotics needed	
Mucoz, 2005 Case Study Not effective	1 Sa	3	XI Sepsis (SAE) n=2 XI Fungemia (SAE) n=3 XXVII Death (unknown cause, bacteremia, stroke) (SAE) n=3		3	0, 0		Antibiotics needed	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Niault, 1999 Case Study Not effective	1 Sa	1	XI Fungemia (SAE) n=1		1	0, 0		Antibiotics needed	
Oggioni, 1998 Case Study Not effective	1 Ba	1	XI Septicemia -death (SAE) n=1 VIII Fever (40C) (2) n=1 XVII Mental confusion (3) n=1 VII Diarrhea n=1 XXVII Death (central nervous system related) (SAE) n=1		1	0, 0	1	Antibiotics needed	
Oh, 1979 Case Study Not effective	1 La	1	XIV D-lactic acidosis (SAE) n=1		1	0, 0	1	Antibiotics needed	
Ohishi, 2010 Case Study Not effective	1 Bi	1	XI Septicemia (SAE) n=1		1	0, 0		Antibiotics needed	
Perapoch, 2000 Case Study Not effective	1 Sa	1	XI Fungemia (4) - patient (SAE) n=1 XI Infection also contracted by second infant in proximity of patient (SAE) n=1	A 2nd patient also developed fungemia believed to be caused by hand contact with the patient #1	1	0, 0		Antibiotics needed	
Piarroux, 1999 Case Study Not effective	1 Sa	1	XI Fungemia (SAE) n=1		1	0, 0		Antibiotics needed	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Piechno, 2007 Case Study Effectiveness unclear	1 Sa	1	XI Fungemia (SAE) n=1 XI Inflammatory bowel n=1 VII Perforated ulcer (SAE) n=1 XXVI State of shock n=1 VII Pseudomembranous colitis (SAE) n=1		1	0, 0		Antibiotics needed Antifungal treatment	
Pletinex, 1995 Case Study Not effective	1 Sa	1	XI Fungemia (SAE) n=1		1	0, 0		Antibiotics needed acetylsalicylic acid	
Presterl, 2001 Case Study Not effective LTFU	1 La	1	XI Endocarditis (4) (SAE) n=1 (PCR shows pathogen is not from yogurt per author) XI Septic arthritis (4) (SAE) n=1 (PCR shows pathogen is not from yogurt per author)		1	0, 0	1	Antibiotics needed Synovectomy, valve replacement	
Rautio, 1999 Case Study Not effective	1 La	1	XI Liver abscess (SAE) n=1		1	0, 0	1	Antibiotics needed	
Richard, 1988 Case Study Not effective	1 Ba	4	XI Bacteremia (SAE) n=4 XXVII Death (SAE) n=2		4	0, 0		Antibiotics needed	
Rijnders, 2000 Case Study Not effective	1 Sa	1	XI Fungemia -death (SAE) n=1 VII Colitis n=1		1	0, 0		Antibiotics needed	
Riquelme, 2003 Case Study Not effective	1 Sa	2	XI Fungemia (4) (SAE) n=2		2	0, 0		Antibiotics needed	

Evidence Table C4. Results (continued)

Author, Year Design Described as Effective LTFU	Arm Genera	N at Random-ization	Reported Harms, SAE and Number of Patients	Other Harms	Patients with AEs	N Drop-outs, Due to AE	Hospi-tali-zations	Antibiotic Therapy Any Other Treatment	Control Category
Tommasi, 2008 Case Study Not effective	1 La	1	XI Bacteremia (SAE) n=1		1	0, 0	1	Antibiotics needed	
Trautmann, 2008 Case Study Effectiveness unclear	1 Sa	1	XI Fungemia (SAE) n=1 XVII Psychomotor disturbance n=1		1	0, 0		Antibiotics needed	
Viggiano, 1995 Case Study Not effective	1 Sa	1	VII Gastrointestinal intolerance n=1 VIII Fever n=1 XXII Respiratory distress requiring use of respirator (SAE) n=1 XI Blood cultures positive for S. cerevisiae/boulardii n=1		1	0, 0		Antibiotics needed	
Zein, 2008 Case Study Effectiveness unclear	1 St	1	XI Lactobacillus septicemia (SAE) n=1		1	0, 0	1	Antibiotics needed	
Zunic, 1991 Case Study Effectiveness unclear	1 Sa	1	XI Fungemia (SAE) n=1		1	0, 0		Antibiotics needed	

Abbreviations
I=Blood and lymphatic system disorders
II=Cardiac disorders
III=Congenital, familial and genetic disorders
IV=Ear and labyrinth disorders
V=Endocrine disorders
VI=Eye disorders
VII=Gastrointestinal disorders
VIII=General disorders and administration site conditions
IX=Hepatobiliary disorders
X=Immune system disorders

XI=Infections and infestations
XII=Injury, poisoning and procedural complications
XIII=Investigations
XIV=Metabolism and nutrition disorders
XV=Musculoskeletal and connective tissue disorders
XVI=Neoplasms benign, malignant and unspecified (incl cysts and polyps)
XVII=Nervous system disorders
XVIII=Pregnancy, puerperiumand and perinatal conditions
XIX=Psychiatric disorders
XX=Renal and urinary disorders
XXI=Reproductive system and breast disorders
XXII=Respiratory, thoracic and mediastinal disorders
XXIII=Skin and subcutaneous tissue disorders
XXIV=Social circumstances
XXV=Surgical and medical procedures
XXVI=Vascular disorders
XXVII=Other
AE=Adverse Events
Ba=Bacillus
Bi=Bifidobacterium
C-RCT=Cross-over Randomized Controlled Trial
CCT=Controlled Clinical Trials
Effective=Described as Effective
En=Enterococcus
La=Lactobacillus
LTFU=Long-term follow-up
ml-milliliter
n=number of participants
n/a=not available or not applicable
RCT=Randomized Controlled Trial
a=Saccharomyces
SAE=Serious Adverse Event
St=Streptococcus

Evidence Table C5. Quality

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Abrahamsson, 2007 3970 RCT	ok	ok	ok		ok	( )	ok	ok	( )	( )	ok	ok	ok		ok	
Agerbaek, 1995 13296 RCT			( )						( )	( )	ok	ok	ok			
Aihara, 2005 2709 RCT	ok	ok	ok		ok			ok	ok	ok	ok	ok		( )	ok	
Alberda, 2007 3979 RCT		( )	ok	( )	ok		ok	( )	( )	( )	ok	ok	ok	ok		ok
Allen, 2010 13253 RCT	ok	( )	ok		ok	( )		ok	ok	ok	ok	ok	( )			
Anderson, 2003 2226 RCT			( )		ok	( )	ok	( )	ok	( )	ok	ok	ok		ok	( )
Andriulli, 2008 4735 RCT	ok	( )	( )		ok		ok	ok	ok	( )	ok	ok	ok	ok		
Anukam, 2006 3319 RCT	ok		ok		( )	( )	ok		ok	( )	ok	ok	( )		ok	( )
Anukam, 2008 4736 RCT			ok		( )		ok	ok			( )	( )	ok			( )
Anukam, 2009 13529 RCT	ok		( )		( )				( )	( )	ok	ok			ok	ok
Arunachalam, 2000 894 RCT	ok		( )		ok		ok		( )	( )	ok	ok	ok	ok	ok	( )
Aso, 1992 12899 RCT	( )		( )		ok			( )	( )	( )	( )	( )	( )			( )
Aso, 1995 12942 RCT			ok			( )		( )	( )	( )	ok	ok	ok			( )
Awad, 2010 13543 RCT	ok		ok		ok	( )	ok	( )	( )	( )	ok	ok	ok	( )	( )	( )
Baerheim, 1994 12960 RCT			ok		ok			( )	( )	( )	ok	ok	ok			
Bajaj, 2008 4750 RCT			ok		ok		ok		ok			ok	ok	ok		( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Banaszkiewicz, 2005 2725 RCT	ok		ok		ok				ok	ok	ok	ok	ok	ok	ok	( )
Barraud, 2010 13579 RCT		( )	ok	( )	ok	( )	ok	ok	ok	ok	ok	ok	ok	ok	( )	ok
Barreto-Zuniga, 2001 7806 RCT			( )	( )	ok				( )	( )	( )	( )		( )	( )	( )
Basu, 2007 4007 RCT	ok	ok	ok	( )	ok			ok	ok	( )	ok	ok	ok			( )
Basu, 2007 4008 RCT	ok	ok	( )	ok	ok	( )	ok	ok	ok	ok	ok	ok	ok			( )
Basu, 2009 4762 RCT	ok		ok		ok	( )	ok		ok	ok	ok	ok	ok			ok
Beausoleil, 2007 4012 RCT			ok				ok	ok	( )	( )	ok	ok	ok			ok
Bellomo, 1979 13309 RCT	ok				ok				( )	( )	ok	ok		( )	( )	( )
Bertolami, 1999 13273 C-RCT			ok		ok		ok		( )	( )	ok	ok	ok	ok	ok	
Besselink, 2008 4767 RCT		( )	ok	ok	ok	( )	ok	ok	ok	( )	ok	ok	ok	ok	ok	
Bin-Nun, 2005 2746 RCT		ok	ok		ok	ok	ok	ok	( )	( )	ok	ok			( )	( )
Black, 1997 13153 CCT			ok		( )			( )			ok	ok	ok	( )	ok	( )
Boge, 2009 13656 RCT			( )		ok		ok	( )	ok	ok	ok	ok	ok	ok		
Boge, 2009 15876 RCT			( )		ok	( )	ok	( )	ok	ok	ok	ok	ok			
Borgia, 1982 15834 RCT	ok	ok	( )		ok	( )	ok	ok	( )	( )	( )	( )	ok		ok	( )
Bousvaros, 2005 2765 RCT	ok		ok		ok		ok		ok	( )	ok	ok	ok	ok	( )	

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Bravo, 2008 4796 RCT			( )		ok		ok	( )	( )	( )	ok	ok	ok	( )		( )
Brophy, 2008 4800 RCT	ok	ok	ok			( )		ok	ok	ok	ok	ok	ok	ok		
Bruno, 1981 12379 RCT	ok	( )			ok		( )	( )	( )	( )	ok	( )		( )	( )	( )
Bruzzese, 2007 4053 C-RCT	ok		ok		ok				ok	( )	ok		ok		ok	ok
Bu, 2007 4054 RCT	ok	( )	( )		ok				ok	( )	ok	ok	ok			( )
Chen, 2005 9337 RCT			( )	ok	ok		ok		ok	ok	ok	ok	ok	( )		ok
Chen, 2010 13804 RCT	ok		ok		ok	( )			ok	ok	ok	ok	ok	ok	( )	( )
Chou, 2010 13817 RCT		ok	ok		ok	( )		ok	ok	ok		( )	ok			ok
Chouraqui, 2004 2291 RCT	ok	ok	( )	( )	ok		( )	( )	ok	ok	ok	ok		ok	ok	
Chouraqui, 2008 4846 RCT	ok	ok	ok		ok	( )		ok	( )	( )	ok	ok	ok	ok		
Chui, 2009 13870 RCT			( )		ok		ok	( )	( )	( )			ok		( )	( )
Coccorullo, 2010 13833 RCT	ok		ok	ok	ok		ok		ok	( )	ok	ok	ok	ok		ok
Connolly, 2005 2805 RCT	ok	ok	ok		( )		( )	ok	( )	ok	ok	ok		( )		
Cooper, 2006 13033 RCT			( )		( )	( )			( )	( )	ok	ok		( )	( )	
Correa, 2005 2809 RCT			ok		ok	( )	ok	ok	( )	( )	ok	ok	ok		ok	
Cui, 2004 9076 RCT			ok		( )	( )		ok	( )	( )	ok	ok	( )	ok		
Cunningham-Rundles, 2000 919 CCT	ok	( )	( )		( )						ok	ok		ok	( )	( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Czaja, 2007 4116 RCT	ok		ok		ok		ok	ok	ok	ok	ok	ok	ok	ok	ok	ok
Dadak, 2006 13232 RCT	ok		( )		ok		ok		( )	( )	( )	( )	( )			( )
De Preter, 2006 13275 C-RCT			( )		ok				( )	( )	( )	( )	ok			( )
de Roos, 1999 13272 RCT	( )		( )		ok		ok		( )	( )	( )	( )	ok			( )
De Simone, 1992 13096 RCT		ok	ok		( )			ok	ok	( )			ok	ok		( )
De Simone, 2001 13264 CCT		ok	ok		( )	( )		ok			( )	( )		( )		( )
Dekker, 2009 12563 RCT	ok	( )	ok		ok	( )	ok	ok	( )	( )	ok	ok	ok	ok	ok	( )
Delia, 2002 1488 RCT			ok	ok	ok	( )	( )		( )	( )	( )	( )	ok	ok	ok	( )
Delia, 2007 4132 RCT			( )	ok	( )			( )	( )	( )	ok	ok	ok		( )	( )
Dewan, 2007 4139 RCT		ok	ok	( )	( )		ok		ok	( )	( )	( )	ok		( )	( )
Dolin, 2009 13961 RCT	ok		( )					ok	( )	( )	ok	ok	ok		( )	ok
Dubey, 2008 4903 RCT		ok	( )		( )	( )	ok	ok	( )	( )	ok	ok	( )	( )		ok
Duman, 2005 2838 RCT			ok		ok	( )	ok		( )	( )			ok		ok	ok
Dupont, 2010 13989 RCT		( )	ok					ok	( )	( )	ok	ok			( )	
Dylewski, 2010 13992 RCT			ok		ok	( )		ok	( )	( )	ok	ok	ok		ok	
Ehrstrom, 2010 14005 RCT	ok		ok		ok		ok		( )	( )	ok	ok			ok	
Eriksson, 2005 2845 RCT		( )	ok		ok	( )		ok	( )	( )	ok	ok			ok	

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Falck, 1999 13279 RCT		( )	( )	ok	( )	( )	ok	ok	( )	( )	ok	ok	ok		ok	
Felley, 2001 12954 RCT	ok		ok		ok		ok		( )	( )	ok	ok	ok		ok	
Feng, 1999 12883 RCT		ok	ok		( )			ok	( )	( )	ok	ok	ok			( )
Folster-Holst, 2006 3503 RCT	ok		ok		ok			ok	( )	( )	ok	ok	ok		ok	
Forestier, 2008 4929 RCT			ok	ok		( )	ok		ok	( )	ok	ok	ok		( )	
French, 2009 13313 RCT	ok	ok	( )		ok			ok	ok	( )	ok	ok	ok		ok	
Frohmader, 2010 14075 RCT			ok	( )	ok		ok	ok	ok	ok	ok	ok	ok	ok	ok	( )
Fujimori, 2009 5672 RCT	ok	ok	ok		ok			ok	ok	( )	( )	( )	ok		( )	( )
Gade, 1989 13050 RCT					( )				ok	( )	ok	ok	ok			
Galpin, 2005 2875 RCT	ok	ok	ok	ok	ok		( )	ok	ok	ok	ok	ok	( )		( )	ok
Gao, 2010 14095 RCT	ok		ok		ok	( )	ok		ok	ok	ok	ok	ok	ok	ok	ok
Garcia Vilela, 2008 4941 RCT	ok	( )	( )		( )				ok	( )	ok	ok	ok	( )	( )	ok
Gerasimou, 2010 14116 RCT	ok		ok		ok		ok		ok	( )	( )	ok	ok		ok	ok
Gibson, 2008 5676 RCT	ok	ok	ok		ok	ok	ok		ok	ok	ok	ok	ok	ok	( )	
Gill, 2001 1192 RCT	ok		ok				ok		( )	( )	ok	( )	ok	( )		
Gionchetti, 2000 944 RCT		ok	ok	ok	ok		( )	ok	ok	ok	ok	ok	ok	ok	ok	( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Gionchetti, 2003 1923 RCT		ok	( )	ok	ok			ok	ok	ok	ok	ok	ok	ok	ok	( )
Goossens, 2003 1928 RCT	ok	ok	ok		( )	( )	ok	ok	( )	( )	ok	ok	ok			( )
Gracheva, 1999 764 CCT		( )	ok		( )		( )				( )	( )	ok	( )		( )
Gruber, 2007 4223 RCT	ok		ok		ok	( )	ok		ok	( )	ok	ok	ok		ok	( )
Guillemard, 2010 14197 RCT		( )	( )		ok	( )	ok	ok	ok	( )	ok	ok	ok	ok		
Guyonnet, 2009 5687 RCT		( )	( )		ok			( )	( )	( )			ok	( )		
Habermann, 2001 12892 RCT	ok		( )		( )			( )	( )	( )	ok	ok	ok	( )	( )	( )
Habermann, 2002 1540 RCT	ok	( )	( )	( )	( )			ok	( )	( )	ok	ok		ok	( )	( )
Haschke-Becher, 2008 4993 RCT	ok	( )	( )		ok		ok	( )	( )	( )	ok	ok	ok	( )		
Hatakka, 2008 4995 C-RCT	ok	( )			ok		ok	( )	ok	( )	ok	ok	ok			
Heimburger, 1994 13228 RCT			( )		( )		ok		( )	( )	ok	ok			ok	
Hemmerling, 2009 14262 RCT	ok	( )	( )		ok		ok	ok	( )	ok	ok	ok	ok	ok		
Higashikawa, 2009 14278 RCT	ok	( )	ok		ok		ok	ok	ok	( )	ok	ok	( )			
Hilton, 1997 548 RCT	ok	( )	( )		( )		ok	( )	( )	( )	ok	ok	( )		( )	( )
Hirata, 2002 12881 CCT		ok	ok		ok		ok	ok			ok	ok	ok			( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Hochter,1990 12996 RCT	ok		( )		( )				( )	( )	ok	ok	ok	( )		( )
Honeycutt, 2007 4253 RCT	ok		ok		ok		ok	( )	ok	( )	ok	ok	ok	ok	ok	ok
Hong, 2010 14295 RCT	ok		( )		ok		ok		ok	ok	ok	ok	ok	ok		( )
Horvat, 2010 14304 RCT	ok	ok	( )		ok		ok	ok	ok	ok	ok	ok	ok		ok	ok
Ishikawa, 2002 1968 RCT		( )	( )		ok		( )	( )	( )	( )	( )	( )	ok	ok	ok	
Ishikawa, 2003 12937 RCT	ok		( )		( )				( )	( )	( )	( )	ok	( )		( )
Ishikawa, 2005 2922 RCT	ok		ok		ok	( )	ok	( )	( )				ok		ok	( )
Isolauri, 1991 12412 RCT	ok	ok	ok				ok	ok	( )	( )	( )	( )	ok	ok	( )	( )
Isolauri,1995 12826 RCT	ok	ok	( )		( )			( )	( )	( )	( )	( )		( )	( )	( )
Jirapinyo, 2002 1566 RCT			( )		( )		ok	ok	ok	( )	ok	ok	ok		ok	( )
Johansson, 1998 653 RCT	ok		( )		ok			ok	( )	( )	ok	ok				( )
Kadooka, 2010 14403 RCT		ok	ok		ok			ok	( )	( )	ok	ok	ok	ok		ok
Kajander, 2005 2937 RCT	ok	( )	( )		ok		ok	ok	ok	( )	ok	ok	ok	( )	ok	
Kajander, 2008 5072 RCT	ok		ok		ok				ok	( )	ok	ok	( )	ok	ok	
Kajimoto, 2002 12882 RCT		ok	ok		ok			ok	( )	( )	ok	ok	ok			( )
Karvonen, 2001 13044 RCT	( )	( )	ok		( )			ok	( )	( )	ok	ok		( )		( )
Kerac, 2009 14441 RCT	ok	ok	ok		ok	( )		ok	ok	ok	ok	ok	ok	ok	ok	( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Kianifar, 2009 14448 RCT			ok		ok		ok	( )	ok	( )	ok	ok	ok			ok
Kim, 2006 13298 RCT		ok	ok		ok		( )	ok	ok	ok	ok	ok	ok	( )		
Kim, 2006 3610 RCT		ok	ok		ok		( )	ok	ok	ok	ok	ok	ok	( )		
Kim, 2008 5096 RCT	ok		ok		ok	( )	ok	( )	ok	( )			ok	ok	ok	( )
Kirjavainen,2003 1993 RCT	ok		ok		( )				( )	( )	ok	ok	ok			( )
Klarin, 2008 5105 RCT			( )		( )		ok		( )	( )	( )	( )	ok			
Klarin,2005 2953 RCT	ok		( )				ok		ok	( )	( )	( )	ok		ok	
Knight, 2007 5110 RCT		( )	ok		ok	( )	ok	ok	ok	( )	ok	ok	ok		ok	
Koning, 2008 5112 RCT	ok	ok	ok		( )		ok	ok	( )	( )	ok	ok	ok		ok	( )
Kopp, 2008 5117 RCT	ok	( )	( )		ok			ok	ok	( )	ok	ok	ok		ok	ok
Kotzampassi, 2006 3597 RCT	ok	ok	ok	ok	ok		ok		( )	ok	ok	ok	ok		ok	( )
Krasse, 2005 3601 RCT	ok		ok		ok				( )	( )	ok	ok	ok	ok	ok	( )
Kuitunen, 2009 14517 RCT	ok	ok	ok	ok	( )	( )	( )	ok	( )	( )	( )	ok	( )			( )
Kurugol, 2005 2972 RCT		( )	ok		ok	( )	ok	ok	( )	( )	ok	ok	ok		ok	( )
La Rosa, 2003 2008 RCT		ok	ok			( )	ok	ok	ok	( )	ok	ok	ok	ok	ok	( )
Laitinen, 2008 5127 RCT	ok		( )		ok	( )	ok		ok	ok	ok	ok	ok			ok
Langhendries, 1995 13114 RCT		ok	( )					ok	( )	( )	ok	ok	ok			

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Larsen, 2006 3613 RCT	( )	ok	ok					ok	( )	( )	ok	ok	ok			
Larsson, 2008 5131 RCT	ok		( )		ok	( )	ok	( )	ok	( )	ok	ok	ok	ok	ok	
Lata, 2009 14560 RCT			ok		ok		ok	( )	( )	( )	ok	ok			ok	( )
Lawrence, 2005 2988 RCT	ok		ok		ok		ok		( )	( )	ok	ok	ok	ok	ok	
Li, 2004 13042 RCT			ok		ok		ok		( )	( )	( )	( )		( )	ok	
Ligaarden, 2010 14622 C-RCT	ok	ok	( )		( )		ok	ok	ok	ok	ok	ok	ok			( )
Lighthouse, 2004 9143 RCT		( )	ok		( )				( )	( )			ok	( )	ok	( )
Lin, 1989 13095 C-RCT	ok		ok		( )	( )	ok	( )	( )	( )	ok	ok				
Lin, 2005 3004 RCT		ok	ok	( )	ok	( )	ok	ok	ok	ok	ok	( )	( )	( )	ok	( )
Lin, 2008 5156 RCT	ok	ok	ok			( )	ok	ok	ok	( )	( )	ok	ok		ok	( )
Ljungberg, 2006 3636 RCT	ok	ok	ok	( )	( )	( )		ok	( )	( )	ok	ok	ok	( )		
Loguercio, 1987 13116 RCT	ok	ok	ok		ok			ok	( )	( )			ok	ok		( )
Lonnermark, 2010 14668 RCT	ok		( )		ok	( )		ok	ok	ok	ok	ok			ok	
Lu, 2004 7077 CCT			ok		( )						ok	ok		( )	( )	( )
Luoto, 2010 14685 RCT	ok		ok		ok	( )		ok	( )	( )	ok	ok	ok			ok
Mäkeläinen, 2003 2031 RCT	ok	( )	( )		( )			ok	( )	( )	ok	ok				( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Malaguarnera, 2007 4374 RCT	ok	ok	ok		ok			ok	ok	( )	ok	ok	ok	ok	ok	( )
Malaguarnera, 2010 14707 RCT			( )		ok	( )	ok	ok	( )	( )	ok	ok		( )	( )	ok
Maldonado, 2009 14708 RCT	ok	ok	ok		ok		ok	ok	( )	( )	ok	ok	ok	ok		
Mandel, 2010 14715 RCT	ok		( )						ok	ok	ok	ok	ok		( )	
Manley, 2007 4378 C-RCT	ok		( )	( )	ok		ok		ok	ok	ok	ok	ok		ok	ok
Manzoni, 2006 3654 RCT	ok	ok	ok		ok		ok	ok	ok	( )	ok	ok	ok	ok	ok	ok
Margreiter, 2006 3656 RCT			( )		ok	( )	ok	ok	( )	( )	ok	ok	( )			( )
Marotta, 2003 8348 C-RCT			ok						( )	( )		( )	ok	ok		( )
Marrazzo, 2006 3658 RCT			( )		( )	( )		( )	( )	( )	( )	( )			ok	( )
Marseglia, 2007 4383 RCT			( )		ok				( )	( )		ok	ok	ok	ok	( )
Marteau, 2004 3661 RCT	ok		ok		ok		ok		ok	ok	ok	ok	ok	ok	ok	
Martiney, 2009 14747 RCT		( )	( )		ok			( )	( )	( )	ok	ok	ok			( )
Martinez, 2008 5755 RCT	ok		( )		ok		ok		( )	( )	ok	ok	ok	ok	ok	( )
Martinez, 2009 5756 RCT	ok		ok		ok				( )	( )	ok	ok	ok		ok	( )
Mayanagi, 2009 14773 RCT	ok		ok		ok				ok	ok	ok	ok	ok			( )
McFarland, 1994 12403 RCT			( )		( )	( )	ok	ok	ok	( )	ok	ok	ok	ok	ok	

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
McFarland, 1995 12753 RCT		ok	( )	ok	ok	( )	ok	ok	( )	ok	ok	ok		ok	ok	
McNaught, 2002 1637 RCT	ok	ok	ok		ok		ok	ok	ok	( )			ok	ok	ok	( )
Merenstein, 2009 14810 RCT		( )	ok		ok	( )		ok	ok	ok	ok	ok	ok		ok	
Merenstein, 2010 14809 RCT		ok	ok		ok	( )	ok	ok	ok	ok	ok	ok	ok	ok		
Metts, 2003 6459 RCT	ok	( )	ok		( )			ok	ok	( )	ok	ok				( )
Miele, 2009 5767 RCT			ok	ok	ok		ok	ok	ok	ok	ok	ok	ok	ok	ok	ok
Millar, 1993 388 RCT	ok	ok	( )		ok		ok	ok	( )	( )	ok	ok	ok	ok	ok	( )
Mimura, 2004 2486 RCT		( )	ok		ok		ok	( )	ok	ok	ok	ok	ok	ok	ok	
Miyaji, 2006 10450 RCT	ok		( )		ok		ok		( )	( )	ok	ok	ok	ok		( )
Morrow, 2010 14862 RCT	ok	( )	ok		ok	( )	ok	ok	ok	( )	ok	ok	ok		ok	ok
Mukerji, 2009 5774 RCT	ok		ok		ok		ok	ok	ok	ok	ok	ok	( )	ok	ok	( )
Naito, 2008 5252 RCT	ok	( )	ok		ok	( )	ok	ok	( )	( )			ok	ok	ok	( )
Newcomer, 1983 13137 RCT		ok	( )		( )			ok	( )	( )	ok	ok	ok			
Niers, 2009 13237 RCT	ok		( )			( )	ok	ok	ok	( )	ok	ok				
Niv, 2005 3096 RCT	ok		ok		ok		ok	ok	( )	( )	ok	ok	ok	ok	ok	
Nobuta, 2009 13315 RCT	ok		ok		( )				ok	ok	ok	ok	ok			( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
O'Mahony, 2005 3107 RCT	ok	( )	( )					ok	ok	ok	ok	ok	ok		ok	ok
Ojetti, 2010 14951 RCT			( )	ok	ok		ok		ok	( )			ok	ok		( )
Olah, 2005 3105 RCT		( )	ok	( )	ok		ok		ok	( )	ok	ok	ok	( )	( )	( )
Olivares, 2006 3718 RCT			( )		( )			ok	( )	( )	ok	ok	ok	( )		( )
Osterlund, 2007 4452 RCT	ok	( )	( )		ok	( )	ok	ok	( )	( )			ok	ok	ok	
Ouwehand, 2009 14975 RCT	ok		( )		ok		ok	( )	( )	ok	ok	ok	( )			
Ozkinay, 2005 13286 RCT			ok		ok	( )	ok	( )	ok	ok	ok	ok	ok	ok		
Panigrahi, 2008 5292 RCT	ok	( )	ok		ok		ok	ok	( )	( )	ok	ok	( )		ok	ok
Parent, 1996 13168 RCT			ok		ok				ok	( )	( )	( )		( )		( )
Parfenov, 2005 3114 CCT		( )	( )	( )	ok			( )			( )	( )	ok			( )
Parfenov, 2005 3115 CCT	ok		( )	( )	ok			( )					( )		( )	( )
Parra, 2004 2523 RCT	ok	( )	( )		( )		ok	ok	( )	( )	ok	ok	ok	ok		
Passeron, 2005 3733 RCT	ok		ok	ok	ok		( )	ok	( )	( )	ok	ok	ok		ok	( )
Peral, 2009 5801 RCT	ok	( )	( )		( )		ok	ok	( )	( )			ok	ok	ok	( )
Pereg, 2010 15027 RCT			ok		ok		ok		( )	( )	ok	ok	ok			( )
Petschow, 2005 12409 RCT	ok	ok	( )		ok			ok	( )	( )	ok	ok	( )	ok		
Prantera, 2002 1692 RCT	ok		( )		ok		ok		ok	( )	ok	ok	ok		ok	

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Pregliasco, 2008 13299 RCT	ok		( )		ok	( )	ok	ok	ok	( )	ok	ok	ok			ok
Pregliasco, 2008 13300 RCT	ok		( )		ok	( )	ok	ok	ok	( )	ok	ok	ok			ok
Pregliasco, 2008 5328 RCT	ok		( )		ok	( )	ok	ok	ok	( )	ok	ok	ok			ok
Puccio, 2007 4504 RCT	ok	ok	( )		ok	( )		ok	( )	( )	ok	ok		ok		
Rampengan, 2010 15104 RCT			( )		( )			( )	( )	( )	( )	( )	ok			( )
Ranganathan 15107 C-RCT	ok		( )		ok				( )	( )	ok	ok	ok			
Rautava, 2008 5350 RCT	ok	( )	ok		ok			ok	( )	ok	ok	ok	ok		ok	ok
Rayes, 2002 12475 RCT	ok	ok	ok				ok	ok	ok	( )	( )	( )	ok		( )	( )
Rayes, 2002 1702 RCT	ok	( )	( )		( )		ok	( )	( )	( )	( )	( )	ok			( )
Rayes, 2005 3152 RCT	ok		ok		ok		ok	ok	ok	( )	ok	ok	ok	ok	ok	( )
Rayes, 2007 4518 RCT	ok		ok		ok		ok	ok	ok	ok	ok	ok	ok		ok	( )
Reid, 1992 12959 RCT	ok	ok	( )		( )			ok	( )	( )	( )	( )			ok	( )
Reid, 1995 12815 RCT	ok		ok				ok	( )	( )	( )	( )	( )	ok			( )
Ren, 2010 15136 RCT			ok		ok		ok		( )	( )			ok	ok	ok	( )
Reuman, 1986 12770 RCT			ok	( )	ok		ok	( )	ok	( )	ok	ok		ok	ok	( )
Richelsen, 1996 12374 RCT			( )		ok				( )	( )	ok	ok	ok			
Rio, 2002 1714 RCT			( )		( )				( )	( )	ok	( )				( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Roos, 1996 13278 RCT			ok		( )	( )	ok	ok	( )	( )	ok	ok	ok		ok	
Roos, 2001 12970 RCT			( )			( )	ok		( )	( )	ok	ok	ok		ok	( )
Rose, 2010 15187 RCT	ok		ok			( )			( )	( )	ok	ok	ok		ok	
Rosenfeldt, 2002 1722 RCT	ok		ok		ok				ok	( )	ok	ok	ok		ok	( )
Rosenfeldt, 2003 6738 C-RCT	ok	ok	( )		ok			ok	( )	( )	ok	( )		( )		
Rouge, 2009 5819 RCT	ok		ok		( )		ok		ok	( )	ok	ok	ok	ok	( )	
Ruiz-Palacios, 1996 13088 RCT			( )		( )			( )	( )	( )	( )	( )		( )		
Saavedra, 2004 2572 RCT	( )	ok	ok		ok	( )	ok	ok	ok	( )	ok	ok	ok		ok	ok
Safdar, 2008 5377 RCT		ok	ok		ok		ok	ok	( )	( )	ok	ok	ok		ok	
Sahagun-flores, 2007 15865 RCT	ok		ok		ok			( )	( )	( )		( )	ok	( )	ok	
Saint-Marc, 1995 15843 RCT			( )		ok				ok	( )	ok	( )	ok	ok	( )	( )
Salminen, 1988 12816 RCT	ok	ok	ok	ok	( )		ok	ok	( )	( )	ok	ok	ok		ok	( )
Salminen, 2004 2578 C-RCT	ok	( )	ok		ok			ok	ok	( )	ok	ok	ok		ok	
Samanta, 2008 5828 RCT			ok		ok	( )	ok	ok	ok	( )	ok	ok		ok		( )
Satokari, 2001 1329 RCT	ok		ok		( )				( )	( )	( )	( )	ok		( )	( )
Savino, 2006 4569 RCT	ok	( )			ok			ok	ok	( )	ok	ok	ok			( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Sazawal, 2010 15858 RCT	ok		ok		ok	( )	ok		ok	( )	ok	ok	ok	ok	( )	
Scalabrin, 2009 15253 RCT	ok	( )	( )		ok	( )	ok	ok	ok	ok	ok	ok				
Schrezenmeir, 2004 2586 RCT		ok	ok		ok		( )	ok	( )	( )	( )	( )	( )		ok	
Schultz, 2004 2588 RCT	ok		( )		ok				( )	( )	ok	ok	( )	( )	ok	ok
Seppo, 2003 12878 RCT	ok		ok		ok			( )	( )	( )	ok	ok	ok		ok	
Sierra, 2010 15343 RCT	ok	ok	( )		( )		ok	ok	( )	( )	ok	ok	ok	ok		
Simons, 2006 3839 RCT	( )		ok				ok	ok	( )	( )	ok	ok	ok		ok	
Simren, 2010 15353 RCT			( )		ok		ok	ok	( )	ok	ok	ok	ok	ok		( )
Song, 2010 15379 RCT	ok		( )		ok	( )	ok	ok	ok	( )			ok	ok	ok	( )
Songisepp, 2005 16079 RCT	ok	ok			( )			ok	( )	( )	ok	ok	ok	( )	( )	( )
Songisepp, 2005 3207 CCT	ok	ok	ok		( )			ok					ok	( )	( )	( )
Sood, 2009 15381 RCT			ok		( )	( )	ok	ok	ok	ok	ok	ok		ok		ok
Spanhaak, 1998 703 RCT	ok	( )	ok		( )		ok	ok	( )	( )	ok	ok		( )	ok	
Stockert, 2007 4607 RCT			( )		ok			( )	ok	( )	ok	ok	ok		ok	( )
Stotzer, 1996 515 C-RCT	ok		( )		ok				( )	( )	ok	ok	ok		ok	( )
Stratiki, 2007 4609 RCT		ok	( )	ok	ok		ok	ok	ok	( )	( )	ok	ok			( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Sullivan, 2003 2156 RCT	ok		ok		( )		( )		( )	( )	ok	ok		( )	ok	( )
Sykora, 2005 3222 RCT	ok	( )	( )		ok		ok	ok	ok	( )	ok	ok	ok	ok	ok	( )
Tamura, 2007 4626 RCT	ok		( )		ok	( )			ok	ok	ok	ok	( )		( )	
Taylor, 2007 4631 RCT	ok	( )	ok		( )	( )	ok	( )	ok	ok	ok	ok	ok		ok	
Tempe, 1985 13083 RCT	ok		( )		ok		ok	( )	( )	( )	ok	( )	ok	ok		( )
Teran, 2008 5482 RCT		( )	( )		ok			( )	( )	( )	ok		ok			ok
Thomas, 2001 6623 RCT	ok	ok	( )		ok		ok	ok	( )	( )	ok	ok	ok		ok	
Tomoda, 1991 13152 CCT		ok	ok		( )			ok								( )
Tsuchiya, 2004 2648 CCT			( )	ok	ok			ok			ok				ok	( )
Turchet, 2003 2182 RCT	ok	( )	( )		ok	( )		( )	( )	( )			( )	ok	ok	
Tursi, 2004 2652 RCT			( )		ok		ok		( )	( )			ok	ok	ok	( )
Tursi, 2008 5505 CCT	ok		( )		( )		ok	ok	( )				ok	ok	( )	( )
Tursi, 2010 15548 RCT			ok		ok	( )		( )	ok	( )	ok	ok	ok	ok	ok	ok
Underwood, 2009 5878 RCT		ok	( )		ok		ok	ok	ok	( )	ok	ok	ok	ok	ok	ok
Urban, 2008 11572 RCT		ok	( )		ok	ok	( )	ok	ok	ok	ok	ok		( )		
Urbansek, 2001 1367 RCT			ok		ok	( )	ok		( )	( )	ok	ok	ok	ok	ok	
Van der Aa, 2010 15566 RCT	ok		( )		ok				ok	( )	ok	ok	ok		ok	

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Van Gossum, 2007 4658 RCT	ok	( )			ok	( )		ok	( )	( )	ok	ok	ok	ok	ok	
Velaphi, 2008 5526 RCT	ok	ok	( )		ok		ok	ok	( )	( )	ok	ok			ok	
Vendt, 2006 3908 RCT	ok	ok	ok				( )	ok	( )	( )	ok	ok	ok		( )	
Vleggaar, 2008 5531 C-RCT			ok		( )		( )		( )	( )	ok	ok	ok		( )	( )
Vlieger, 2009 5893 RCT	ok	ok	ok			ok		ok	ok	( )	ok	ok	ok	ok		
Wada, 2010 15642 RCT	ok	( )	( )		ok		ok	ok	( )	( )	( )	( )	ok		ok	( )
Wang, 2004 2671 RCT			( )		ok		ok	( )	( )	( )	ok	ok	ok	ok		
Wang, 2007 11346 RCT	ok		( )		ok		ok		( )	( )	( )	( )	( )	( )	ok	( )
Weizman, 2005 3278 RCT	ok	( )	ok		ok	( )	( )	ok	ok	( )	ok	ok	ok	ok	ok	ok
Weizman, 2006 3925 RCT	ok	ok	ok		ok	ok	ok	ok	( )	( )	ok	ok	ok	ok		( )
Weston, 2005 3280 RCT	ok		ok		ok		ok	( )	ok	( )	ok	ok	ok		ok	ok
Wewalka, 2002 1792 RCT			ok					ok	( )	( )	( )	( )		ok		( )
Wheeler, 1997 12498 C-RCT			ok		( )				ok	( )	ok	ok	ok			
Wildt, 2006 3935 RCT	ok	( )	ok				ok	ok	ok	( )	ok	ok	ok		ok	
Williams, 2008 5562 RCT	ok		ok				( )		( )	( )	ok	ok	ok			
Wind, 2010 15719 RCT	ok	ok	( )		ok		ok	ok	( )	( )	ok	ok	ok	ok		ok
Wolf, 1994 12856 RCT	ok	ok	( )		( )		ok	ok	( )	( )	ok	ok	ok	( )		( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Wolf, 1998 718 RCT	ok	ok	ok		ok	ok		ok	( )	ok	ok	ok	( )	ok	ok	( )
Worthley, 2009 15730 C-RCT	ok	( )	( )		( )		ok	ok	( )	( )	ok	ok	ok			ok
Xia, 2010 15742 RCT	ok	ok	ok		ok		ok	ok	ok	( )	( )	( )	ok	ok		( )
Xiang, 2006 10102 RCT			ok		ok				( )	( )	( )	( )	ok	ok		( )
Xiao, 2003 2206 RCT	( )		ok		ok		ok		( )	( )	( )	( )	ok	ok	( )	
Xiao, 2003 2207 RCT			ok		ok	( )		ok	( )	( )			ok		( )	( )
Yang, 2008 5576 RCT		ok	ok		ok	( )		ok	( )	( )	ok	ok	( )			
Yao-Zong, 2004 2684 RCT			( )		ok				( )	( )			ok	ok	ok	
Yonekura 15779 RCT	ok	ok	( )		ok	( )		ok	( )	ok	ok	ok	ok			( )
Zhang, 2010 15796 RCT		ok	ok		ok		ok	ok	ok		( )	( )	ok	ok	( )	( )
Ziegler, 2003 8418 RCT		ok	( )		( )	( )		ok	( )	( )	ok	ok				( )
Zocco, 2003 13023 RCT	ok		( )		( )				( )	( )		( )		( )		( )
An, 2010 13513 Case Series	ok	ok						ok					( )			ok
Barrett, 2008 4760 Case Series	ok		ok				ok	( )					ok		( )	
Beck, 1961 13117 Case Series			( )										ok			( )
Bekkali, 2007 4013 Case Series		ok	ok					ok					ok			( )
Bellomo, 1979 13195 Case Series	ok								( )		ok				( )	( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Benchimol, 2004 2238 Case Series	ok		( )				( )						ok			( )
Berman, 2006 10085 Case Series			ok				ok						ok			
Bibiloni, 2005 2745 Case Series		( )	( )					ok					ok		( )	
Bruce, 1988 12963 Case Series	ok		ok				( )						ok		( )	( )
Bruni, 2008 5627 Case Series		ok	( )	ok			ok	ok					ok			( )
Carlsson, 2009 13758 Case Series	ok		ok										ok		( )	ok
Cobo Sanz, 2006 9897 Case Series	ok	( )	( )				( )	ok					ok			
Colecchia, 2006 3427 Case Series	ok	( )	ok			( )		ok					( )			( )
Di Pierro, 2009 13935 Case Series			ok										ok			( )
Dughera, 2007 4153 Case Series	ok	( )	ok					ok								( )
Elmer, 1995 13220 Case Series			ok										( )			
Fukuda, 2008 11700 Case Series	ok	ok	ok					ok					ok			( )
Gabrielli, 2009 14088 Case Series			ok	ok			ok	( )					ok			( )
Garrido, 2005 2878 Case Series			( )										ok			
Gionchetti, 2007 4209 Case Series		ok	( )	ok				ok					ok		( )	( )
Glintborg, 2006 12738 Case Series	ok		( )	( )									ok			
Gniwotta, 1977 13081 Case Series	ok															( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Gotteland, 2003 13214 Case Series	ok		ok										ok	( )		( )
Gruenwald, 2002 1533 Case Series		( )	( )					( )					ok			( )
Hensgens, 1976 12902 Case Series			( )				ok						ok		( )	( )
Huynh, 2009 5699 Case Series			ok				ok	ok					ok		( )	
Karimi, 2005 2943 Case Series	( )	( )	ok				ok	ok							( )	ok
Kawamura,1981 12842 Case Series	( )		( )										ok			( )
Kirchhelle, 1996 13030 Case Series			ok					( )					ok			( )
Kitajima, 1997 6362 Case Series	ok		ok				ok						ok			( )
Lamiki, 2010 14545 Case Series	ok	( )	ok	ok			ok	( )					ok			ok
Lee, 2010 14586 Case Series	ok		ok					( )					ok		( )	( )
Lombardo, 2009 14662 Case Series	ok		ok				( )	( )								ok
Luoto, 2010 14683 Case Series	ok	ok	ok			( )	ok	ok					ok			ok
Malin, 1996 13109 Case Series	ok		ok					( )					( )		( )	( )
Malkov, 2006 3653 Case Series	ok		( )				ok						ok		( )	( )
Mego, 2005 3051 Case Series	ok	ok	ok					ok							( )	( )
Mego, 2006 3675 Case Series	ok		( )					ok					ok		( )	( )
Michetti, 1999 12400 Case Series	ok		ok				ok		( )		ok	ok	ok		( )	

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Muting, 1968 13121 Case Series			( )													( )
Nobuta, 2009 15883 Case Series	ok		( )		( )			ok					ok			( )
Reid, 2001 1309 Case Series	ok	ok	( )					ok					ok			( )
Rosenfeldt, 2003 13297 Case Series	ok		( )										( )		( )	
Sakamoto, 2001 1322 Case Series	ok		( )										ok			( )
Schneider, 2005 3191 Case Series			ok													
Shen, 2005 3198 Case Series		ok	ok	ok				ok					ok		( )	( )
Srinivasan, 2006 3854 Case Series	ok		( )				ok	ok					ok			ok
Tasli, 2006 10000 Case Series	ok	ok	ok	ok				ok					ok			( )
van Bodegraven, 2004 8828 Case Series			( )												( )	( )
Weiss, 2010 15681 Case Series			ok				ok						ok		( )	( )
Yim, 2006 9923 Case Series			( )					ok								
Zahradnik, 2009 15788 Case Series	ok		ok					ok					ok			
Zahradnik, 2009 15877 Case Series	ok		ok					ok					ok			
Barton, 2001 1109 Case Study			ok				ok					ok	ok		( )	( )
Bassetti, 1998 12397 Case Study			ok				ok						ok		( )	( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Burkhardt, 2005 13039 Case Study			ok				ok						ok		( )	( )
Cesaro, 2000 12395 Case Study			ok				ok						ok			( )
Cherifi, 2004 2290 Case Study		ok	ok				ok								( )	( )
Conen, 2009 13233 Case Study			ok										ok			( )
De Groote, 2005 2814 Case Study	ok		ok									ok	ok		( )	( )
Force, 1995 12806 Case Study			ok										ok		( )	( )
Fredenucci, 1998 12788 Case Study			ok					ok					ok			( )
Hennequin, 2000 959 Case Study		( )	( )				ok								( )	( )
Henry, 2004 13015 Case Study			ok				ok						ok		( )	( )
Hwang, 2009 14335 Case Study			ok										ok		( )	ok
Jensen, 1974 12870 Case Study			ok										ok		( )	( )
Kniehl, 2003 1996 Case Study	ok	( )	ok				ok						ok			( )
Ku, 2006 10240 Case Study			ok				( )						ok			( )
Kunz, 2004 2424 Case Study	ok		ok				ok						ok		( )	( )
Land, 2005 2984 Case Study	ok		ok				ok						ok		( )	ok
LeDoux, 2006 3617 Case Study			ok										ok			( )
Lestin, 2003 2017 Case Study	ok	ok	ok				ok	( )								ok

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Lherm, 2002 12398 Case Study			ok													( )
Lolis, 2008 5164 Case Study	ok		ok				ok						ok		( )	ok
Lungarotti, 2003 12924 Case Study			ok				ok						ok		( )	( )
Mackay, 1999 812 Case Study		( )	ok										ok			( )
Munakata, 2010 14875 Case Study			ok				( )						ok			( )
Muñoz, 2005 3076 Case Study	( )		ok				ok						ok			ok
NA 14585 NA																
NA 15045 NA																
NA 4095 NA																
NA 4912 NA																
Niault, 1999 817 Case Study			ok				ok						ok			( )
Oggioni, 1998 679 Case Study	ok		ok										ok			( )
Oh, 1979 13223 Case Study			ok										ok			( )
Ohishi, 2010 14945 Case Study	ok		ok				ok	( )					ok			ok
Perapoch, 2000 12396 Case Study			ok				ok						ok			( )
Piarroux, 1999 12804 Case Study			ok									ok	ok			( )
Piechno, 2007 4488 Case Study	ok		( )				ok								( )	( )

Evidence Table C5. Quality (continued)

Author, Year	Genus, Species, and Strain reporting	Assessment Reporting	Harm Reporting	Selection Bias	Comparability	Power	Compliance	Surveillance	Randomization	Concealment	Participant Blinding:	Assessor Blinding:	Dropouts	ITT	Confounding	Conflict of Interest
Pletinex, 1995 12363 Case Study			ok				ok						ok		( )	( )
Presterl, 2001 1299 Case Study			ok										ok			( )
Rautio, 1999 12357 Case Study	ok		ok										ok			( )
Richard, 1988 12358 Case Study			ok				ok						ok			( )
Rijnders, 2000 1033 Case Study		( )	ok				ok						ok			( )
Riquelme, 2003 2094 Case Study			ok				ok						ok			( )
Tommasi, 2008 5492 Case Study			ok										ok			ok
Trautmann, 2008 11966 Case Study	ok	ok	( )				ok								( )	( )
Viggiano, 1995 12787 Case Study	ok		ok				ok								( )	( )
Zein, 2008 5583 Case Study	ok	ok	ok										ok		( )	ok
Zunic, 1991 12362 Case Study	( )	( )	( )				ok	( )					ok			ok

Note: ( ): quality criterion partially met; ok: quality criterion met

*Abbreviations

ITT=Intention to treat analysis - Was an intention to treat (ITT) analysis described for the effectiveness data? (Were all participants' data included in the analysis, according to the treatment group to which they were originally assigned, regardless of whether they completed the treatment/study?)

Evidence Table C6. Nonspecific safety statements

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Agarwal, 2002 RCT	**Genus, Species, Strain** Lactobacillus* casei DN-114001 , n/a , 10^8 cfu , t.i.d. Lactobacillus* bulgaricus n/a , n/a , 10^8 cfu , 100 ml t.i.d. Streptococcus* thermophilus n/a , n/a , 10^8 cfu , 100 ml t.i.d. Lactococcus lactis n/a , n/a , 10^8 cfu/g , 100 ml t.i.d. Lactococcus lactis cremoris , n/a , n/a , n/a Leuconostoc mesenteroids cremoris , n/a , n/a , n/a NA **Product Name** *Actimel® #Dahi	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; 1-5 yrs	**Assessment** n/a **Result Statement** All products were well accepted.
Agustina, 2007 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus LMG P-227 99 , n/a , 5*10^8 cfu , ad libitum NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No treatment failure or other side effects occurred.
Ahuja, 2001 RCT	**Genus, Species, Strain** Lactobacillus n/a n/a , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Cataract surgery patients	**Assessment** At followup evaluation a week later… emergence of any other new symptoms attributable to trial drug therapy. **Result Statement** Very well tolerated.
Alm, 1983 CT	**Genus, Species, Strain** Lactobacillus* acidophilus NCDO 1748 , n/a , 10^9 cfu/ml , ad libitum Lactobacillus# acidophilus NCDO 1748 , n/a , 10^9 cfu/ml , 200 ml q.d. Lactobacillus** acidophilus NCDO 1748 , n/a , 10^9 cfu/ml , 300 ml q.d Streptococcus** lactis n/a , n/a , 10^9 cfu/ml , 300 ml q.d. Streptococcus** cremoris n/a , n/a , 10^9 cfu/ml , 300 ml q.d Streptococcus** diacetylactis n/a , n/a , 10^9 cfu/ml , 300 ml q.d NA **Product Name** n/a	**Direct Comparison** Timing **Subgroup Analysis** n/a **Cotreatment** n/a	>65	**Assessment** n/a **Result Statement** No adverse effects on constipation.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Arrola, 1999 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , 2*10^10 cfu/capsule , 2*10^10 b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs; 2 wks-12.8 yrs	**Assessment** The parents kept a daily symptom diary. **Result Statement** Parents reported no adverse effects.
Ataie-Jafari, 2009 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , n/a , n/a Bifidobacterium lactis n/a , n/a , n/a , n/a NA **Product Name** ABY-1	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** There was a check up every week by phone to ask about compliance and side effects. **Result Statement** No adverse effects or symptoms were experienced by the subjects.
Attar, 1999 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 1500 mg /day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	small bowel bacterial overgrowth	**Assessment** Other indication taken and any side effects were also recorded. **Result Statement** n/a

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Barone, 1999 RCT	**Genus, Species, Strain** Lactobacillus* delbrueckii Bulgaricus , n/a , 3*10^8/g , n/a Lactobacillus* acidophilus n/a , n/a , 2*10^9/g , n/a Lactobacillus* plantarum n/a , n/a , 2.2*10^8/g , n/a Lactobacillus* casei n/a , n/a , 2.2*10^8/g , n/a Streptococcus* salivarius thermophilus , n/a , 2.04*10^11/g , n/a Streptococcus* faecium n/a , n/a , 3*10^7/g , n/a Bifidobacterium* longum n/a , n/a , 9.3*10^9/g , n/a Bifidobacterium (Yovis) breve n/a , n/a , 9.3*10^9cfu/g , n/a Bifidobacterium (Yovis) infantis n/a , n/a , 9.3*10^9cfu/g , n/a Lactobacillus# acidophilus n/a , n/a , 10^9/vial , n/a #Bifidobacterium bifidum n/a , n/a , 5*10^8cfu/g , n/a #Streptococcus thermophilus n/a , n/a , 10^9cfu/vial , n/a #Lactobacillus bulgaricus n/a , n/a , 10^9cfu/vial , NA **Saccharomyces boulardii n/a , n/a , 5*10^9cfu/250mg capsule , n/a **Product Name** *Yovis #Lactogermine **Codex	**Direct Comparison** Genera **Subgroup Analysis** n/a **Cotreatment** n/a	Children	**Assessment** Following items have been analyzed during the clinical courses… other associated symptoms. **Result Statement** No associated symptoms were recorded in all subjects.
Bausserman, 2005 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , 10^10 cfu , 1 capsule NA **Product Name** n/a	**Direct Comparison** Mode of administration **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Patients were withdrawn … based on … any unexpected intolerance or side effect. **Result Statement** There were no adverse effects noted with Lactobacillus GG treatment.
Bellomo, 1980 RCT	**Genus, Species, Strain** Lactobacillus* bulgaricus n/a , Lyophilized , 5*10^8cfu/unit , 1 unit b.i.d., 2 unit t.i.d. Streptococcus* lactis n/a , Lyophilized , 4*10^9cfu/unit , 1 unit b.i.d., 2 unit t.i.d. Lactobacillus* acidophilus n/a , Lyophilized , 5*10^8cfu/unit , 1 unit b.i.d., 2 unit t.i.d. Streptococcus# faecium SF68 , Lyophilized , >3.75*10^7cfu /unit , 1 unit b.i.d., 2 unit t.i.d. NA **Product Name** *n/a (control)#Bioflorin	**Direct Comparison** Genera mix **Subgroup Analysis** Age **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** No untoward side effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Benhamou, 1999 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 226 mg/day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs; antibiotic induced diarrhea	**Assessment** n/a **Result Statement** Despite rare cases of fungemia during administration of high doses of Saccharomyces boulardii, products were tolerated, as we have noted in this study.
Billoo, 2006 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , 250mg , b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a		**Assessment** The second visit information variables included … tolerance and acceptability of treatment. **Result Statement** Tolerance and acceptability of treatment were recorded in the study record forms. S. boulardii was well accepted and tolerated and there were no reports of any side effects during the study period.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Bittner, 2005 RCT	**Genus, Species, Strain** Blend including Bacillus strains n/a n/a , n/a , n/a , 1 500 mg capsule b.i.d. NA **Product Name** Prescript-Assist	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	: Irritable Bowel Syndrome	**Assessment** Data on the … symptoms collected as part of the 64-item instrument allowed basic analysis of the safety profile, in that any significant increase in a…symptom with treatment would point toward an adverse event or tolerability concern… **Result Statement** No safety/tolerability concerns emerged.
Black, 1988 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized, live , 3*10^9cfu/capsule , 1 capsule t.i.d. Bifidobacterium bifidum n/a , Lyophilized, live , 3*10^9cfu/capsule , 1 capsule t.i.d Lactobacillus bulgaricus n/a , Lyophilized, live , 3*10^9cfu/capsule , 1 capsule t.i.d. Streptococcus thermophilus n/a , Lyophilized, live , 3*10^9cfu/capsule , 1 capsule t.i.d NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse effects were recorded in any of the two groups.
Bleichner, 1997 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , Lyophilized , n/a , 500mg b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** Disease or immunologic status **Cotreatment** n/a	Immune compromised / critically ill	**Assessment** n/a **Result Statement** Tolerance of S. boulardii was good and no adverse effect was noted.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Bruno, 1983 RCT	**Genus, Species, Strain** Enterococcus faecium SF 68 , n/a , 7.5*10^7cfu/capsule , 1 capsule t.i.d. NA **Product Name** Bioflorin	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Enterocolitis	**Assessment** Patients were assessed daily, recording the presence of … possible side-effects attributable to the drugs. **Result Statement** No side effects attributable to drugs.
Bruns, 1995 RCT	**Genus, Species, Strain** Saccharomyces cerevisiae Hansen CBS 5926 , n/a , n/a , 150 mg q.i.d. NA **Product Name** Perenterol	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Undesired events were assessed and documented. **Result Statement** There were no adverse drug reactions in both groups.
Buydens, 1996 RCT	**Genus, Species, Strain** Enterococcus faecium SF 68 , n/a , 75*10^6 cfu/capsule , 2 capsules t.i.d. NA **Product Name** Bioflorin	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No side effects.
Cadieux, 2002 RCT	**Genus, Species, Strain** Lactobacillus* rhamnosus GR-1 , Lyophilized , 10^9 cfu/capsule , 1 capsule Lactobacillus fermentum RC-14 , Lyophilized , 10^9 cfu/capsule , 1 capsule /day Lactobacillus# rhamnosus GG , Lyophilized , 10^9 cfu/capsule , 1 capsule /day NA **Product Name** n/a	**Direct Comparison** Strains **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse events reported.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Caglar, 2006 RCT	**Genus, Species, Strain** Lactobacillus reuteri Acid 55730 , n/a , >10^8 cfu/straw , 1/day Lactobacillus reuteri Acid 55730 , n/a , 10^8 cfu/tablet , 1 tablet /day NA **Product Name** (1)Life top straw (BioGaia); (2) ProDenta (BioGaia)	**Direct Comparison** Delivery vehicles **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Compliance was excellent in all groups, with no drop-outs or reported side or adverse effects.
Camarri, 1981 RCT	**Genus, Species, Strain** Streptococcus faecium SF 68 , Lyophilized , >7.5*10^7 cfu/capsule , 1 capsule t.i.d. NA **Product Name** Bioflorin	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	acute enteritis	**Assessment** n/a **Result Statement** No side effects were observed with either treatment.
Can, 2006 RCT	**Genus, Species, Strain** Saccaromyces* boulardii n/a , n/a , 5*10^9 cells , 5*10^9 cells b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** No serious side effects (per abstract).
Canani, 2007 RCT	**Genus, Species, Strain** Lactobacillus* casei Rhamnosus GG , n/a , 6*10^9 cfu , b.i.d. Saccharomyces# boulardii lt , Live , 5*10^9 cfu , b.i.d. Bacillus** clausii O/C84, N/R84, T84, SIN84(mix of strains) , n/a , 10^9 cfu , b.i.d Lactobacillus## delbrueckii LMG-P17550 Bulgaricus , n/a , 10^9 cfu , b.i.d Lactobacillus## acidophilus LMG-P17549 , n/a , 10^9cfu , b.i.d Streptococcus## thermophilus LMG-P17503 , n/a , 10^9 cfu , b.i.d Bifidobacterium## bifidum LMG-P17500 , n/a , 5*10^8 cfu , b.i.d Enterococcus*** faecium SF 68 , n/a , 7.5*10^7 cfu , b.i.d NA **Product Name** *Dicoflor 60; #Codex; **Enterogermina; ##Lactogermina; ***Bioflorin	**Direct Comparison** Genera, Genera mix, Species, Strains **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; Acute Diarrhea	**Assessment** We also investigated safety and tolerability. **Result Statement** Probiotic preparations… were well received by nearly all the children and no adverse events were observed.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Carrierol, 2007 CT	**Genus, Species, Strain** Lactobacillus plantarum P17630 , n/a , 10^8 cfu/capsule , 1 capsule q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Candida vulvovaginitis	**Assessment** Tolerability and safety were evaluated by putting a non leading question to the patient to ascertain whether any adverse events had occurred; if any had occurred, additional information was to be collected, i.e. its time of onset, nature, duration, outcome, relation to treatment, severity and any action taken. **Result Statement** No adverse events worthy of note were reported.
Cetina-Sauri, 1994 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 200mg t.i.d. NA **Product Name** Ultra-Levure	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; acute diarrhea	**Assessment** On the clinical records were recorded … and possible side effects. **Result Statement** Didn't have secondary effects.
Chapoy, 1985 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 250 mg b.i.d. NA **Product Name** Ultra-Levure	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; acute diarrhea	**Assessment** n/a **Result Statement** No undesirable effect was noted and the acceptability of the treatment was excellent.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Chapoy, 1986 CT	**Genus, Species, Strain** Saccharomyces cerevisiae Hansen CBS 5926 , , n/a , 500 mg q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; diarrhea	**Assessment** n/a **Result Statement** No undesirable effects were measured.
Chen, 2010 RCT	**Genus, Species, Strain** Bacillus mesentericus TO-A , n/a , 5*10^7 cfu/mixed sachet (3*10^8 cfu total) , 2.2*10^6 cfu/kg t.i.d Enterococcus faecalis T-110 , n/a , 2*10^8 cfu/mixed sachet , 4.2*10^6 cfu/kg t.i.d Clostridium butyricum n/a , lyophilized , 5.0*10^7 cfu/mixed sachet , 2.2*10^6 cfu/kg t.i.d NA **Product Name** Bio-three	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No adverse effects were recorded.
Chitapanarux, 2010 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized , 10^9 /capsule , 2 capsules b.i.d Bifidobacterium bifidum n/a , Lyophilized , 10^9 /capsule , 2 capsules b.i.d. NA **Product Name** Infloran	**Direct Comparison** n/a **Subgroup Analysis** Disease or immunologic status **Cotreatment** n/a	Immune compromised / critically ill	**Assessment** Patients were evaluated weekly. An adverse event or adverse drug reaction was recorded in each week of treatment. **Result Statement** There were no adverse events attributable to the study drug.
Cildir, 2009 RCT	**Genus, Species, Strain** Bifidobacterium acidophilus Lactis DN 173010 , n/a , 4*10^10 , 4*10^10 q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Adolescents	**Assessment** n/a **Result Statement** No side effects or adverse effects were registered.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Cindoruk, 2007 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , 250 mg/dose , 1 dose, b.i.d. NA **Product Name** Reflor	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** No major side effects leading to treatment discontinuation were observed.
Cohen, 2007 RCT	**Genus, Species, Strain** Lactobacillus GG n/a , n/a , 2x10^10 organisms / capsule , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** There were no significant adverse events recorded.
Costalos, 2003 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 10^9 cfu/kg body weight b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Preterm	**Assessment** n/a **Result Statement** Drug is well tolerated by the infants and caused no side effects.
Cremonini, 2002 RCT	**Genus, Species, Strain** Lactobacillus* casei subsp. Rhamnosus GG , n/a , 6*10^9 cfu/sachet , 1 sachet b.i.d. Saccharomyces# boulardii n/a , n/a , 5*10^9 cfu/sachet , 1 sachet b.i.d. Lactobacillus** acidophilus n/a , n/a , 5*10^9 cfu/capsule (in sachet) , 1 capsule b.i.d. Bifidobacterium** lactis n/a , n/a , n/a , 5*10^9 cfu b.i.d. NA **Product Name** *Giflorex; #Codex; **Ferzyme	**Direct Comparison** Genera, Genera mix **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Hylicobacter pylori infection	**Assessment** n/a **Result Statement** No major side effects leading to treatment discontinuation were observed.
D'Apuzzo, 1982 CT	**Genus, Species, Strain** Streptococcus faecium SF-68 , Lyophilized , 7.5*10^7 cfu , t.i.d. NA **Product Name** Bioflorin	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; 2-144 mos old	**Assessment** n/a **Result Statement** No adverse effects were noticed in either patient group.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
De Francesco, 2000 CT	**Genus, Species, Strain** Lactobacillus acidophilus LB , Spent culture supernatant , Equivalent to 10^10 cfu/0.8 g , 0.8g b.i.d. NA **Product Name** LB-SCS	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Helicobacter pylori	**Assessment** Patients were specifically questioned concerning side-effects during therapy. **Result Statement** No severe side effects were reported.
Delforge, 1983 RCT	**Genus, Species, Strain** Saccharomyces cerevisiae Hansen CBS 5926 , n/a , n/a , 3 capsules t.i.d. NA **Product Name** Perenterol	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** n/a **Result Statement** No sign of intolerance was recorded during this trial.
Delia, 2006 RCT	**Genus, Species, Strain** Lactobacillus* acidophilus n/a , n/a , n/a , n/a Lactobacillus# paracasei paracasei F19 , n/a , n/a , n/a NA **Product Name** *Calagin; #Genefilus	**Direct Comparison** Species **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** All patients tolerated the treatment well, and there was not a single dropout.
Delia, 2003 CT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , 3.00*10^6cfu mixture/gm , n/a Lactobacillus casei n/a , n/a , n/a , Lactobacillus delbrueckii bulgaricus , n/a , n/a , Lactobacillus plantarum n/a , n/a , n/a , Bifidobacterium longum n/a , n/a , n/a , Bifidobacterium infantis n/a , n/a , n/a , Bifidobacterium breve n/a , n/a , n/a , Streptococcus salivarius thermophilus , n/a , n/a , Streptococcus faecium n/a , n/a , n/a , NA **Product Name** Yovis	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Radiapy	**Assessment** n/a **Result Statement** Well-tolerated (3 patients excluded due to intolerance of the taste of Yovis).

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
DePaula, 2008 RCT	**Genus, Species, Strain** Bifidobacterium animalis DN 173010 , n/a , 10^8 cfu/gm , 116 gm b.i.d. Lactobacillus bulgaricus n/a , n/a , 10^7cfu/gm , 116 gm b.i.d. Streptococcus thermophilus n/a , n/a , 10^7 cfu/gm , 116 gm b.i.d. NA **Product Name** Activia	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	constipation	**Assessment** … instructed to withdraw due to intolerance **Result Statement** No adverse effects were seen related to either intervention.
deVrese, 2005 RCT	**Genus, Species, Strain** Lactobacillus gasseri PA 16/8 , Viable , 5*10^7 cfu/tablet , q.d. Bifidobacterium longum SP 07/3 , Viable , 5*10^7 cfu/tablet , q.d. Bifidobacterium bifidum MF 20/5 , Viable , 5*10^7 cfu/tablet , q.d. NA **Product Name** Tribion harmonis	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	n/a	**Assessment** n/a **Result Statement** No report of adverse events.
Diop, 2008 RCT	**Genus, Species, Strain** Lactobacillus acidophilus Rosell-52 , n/a , 3*10^9 cfu , 3*10^9 cfu q.d. Bifidobacterium longum Rosell-175 , n/a , 3*10^9 cfu/day , 3*10^9 cfu q.d. NA **Product Name** Probio-stick	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse reactions were reported during the study. The product was safe and well tolerated.
Falcao, 2004 RCT	**Genus, Species, Strain** Lactobacillus johnsonii La1 , n/a , n/a , n/a NA **Product Name** Nestle LC1	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	Immune compromised / critically ill	**Assessment** n/a **Result Statement** No complications

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Fanigliulo, 2006 RCT	**Genus, Species, Strain** Bifidobacterium longum W 11 , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** Patients who developed complications or side effects, recorded by means of a structured clinical interview during each clinical evaluation or whenever necessary, were withdrawn from the study. **Result Statement** n/a
Fisberg, 2002 RCT	**Genus, Species, Strain** Lactobacillus casei n/a , n/a , 3*10^7 cfu/g , 375-750 ml/daily Bifidobacterium n/a n/a , n/a , 3*10^7 cfu/g , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Adverse events were monitored throughout the study. **Result Statement** Both study findings were well tolerated and the overall incidence of adverse events were very low. None of the serious adverse events were considered study related.
Francavilla, 2008 RCT	**Genus, Species, Strain** Lactobacillus reuteri ATCC 55730 , Lyophilized , 1*10^8 cfu/tablet , 1 tablet q.d. NA **Product Name** Reuterin	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Helicobacter pylori	**Assessment** n/a **Result Statement** No adverse events were reported.
Fukushima, 2007 RCT	**Genus, Species, Strain** Lactobacillus johnsonii La 1 NCC 533 , n/a , 10^9 cfu/90g , 90g q.d. NA **Product Name** LC1	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	>65	**Assessment** n/a **Result Statement** Accepted well; no adverse health conditions were observed.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Furrie, 2005 RCT	**Genus, Species, Strain** Bifidobacterium longum n/a , Lyophilized, viable , 2*10^11 cfu b.i.d. , 2x/d for 4 weeks NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Ulcerative colitis	**Assessment** n/a **Result Statement** No reports of adverse reactions.
Gaon, 2002 RCT	**Genus, Species, Strain** Lactobacillus casei n/a , Lyophilized, viable , n/a , 1.5g b.i.d. Lactobacillus acidophilus n/a , Lyophilized, viable , n/a , 1.5g b.i.d. NA **Product Name** CERELA	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** …and any side effects were also recorded (by the patients). **Result Statement** No side effects.
Gaon, 2003 RCT	**Genus, Species, Strain** Lactobacillus* acidophilus CRL 730 , Lyophilized , 10^10-10^12 cfu/g , 175g b.i.d. Lactobacillus (cerela)* casei CRL 431 , Lyophilized , 10^10-10^12 cfu/g , 175g b.i.d. Saccharomyces# boulardii n/a , Lyophilized , 10^10 cfu/g , 175g b.i.d. NA **Product Name** *CERELA; #n/a	**Direct Comparison** Genera mix **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No treatment failures, neither appearance of symptoms possibly related to treatment.
Gawronska, 2007 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , n/a , 3*10^9 cfu b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** All patients received a diary to record … any symptoms they considered important. **Result Statement** Well tolerated; no adverse effects were reported.
Giralt, 2008 RCT	**Genus, Species, Strain** Lactobacillus casei DN-114 001 , n/a , 1*10^cfu/g , 96 ml, t.i.d. Streptococcus thermophilus n/a , n/a , n/a , Lactobacillus delbrueckii bulgaricus n/a , n/a , n/a , NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Cancer, receiving radiation	**Assessment** n/a **Result Statement** The study product was well tolerated and none of the adverse events reported were considered related.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Girola, 1995 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized, live , n/a , 10^9 cfu q.d. in the AM Lactobacillus bulgaricus n/a , Lyophilized, live , n/a , 10^9 cfu q.d. in the AM Lactobacillus lactis n/a , Lyophilized, live , n/a , 10^9 cfu q.d. in the AM Saccharomyces cerevisiae n/a , Lyophilized, live , n/a , 10^9 cfu q.d. PM NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** During the study no side effect was observed that could be associated (or attributed) to the two treatments.
Gosselink, 2003 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , Live , n/a , 1.4*10^10 cfu q.d. NA **Product Name** Vifit ®	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Ulcerative Colitis	**Assessment** n/a **Result Statement** None of the patients had complaints that were possibly connected with the intake of Lactobacillus rhamnosus.
Grigoriev, 1997 RCT	**Genus, Species, Strain** Bifidobacterium n/a n/a , Lyophilized , n/a , 10^6-10^8 cfu Bifidobacterium n/a n/a , n/a , n/a , NA **Product Name** Bifidumbacterin forte	**Direct Comparison** Genera **Subgroup Analysis** Age, Disease or immunologic status **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** ADR were not observed, no there were no treatment discontinuations.
Grudyanov, 2002 CT	**Genus, Species, Strain** Bifidobacterium bifidum n/a , n/a , n/a , Varies by patients Lactobacillus acidophilus n/a , n/a , n/a , Varies by patients NA **Product Name** n/a	**Direct Comparison** Genera **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** The probiotics are well tolerated and no side effects, no contraindications.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Guandalini, 2010 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets/d) Lactobacillus casei n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets/day) Lactobacillus bulgaricus n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets /day) Lactobacillus plantarum n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets/d) Bifidobacterium longum n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets/d) Bifidobacterium infantis n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets /day) Bifidobacterium breve n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets /day) Streptococcus salivarius thermophilus n/a , Lyophilized, live , 4.5*10^11 bacteria /sachet , varies by age (1-2 sachets /day) NA **Product Name** VSL#3	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Data were recorded in a daily questionnaire/dairy. **Result Statement** No adverse event was reported in any of the participating patients throughout the duration of the study.
Guandalini, 2000 RCT	**Genus, Species, Strain** Lactobacillus casei GG ATCC 53103 , Live , 10^10 cfu/250ml , Single dose NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	<2yrs	**Assessment** n/a **Result Statement** Can be safely administered.
Guslandi, 2000 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 500 mg b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Crohn's Disease	**Assessment** n/a **Result Statement** All patients completed the study without reporting any side effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Guyonnet, 2009 RCT	**Genus, Species, Strain** Bifidobacterium lactis DN-173 , n/a , 1.25*10^10 cfu/125 g , 125g b.i.d Streptococcus thermophilus I-1630 , n/a , 1.2*10^9 cfu/125g , 125g b.i.d. Lactobacillus bulgaricus I-1632, I-1519 , n/a , 1.2*10^9 cfu/125g , 125g b.i.d. Lactobacillus cremoris CMI-1631 , n/a , 1.25*10^9 cfu/125g , 125g b.i.d. NA **Product Name** Activia ®	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** These data, taken together with previous data obtained on GI transit and in IBS, suggest that this specific probiotic food may represent a promising nutritional and safe solution for the management of GI symptoms.
Guyonnet, 2007 RCT	**Genus, Species, Strain** Bifidobacterium animalis DN-173010 , n/a , 1.25*10^10 cfu/pot , b.i.d. Streptococcus thermophilus n/a , n/a , 1.25*10^9 cfu/pot , b.i.d. Lactobacillus bulgaricus n/a , n/a , 1.25*10^9 cfu/pot , b.i.d. NA **Product Name** Activia	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	adu<s with irritable bowel syndrome (IBS)	**Assessment** Subjects recorded daily in their diary… as well as any adverse events. **Result Statement** Ten subjects from the control group and 13 from the test product group reported minor adverse events throughout the study. Four subjects in the control group and three in the test group stopped the consumption of the product after an adverse event. Two subjects reported serious adverse events in the control group.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Hafeez, 2002 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , Lyophilized , 250 mg b.i.d. , twice daily for 6 days NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	2-5 yrs	**Assessment** n/a **Result Statement** The drug was accepted well...and there were no reported side effects in this study population.
Hatakka, 2001 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG ATCC 53103 , n/a , 5-10 *10^5 cfu/ml , t.i.d. to achieve 200 ml daily NA **Product Name** Gefilus	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; Children 1-6 yrs	**Assessment** n/a **Result Statement** No apparent side effects.
Hatakka, 2003 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG ATCC 53103 , n/a , ?5*10^9 cfu/capsule , 2 b.i.d. NA **Product Name** Gefilus	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Mild RA	**Assessment** n/a **Result Statement** No clinical relevant adverse effects were seen.
Hatakka, 2007 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG ATCC 53103 , n/a , 8-9*10^9 cfu/capsule , 1 q.d. Lactobacillus rhamnosus LC 705 , n/a , 8-9*10^9 cfu/capsule , 1 q.d. Bifidobacterium breve 99 , n/a , 8-9*10^9 cfu/capsule , 1 q.d. Propionibacterium freudenreichii shermanii JS , n/a , 8-9*10^9 cfu/capsule , 1 q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** Age **Cotreatment** n/a	<2yrs	**Assessment** Reasons for dropout … adverse effects. **Result Statement** n=1 dropout due to adverse effects in probiotics group, n=0 in placebo group.
Hickson, 2007 RCT	**Genus, Species, Strain** Lactobacillus casei immunitas DN 114-001 , n/a , 10^8 cfu/ml , b.i.d. Streptococcus thermophilus n/a , n/a , 10^8 cfu/ml , b.i.d. Lactobacillus delbrueckii Bulgaricus , n/a , 10^7 cfu/ml , b.i.d. NA **Product Name** Actimel ®	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Hospitalized Patients	**Assessment** n/a **Result Statement** No reported adverse events related to the study drinks.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Hojsak, 2010 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , 10^9 cfu/100 ml , 100ml/day NA **Product Name** LGG	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Patients were checked every day by pediatrician. **Result Statement** No adverse effects were noted during study and both products were well tolerated.
Hojsak, 2010 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , 10^9 cfu/100 ml , 100c ml q.d. NA **Product Name** LGG (Dukat)	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** Every 10 days, investigators contacted parents to find out whether their children had developed any … side effects. **Result Statement** No side effects of adverse effects were noted during the study.
Hol, 2008 RCT	**Genus, Species, Strain** Lactobacillus casei CRL431 paracasei , n/a , 10^7 cfu/gr formula , n/a Bifidobacterium animalis lactis Bb-12 , n/a , 10^7 cfu/gr formula , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics, Corticosteroid use	<2yrs	**Assessment** Structure interviews… adverse events…were performed. **Result Statement** The study formula with or without the probiotic supplementation was well tolerated.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Hoyos, 1999 CT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Live , 10^9 cfu/capsule , 1/4 capsule q.d. Bifidobacterium infantis n/a , Live , 10^9 cfu/capsule , 1/4 capsule q.d. NA **Product Name** Infloran Berna 7	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; Immune compromised / critically ill	**Assessment** n/a **Result Statement** No complications attributed to the use of the probiotic preparation were observed.
Htwe, 2008 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , Active , n/a , 250 mg b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; 2-10 yrs	**Assessment** n/a **Result Statement** No severe side effects were observed during the trial.
Hun, 2009 RCT	**Genus, Species, Strain** Bacillus coagulans GBI-30, 6086 , n/a , 8*10^8 cfu/dose , 1 dose q.d. NA **Product Name** GanedenBC	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>65	**Assessment** Add adverse events were reported … event duration, severity and causal relationship to the study drug were recorded. **Result Statement** There were 4 adverse events reported in the placebo groups and 2 in the study group, all of which were unrelated to the treatments. No treatment related adverse events or serious adverse events were reported during the 8-week study period.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Hun, 2009 RCT	**Genus, Species, Strain** Bacillus coagulans GB1-30 6086 , n/a , n/a , q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** All adverse events were reported regardless of whether they were related to the study drug. Event duration, severity, and causal relationship to the study drug were recorded. **Result Statement** No treatment related or serious adverse events were reported.
Indrio, 2009 RCT	**Genus, Species, Strain** Lactobacillus reuteri n/a , n/a , 10^8 cfu/dose , 1 dose q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** Adverse events were recorded throughout they study as they occurred. **Result Statement** No adverse events were reported.
Indrio, 2008 RCT	**Genus, Species, Strain** Lactobacillus reuteri ATCC 55730 , n/a , 10^8 cfu , q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; Preterm	**Assessment** n/a **Result Statement** No adverse events were reported related to the trial.
Jasinski, 2002 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG ATCC 53103 , Viable , 1*10^9 cfu , Varies NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** Well tolerated.
Kalliomaki, 2003 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG ATCC 53103 , n/a , 10^10 cfu , q.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Pregnant women	**Assessment** n/a **Result Statement** Was promising and safe.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Kalman, 2009 RCT	**Genus, Species, Strain** Bacillus coagulans GBI-30,6086 , n/a , 2*10^9 cfu/capsule , 1 capsule, q.d. NA **Product Name** GanedenBC	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** The Bacillus coagulans based probiotic product was effective and safe for abating symptoms of GSRS abdominal pain and distention pain in the post-prandial period.
Kaplas, 2007 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG (ATCC 53103) , n/a , 10^9 cfu/dose , 1 dose q.d. Bifidobacterium lactis Bb12 , n/a , 10^9 cfu/dose , 1 dose q.d. NA **Product Name** n/a	**Direct Comparison** Genera **Subgroup Analysis** n/a **Cotreatment** Diet therapies	n/a	**Assessment** n/a **Result Statement** The pregnancies were uncomplicated and all infants were delivered at term.
Katelaris, 1995 RCT	**Genus, Species, Strain** Lactobacillus fermentum KLD , n/a , 10^11 cfu/capsule , 2 capsules q.d. Lactobacillus acidophilus n/a , n/a , 10^11 cfu/capsule , 2 capsules q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse effects were reported.
Kato, 2004 RCT	**Genus, Species, Strain** Lactobacillus acidophilus Yakult , Live , 10^10 cfu/100 ml , 100 ml q.d. Bifidobacterium breve Yakult , Live , 10^10 cfu/100 ml , 100ml q.d. Bifidobacterium bifidum Yakult , Live , 10^10 cfu/100 ml , 100ml q.d. NA **Product Name** Yakult BFM	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Ulcerative Colitis	**Assessment** n/a **Result Statement** Well tolerated; …no subjects reported adverse events that might have been related to BFM.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Kawase, 2009 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG(ATCC53103) , n/a , >2*10^10 cfu/2g , 2g q.d. Lactobacillus gasseri TMC0356 , n/a , >1*10^9 cfu/2g , 2 g/day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** None of the 35 subjects showed any disorder related to the ingestion of LGG and TMC 0356 during the trial period.
Kim, 2010 RCT	**Genus, Species, Strain** Bifidobacterium bifidum BGN4 , n/a , 1.6*10^9 cfu/dose , 1 dose q.d. Bifidobacterium lactis AD011 , n/a , 1.6*10^9 cfu/dose , 1/day Lactobacillus acidophilus AD031 , n/a , 1.6*10^9 cfu , 1 /day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs	**Assessment** The parents were asked to report any adverse effects whenever they happen. **Result Statement** No serious adverse effects developed and although non-specific mild symptoms developed, these were unlikely to have been related to the administration of probiotics.
Kim, 2005 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized , 4.5*10^11 cfu mixture/sachet , 1 sachet b.i.d. Bifidobacterium infantis n/a , Lyophilized , n/a , Bifidobacterium breve n/a , Lyophilized , n/a , Bifidobacterium longum n/a , Lyophilized , n/a , Lactobacillus casei n/a , Lyophilized , n/a , Lactobacillus delbrueckii Bulgaricus , Lyophilized , n/a , Lactobacillus plantarum n/a , Lyophilized , n/a , Streptococcus salivarius thermophilus , Lyophilized , n/a , NA **Product Name** VSL#3	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** n/a **Result Statement** There were no adverse effects attributable to treatment with either VSL#3 or placebo.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Kim, 2003 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized , 2.25*10^11 cfu mixture/packet , 1 packet b.i.d. Lactobacillus casei n/a , Lyophilized , n/a , Lactobacillus delbrueckii Bulgaricus , Lyophilized , n/a , Lactobacillus plantarum n/a , Lyophilized , n/a , Bifidobacterium longum n/a , Lyophilized , n/a , Bifidobacterium infantis n/a , Lyophilized , n/a , Bifidobacterium breve n/a , Lyophilized , n/a , Streptococcus (VSL#3) salivarius thermophilus , Lyophilized , n/a , NA **Product Name** VSL#3	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Imtable Bowel	**Assessment** n/a **Result Statement** No adverse events noted.
Kim, 2006 RCT	**Genus, Species, Strain** Bacillus subtilis n/a , n/a , n/a , 1*10^9 cfu Streptococcus faecium n/a , n/a , n/a , 9*10^9 cfu NA **Product Name** Medilac DS	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** n/a **Result Statement** Medilac DS was well tolerated without adverse events... a safe and useful probiotic agent.
Klarin, 2008 CT	**Genus, Species, Strain** Lactobacillus plantarum LP 299V , n/a , 8*10^8 cfu/ml , 100 ml b.i.d., then 50 ml b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics, Corticosteroid use, Diet therapies	Immune compromised / critically ill	**Assessment** n/a **Result Statement** No adverse impact of the given probiotic preparations; well tolerated.
Koebnick, 2003 CT	**Genus, Species, Strain** Lactobacillus casei Shirota , n/a , 10^8 cfu/ml , 65 ml q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	18-70 yrs; Chronic Constipation	**Assessment** Patients were asked weekly for product tolerability during the intervention phase. **Result Statement** No side effects were reported.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Kollaritsch, 1993 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 250mg q.d. Saccharomyces boulardii n/a , n/a , n/a , 1000mg q.d. NA **Product Name** Perenterol	**Direct Comparison** Dose **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** A questionnaire… recorded undesirable side effects. **Result Statement** Serious side effects or complaints were not reported.
Kollaritsch, 1989 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , 2*10^8 - 2*10^9 cfu b.i.d. , 2 per day, duration varies NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Prophylaxis of traveller's diarrhea	**Assessment** Side effect due to prophylaxis had to be listed and commented. **Result Statement** n/a
Koning, 2010 RCT	**Genus, Species, Strain** Bifidobacterium bifidum NIZO 3804 , n/a , 10^8 cfu/g , 5g b.i.d Bifidobacterium lactis NIZO 3680 , n/a , 10^8 cfu/g , 5g b.i.d. Enterococcus faecium NIZO 3886 , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus rhamnosus NIZO 3689 , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus paracasei NIZO 3672 , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus plantarum NIZO 3684 , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus acidophilus NIZO 3678 , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus acidophilus NIZO 3887 , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus salivarius NIZO 3675 , n/a , 10^8 cfu/g , 5g b.i.d NA **Product Name** Ecologic AAD	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** There were no reported adverse events related to the study product.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Kontiokari, 2001 RCT	**Genus, Species, Strain** Lactobacillus casei GG , n/a , 4*10^10 cfu/100 ml , 50 ml b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse events were reported except occasional complaints about the bitter taste of the cranberry juice.
Kotowska, 2005 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 250 mg b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs; antibiotic associated diarrhea	**Assessment** The secondary outcomes were…and adverse events. **Result Statement** Well tolerated and no adverse events associated with this therapy were reported.
Kowalska, 2002 RCT	**Genus, Species, Strain** Bifidobacterium ruminatium n/a , n/a , 10^9 cfu b.i.d. , twice daily for 5 days NA **Product Name** Lactobif	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	<2yrs	**Assessment** n/a **Result Statement** No adverse reactions were reported.
Kowalska Duplaga, 2005 RCT	**Genus, Species, Strain** lactobacillus acidophilus n/a , Active , n/a , 1.6*10^9 cfu b.i.d. Lactbacillus bulgaricus n/a , Active , n/a , 1.6*10^9 cfu b.i.d. Bifidobacterium bifidum n/a , Active , n/a , 1.6*10^9 cfu b.i.d. NA **Product Name** Trilac	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Acute diarrhea	**Assessment** Investigation of … and safety. **Result Statement** No adverse effects of the treatment were noted.
Kuisma, 2003 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , 0.5-1*10^10 cfu/capsule , 1 capsule q.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Ulcerative Colitis patients; who underwent protocolectomy	**Assessment** n/a **Result Statement** well tolerated and none of the patients was withdrawn because of side effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Laake, 1999 RCT	**Genus, Species, Strain** Lactobacillus* acidophilus La-5 , Live , >10^8 cfu/ml , 500 ml q.d. Bifidobacterium* lactis Bb-12 , Live , >10^8cfu/ml , 500 ml q.d. Lactobacillus# acidophilus La-5 , Heat-treated , Bifidobacterium# lactis Bb-12 , Heat-treated , NA **Product Name** *Cultura, #heat-treated Cultura	**Direct Comparison** Forms **Subgroup Analysis** n/a **Cotreatment** n/a	Ulcerative colitis	**Assessment** … and adverse events were recorded by the patients during the study on a daily basis in a diary card. **Result Statement** No adverse effects were recorded.
Lara, 2007 CT	**Genus, Species, Strain** Lactobacillus bulgaricus Delbrueckii , n/a , 2*10^7 cfu/ml , 200 ml q.d. Streptococcus thermophilus n/a , n/a , 5*10^5 cfu/ml , 200 ml q.d. Streptococcus# thermophilus n/a , n/a , 5*10^5 cfu/ml , 80 ml q.d. Lactobacillus# coryniformis CECT 5711 , n/a , 1.8*10^7 cfu/gm , 80 ml q.d. Lactobacillus# gasseri CECT 5714 , n/a , 0.2*10^7 cfu/g , 80 ml q.d. NA **Product Name** Puleva Max defensas	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Well tolerated; No adverse effects.
Larustovskaia, 2008 CT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , n/a , n/a Bifidobacterium longum n/a , n/a , n/a , n/a Bifidobacterium bifidum n/a , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	chronic non-specific Salpingo-oophoritis and colon disbacteriosis	**Assessment** n/a **Result Statement** Good tolerability by all treatment group patients.
Lewis, 1998 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 113 mg b.i.d. NA **Product Name** Ultra-Levure	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	>65	**Assessment** Subjects were seen daily…to monitor for side effects. **Result Statement** No side effects attributable to S. boulardii were observed.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Leyer, 2009 RCT	**Genus, Species, Strain** Lactobacillus acidophilus NCFM (ATCC 700396) , n/a , 5*10^9 cfu/g , 1g, b.i.d. Lactobacillus acidophilus NCFM , n/a , 5*10^9 cfu/g , 0.5g, b.i.d. Bifidobacterium animalis lactis Bi-07 (ATCC PTA-4802) , n/a , 5*10^9 cfu/g , 0.5g, b.i.d. NA **Product Name** n/a	**Direct Comparison** Genera mix **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** No notable adverse events were attributed to study probiotic strains.
Ligny, 1976 RCT	**Genus, Species, Strain** Saccharomyces hansen CBS 5926 , n/a , n/a , 3-4 capsules q.d. NA **Product Name** Perenterol	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	side-effect of antibiotics	**Assessment** n/a **Result Statement** In both studies the safety...was complete. Its tolerance was very good and we found no contraindication.
Lionetti, 2006 RCT	**Genus, Species, Strain** Lactobacillus reuteri ATCC 55 730 , Lyophilized , 10^8 cfu/pill , 1 pill q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** No adverse events were reported.
Luyer, 2010 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , 26 mg/100ml , 200+/-50 mg/day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	<2yrs	**Assessment** n/a **Result Statement** No undesirable occurrence was experienced.
Marcone, 2008 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus n/a , Lyophilized , 4*10^4 cfu/tablet , 1 tablet once a wk NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Bacterial Vaginosis	**Assessment** n/a **Result Statement** ...safe.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Marschan, 2008 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG ATCC 53103 , n/a , 5*10^9 cfu/capsule , 1 capsule b.i.d. to mothers, q.d. to infants Bifidobacterium breve Bb99 , n/a , 2*10^8 cfu/capsule , 1 capsule b.i.d. to mothers, q.d. to infants Lactobacillus rhamnosus LC 705 , n/a , 5*10^9 cfu/capsule , 1 capsule b.i.d. to mothers, q.d. to infants Propionibacterium freudenreichii shermanii JS , n/a , 2*10^9 cfu/capsule , 1 capsule b.i.d. to mothers, q.d. to infants NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No major side effects were observed.
Mastromarino, 2008 RCT	**Genus, Species, Strain** Lactobacillus brevis CD2 , Viable , 10^9 , 1 tablet daily Lactobacillus salivarius salicinius FV2 , n/a , 10^9 cfu mixture /tablet , n/a Lactobacillus plantarum FV9 , n/a , 10^9 , n/a NA **Product Name** Florisia	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a		**Assessment** At each follow up visit, patients were requested to report any unexpected symptom. **Result Statement** The tablets caused no detectable side effects.
Maupas, 1983 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 1 capsule, t.i.d. NA **Product Name** Ultra-Levure	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Colitis, irritable colon	**Assessment** n/a **Result Statement** No sign of intolerance was observed in the course of the study.
Mihatsch, 2004 RCT	**Genus, Species, Strain** Bifidobacterium lactis Hansen , n/a , n/a , 6*10^9 cfu/kg/day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs - premature	**Assessment** n/a **Result Statement** Appeared to be safe.
Miniello, 2010 RCT	**Genus, Species, Strain** Lactobacillus reuteri ATCC 55730 , Viable , 10^8 cfu/tablet , 1 tablet q.d. NA **Product Name** Nóos, BioGaia AB	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Active probiotic treatment or placebo was well accepted by the patients.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Mitra, 1990 RCT	**Genus, Species, Strain** Streptococcus faecium SF 68 , Live , 10^8 cfu/capsule , 1 capsule t.i.d. NA **Product Name** Bioflorin	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Adu<s with acute diarrhea	**Assessment** n/a **Result Statement** Well tolerated; no unpleasant effects.
Mohan, 2006 RCT	**Genus, Species, Strain** Bifidobacterium lactis Bb12 , n/a , n/a , 5*10^9 cfu NA **Product Name** Nestle FM 2000A	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2 years; Immune compromised / critically ill	**Assessment** Routine clinical data were collected for all infants and their mothers. **Result Statement** No adverse effect was observed in any of the infants supplemented with Bifidobacterium lactis Bb12.
Montalto, 2010 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. Lactobacillus casei n/a , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. Lactobacillus plantarum n/a , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. Lactobacillus bulgaricus n/a , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. Bifidobacterium longuum n/a , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. Bifidobacterium breve n/a , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. Bifidobacterium infantis n/a , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. Streptococcus salivarius thermophilus , Lyophilized , 9*10^11 bacteria/sachet (4.4g) , 1 sachet q.d. NA **Product Name** VSL #3	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** A safety assessment was performed on documentation of any adverse events that occurred during the study period. **Result Statement** No adverse events were reported during dosing with both regimens.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Morosova, 1996 CT	**Genus, Species, Strain** Streptococcus salivarius n/a , n/a , n/a , n/a Streptococcus sanguis n/a , n/a , n/a , n/a Lactobacillus acidophilus n/a , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	peridontitis	**Assessment** n/a **Result Statement** The developed treatment therapy...has no negative side effects and was positively evaluated by patients.
Myllyluoma, 2007 CT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , n/a , 2.5*10^9 cfu q.d. Lactobacillus rhamnosus LC705 , n/a , n/a , 2.5*10^9 cfu q.d. Propionibacterium freudenreichii Shermanii JS , n/a , n/a , 2.5*10^9 cfu q.d. Bifidobacterium lactis Bb12 , n/a , n/a , 2.5*10^9 cfu q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Helicobacter infection	**Assessment** n/a **Result Statement** No adverse events were reported during ingestion of the probiotic combination drink.
Narayanappa, 2008 RCT	**Genus, Species, Strain** Streptococcus faecalis T-110 , Live , 3*10^7 cfu/sachet , 1 sachet t.i.d. Clostridium butyricum TO-A , Live , 2*10^6 cfu/sachet , 1 sachet t.i.d. Bacillus mesentericus TO-A , Live , 10^6 cfu/sachet , 1 sachet t.i.d. Lactobacillus sporogenes 1 sachet t.i.d. up to 14 days , Live , 5*10^7 cfu/sachet , 1 sachet t.i.d. NA **Product Name** Bifilac	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	<2yrs; 3mos-3yrs acute viral diarrhea	**Assessment** n/a **Result Statement** None of the patients had any adverse events.
Naruszewicz, 2002 RCT	**Genus, Species, Strain** Lactobacillus plantarum 299v , n/a , 5*10^7 cfu/ml , 400ml q.d. NA **Product Name** ProViva	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Smokers	**Assessment** n/a **Result Statement** Well accepted; no adverse effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Niedzielin, 2001 RCT	**Genus, Species, Strain** Lactobacillus plantarum 299V , n/a , 5*10^7 cfu/ml , 200ml b.i.d. NA **Product Name** ProViva	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** n/a **Result Statement** No treatment related side effects were observed.
Noback, 2000 RCT	**Genus, Species, Strain** Lactobacillus plantarum DSM 9843 strain 299v , n/a , 5*10^7 cfu/400ml , 400ml q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** n/a **Result Statement** All patients tolerated the products well, and no adverse events were reported during the period of intake.
Oksanen, 1990 RCT	**Genus, Species, Strain** Lactobacillus casei GG , Lyophilized , 10^9 cfu/sachet , 1 sachet b.i.d. NA **Product Name** LGG	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	10-80 yrs	**Assessment** n/a **Result Statement** No side effects related to Lactobacillus GG were observed.
Olivares, 2007 RCT	**Genus, Species, Strain** Lactobacillus fermentum CECT5716 , n/a , 10^10 cfu/capsule , 1 capsule q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Capsules were well-tolerated…and none reported any adverse effect.
O'Sullivan, 2000 RCT	**Genus, Species, Strain** Lactobacillus casei GG , Lyophilized , 2.5*10^9 cfu/tablet , 2 tablets b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** n/a **Result Statement** No patient developed a serious illness or events.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Ouwhand, 2008 RCT	**Genus, Species, Strain** Lactobacillus acidophilus NCFM , n/a , 2*10^9 cfu /gm, 5-5.5gm/sachet , 1 sachet b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>65	**Assessment** Subjects recorded in a study dairy… health status. **Result Statement** No significant differences in side effects were observed between the two groups.
Ozkan, 2007 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 250 mg, b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No adverse reaction related to S. boulardii therapy was observed during the study.
Pantoflickova, 2003 RCT	**Genus, Species, Strain** Lactobacillus johnsonii Lj 1 , Live , 10^6-10^7 cfu/gm , 125 gm b.i.d. then q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Helicobacter pylori. Gastritis	**Assessment** Adverse events… were recorded during the whole study. **Result Statement** No serious adverse events were reported.
Pedone, 2000 RCT	**Genus, Species, Strain** Lactobacillus*# bulgaricus n/a , n/a , >10^7 cfu/ml , twice daily for 5 days a week Streptococcus*# thermophilus n/a , n/a , >10^7 cfu/ml , n/a Lactobacillus# casei DN-114 001 , n/a , 3.2*10^8 cfu/ml , b.i.d. 5 days a week NA **Product Name** *n/a, #Actimel	**Direct Comparison** Delivery vehicles **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** Nursing assistants recorded daily … product tolerance. **Result Statement** The acceptability of the products was found to be good.
Peng, 2005 RCT	**Genus, Species, Strain** Lactobacillus paracasei LP33 , Live , 5*10^9cfu/capsule , b.i.d. Lactobacillus paracasei LP33 , Heat-killed , 5*10^9 cfu/capsule , b.i.d. NA **Product Name** n/a	**Direct Comparison** Forms **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No participants left the trial prematurely due to adverse effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Pereg, 2004 RCT	**Genus, Species, Strain** Lactobacillus casei DN-114 001 , n/a , 10^8 cfu/ml , 100 ml q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse effects were reported.
Piano, 2010 RCT	**Genus, Species, Strain** Lactobacillus (group A) plantarum LP01 (LMG P-21021) , Viable , 5*10^9 cfu/sachet , 1 sachet q.d. Bifidobacterium(group A) breve BR03 (DSM 16604) , Viable , 5*10^9 cfu/sachet , 1 sachet q.d. Lactobacillus (group B) plantarum LP01 , Viable , 1*10^9 cfu/sachet , 1 sachet q.d. Bifidobacterium (group B) breve BR03 , Viable , 1*10^9 cfu/sachet , 1 sachet q.d. NA **Product Name** n/a	**Direct Comparison** Delivery vehicles, Dose **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse events were reported.
Pirotta, 2004 RCT	**Genus, Species, Strain** Lactobacillus* rhamnosus n/a , n/a , n/a , n/a Bifidobacterium* longum n/a , n/a , n/a , Lactobacillus# rhamnosus n/a , n/a , n/a , Lactobacillus# delbrueckii n/a , n/a , n/a , Lactobacillus# acidophilus n/a , n/a , n/a , Streptococcus# thermophilus n/a , n/a , n/a , NA **Product Name** *Lactobac (oral), #Femilac (vaginal)	**Direct Comparison** Delivery vehicles **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Non pregnant women 18-50 yrs	**Assessment** Reasons for withdrawal… **Result Statement** One participant in the oral Lactobacillus and vaginal placebo group withdrew due to side effects.
Pitkala, 2007 RCT	**Genus, Species, Strain** Bifidobacterium* longum 46 and 2C , Viable , 10^9 cfu , q.d. Bifidobacterium# lactis Bb12 , Viable , 10^9 cfu , q.d. NA **Product Name** *n/a, #Yosa	**Direct Comparison** Species **Subgroup Analysis** Disease or immunologic status **Cotreatment** n/a	>65	**Assessment** n/a **Result Statement** Well accepted.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Rafter, 2007 RCT	**Genus, Species, Strain** Bifidobacterium lactis Bb12 , Lyophilized , >10^10 cfu/g , n/a Lactobacillus delbrueckii rhamnosus GG , >10^10 cfu/g , n/a 7 days , NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Colon cancer and polypectomized patients	**Assessment** The subjects were interviewed at time 2 and time 3 … and any adverse events that had occurred in each 6-wk period were recorded. **Result Statement** No adverse effects of the intervention were reported.
Rao, 2009 RCT	**Genus, Species, Strain** Lactobacillus casei Shirota , n/a , 8*10^9 cfu/sachet , 1 sachet t.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Adu<s 18-65 yrs with Chronic Fatigue Syndrome	**Assessment** n/a **Result Statement** Well-tolerated; no significant adverse events.
Rautava, 2002 RCT	**Genus, Species, Strain** Bifidobacterium rhamnosus GG(ATCC 53103) , n/a , 2*10^10 cfu , q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** Disease or immunologic status **Cotreatment** n/a	<2yrs; m breastfeeding infants <3 mos	**Assessment** The infants' clinical … status were assessed at scheduled visits at the ages of 3, 6, 12, and 24 months. **Result Statement** No adverse reactions or clinical side effects were observed during probiotic supplementation or clinical followup.
Reid, 2001 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GR-1 , Lyophilized , n/a , 8*10^8 cfu q.d., 6*10^9 cfu q.d., 8*10^8 cfu b.i.d. Lactobacillus freudenreichii RC-14 , Lyophilized , n/a , 8*10^8 cfu q.d., 6*10^9 cfu q.d., 8*10^8 cfu b.i.d. Lactobacillus rhamnosus GG , n/a , 8*10^8 cfu , q.d. (Arm 4) NA **Product Name** n/a	**Direct Comparison** Dose, Species, Strains **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** None of the patients reported adverse side effects during the 6 week test period.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Reid, 2003 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GR-1 , Lyophilized , >10^9 cfu /capsule , 1 capsule q.d. Lactobacillus fermentum RC-14 , Lyophilized , >10^9 cfu/capsule , 1 capsule q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** The research nurse, supervised by a physician, followed every patient throughout the study. This entailed … and monitor any perceived adverse events. Upon completion of the study, each subject filled out a questionnaire to determine whether any adverse events ... occurred. **Result Statement** Patients did not report any side effects associated with probiotic therapy.
Riccia, 2007 CT	**Genus, Species, Strain** Lactobacillus brevis n/a , Lyophilized , 2*10^7 cfu/lozenge , 4 lozenges q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** The tolerability was considered as very good by all patients.
Ritchie, 2009 RCT	**Genus, Species, Strain** Lactobacillus casei GG , n/a , >5*10^9 cfu/capsule , 1 capsule t.i.d NA **Product Name** Gelfilus	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs	**Assessment** Adverse events related to the study product and/or protocol investigations were reported to the ethics committee approving the study. **Result Statement** No adverse effect attributable to LGG in the present study protocol.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Roessler, 2007 RCT	**Genus, Species, Strain** Bifidobacterium animalis Lactis DGCC 420 , Active , 5.9*10^4 cfu/g , 100ml b.i.d. Lactobacillus paracasei Lpc-37 , Active , 3.9*10^8 cfu/g , 100ml b.i.d. Lactobacillus acidophilus 74-2 , Active , 2.9*10^4 cfu/g , 100ml b.i.d. Streptococcus thermophilus n/a , Active , n/a , 100ml b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** Disease or immunologic status **Cotreatment** Corticosteroid use	n/a	**Assessment** n/a **Result Statement** No adverse effects of the regular intake of the probiotic drink were reported.
Roggero, 1990 RCT	**Genus, Species, Strain** Streptococcus lactis n/a , Active , 8*10^9 cfu/capsule , b.i.d. or q.i.d. Lactobacillus bulgaricus n/a , Active , 1*10^9 cfu , b.i.d. or q.i.d. Lactobacillus acidophilus n/a , Active , 1*10^9 cfu , b.i.d. or q.i.d. NA **Product Name** Lactipan	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; chronic diarrhea	**Assessment** Particular attention was paid to the detection of any undesirable effect in the course of the treatment. **Result Statement** During the treatment period no side effect was observed for both groups.
Romano, 2010 RCT	**Genus, Species, Strain** Lactobacillus reuteri DSM 17938 , Lyophilized , 10^8 cfu/5 drops , 5 drops, b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** The patients used a diary to record… any other symptoms. **Result Statement** L. reuteri supplementation was well tolerated and no adverse effects or other unexpected symptoms were reported in either study.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Romeo, 2009 RCT	**Genus, Species, Strain** Lactobacillus reuteri ATCC 55730 , n/a , 10^8 cfu/5 drops , 5 drops, q.d. Lactobacillus rhamnosus ATCC 53103 , n/a , 6*10^9 cfu/capsule , 1 capsule, q.d. NA **Product Name** n/a	**Direct Comparison** Delivery vehicles, Species **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs	**Assessment** Nutrition administrated through oral access… was progressively increased if tolerated. **Result Statement** Both used probiotics had good safety and did not show any adverse reactions or side effects in preterm infants.
Roos, 1993 CT	**Genus, Species, Strain** Streptococcus sanguis 3 strains unspecified , n/a , 10^7 cfu each strain /treatment , b.i.d. Streptococcus mitis n/a , n/a , 10^7 cfu /treatment , b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Recurrent streptococcal tonsillitis	**Assessment** n/a **Result Statement** No adverse effects have been noted.
Roos, 1993 RCT	**Genus, Species, Strain** Streptococcus sanguis 3 strains unspecified , Lyophilized , 10^6 cfu /puff , 3 puffs b.i.d. Streptococcus mitis n/a , Lyophilized , 10^6 cfu /puff , 3 puffs b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	History of strep infection (tonsillitis)	**Assessment** n/a **Result Statement** No side effects … were reported and all patients were able to complete the 2 treatment regimens.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Ruszczy?ski, 2008 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus Pen 2593 , n/a , 2*10^9 cfu , b.i.d. Lactobacillus rhamnosus E/N 2594 , n/a , 2*10^9 cfu , b.i.d. Lactobacillus rhamnosus Oxy 2595 , n/a , 2*10^9 cfu , b.i.d. NA **Product Name** Lakcid Forte	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs; 2-14 yrs	**Assessment** The secondary outcome measures were… and adverse events. **Result Statement** Lactobacillus rhamnosus was well-tolerated, and no adverse event associated with this therapy (or with the use of placebo) was reported.
Saavedra, 1994 RCT	**Genus, Species, Strain** Bifidobacterium bifidum n/a , n/a , 1.9*10^8 cfu/g powdered formula, 3.6*10^8 cfu/100kcal , n/a Streptococcus thermophilus n/a , n/a , 1.4*10^7 cfu/g or 2.7*10^8 cfu/100kcal , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No adverse effects judged to be associated with the feeding of the supplemented formula.
Salazar-Lindo, 2004 RCT	**Genus, Species, Strain** Lactobacillus casei GG , n/a , 10^9 cfu/ml , 150 ml/kg/d up to 1L (10^12 cfu) q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** Early withdrawals defined as patient who develops a complicating illnesses **Result Statement** No adverse effects due to the study formula.
Sazawal, 2010 RCT	**Genus, Species, Strain** Bifidobacterium lactis HN019 , n/a , 6.3*10^6 cfu/dose , 1 dose, t.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** Disease or immunologic status **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No adverse effects were reported or observed.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Schaafsma, 1998 RCT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , 10^7-10^8 cfu/gm , 125 ml t.i.d. NA **Product Name** Actimel	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Questionnaire on well-being **Result Statement** n/a
Senay, 2009 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , Lyophilized, live , 5*10^6 microorganisms/250 mg , 250 mg, q.d. NA **Product Name** Reflor	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** Daily record of… the side effects of the treatment. All data were recorded on a study record sheet during the 10 days of treatment by patients and patients were reevaluated after 10 days. **Result Statement** S. boulardii wall tolerated by all children and no side effect was recorded during the active treatment period.
Shanahan, 2010 RCT	**Genus, Species, Strain** Lactobacillus salivarius salivarius UCC118 , Live , 10^9 cfu/dose , 1 dose, q.d. Bifidobacterium infantis 35624 , Live , 10^9 cfu/dose , 1 dose, q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Corticosteroid use	n/a	**Assessment** n/a **Result Statement** Adverse events were uncommon, unrelated to the treatment, and similar across the groups. Prolonged feeding with live probiotics is safe in patients with ulcerative colitis.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Sharma, 2008 RCT	**Genus, Species, Strain** Lactobacillus n/a n/a , n/a , 10^8 cfu/capsule , 1 capsule t.i.d. Clostridium butyricum n/a , n/a , 4*10^6 cfu/capsule , 1 capsule t.i.d. Bacillus mesentericus n/a , n/a , 2*10^6 cfu/capsule , 1 capsule t.i.d. Streptococcus faecalis n/a , n/a , 6*10^7 cfu/capsule , 1 capsule t.i.d. NA **Product Name** n/a	**Direct Comparison** Prebiotic mix **Subgroup Analysis** n/a **Cotreatment** n/a	minimal hepatic encephalopathy	**Assessment** n/a **Result Statement** Probiotics treatment also had no side effect.
Sheu, 2006 RCT	**Genus, Species, Strain** Lactobacillus acidophilus La 5 , n/a , ?10^9 bacteria/ml , 200ml b.i.d. Bifidobacterium lactis Bb 12 , n/a , ?10^9 bacteria/ml , 200 ml b.i.d. Lactobacillus bulgaricus n/a , n/a , ?10^9 bacteria/ml , 200ml b.i.d. Streptococcus thermophilus n/a , n/a , ?10^9 bacteria/ml , 200 ml b.i.d. NA **Product Name** AB-yogurt	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Helicobacter pylori infection	**Assessment** n/a **Result Statement** Only 4 patients in the yogurt-plus-quadruple therapy group did not complete the study design. However, only 1 of the 4 patients had poor tolerance of the 4-wk ingestion of AB-yogurt. This indicates that the pretreatment with Ab-yogurt can be well tolerated in milk-tolerant patients who have residual H. pylori after failed triple therapy.
Shimauchi, 2008 RCT	**Genus, Species, Strain** Lactobacillus salivarius WB21 , Lyophilized , 6.7*10^8 cfu/tablet , 1 tablet t.i.d. NA **Product Name** Wakamate D	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse events were reported.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Shimizu, 2009 CT	**Genus, Species, Strain** Bifidobacterium breve Yakult , Live , 10^8 cfu/gm , 3g mixture q.d. Lactobacillus casei Shirota , Live , 10^8 cfu/gm , 3g mixture q.d. NA **Product Name** Yakult BL	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	Immune compromised / critically ill	**Assessment** n/a **Result Statement** No adverse events in any patients.
Shornikova, 1997 RCT	**Genus, Species, Strain** Lactobacillus reuteri n/a , Lyophilized, viable , 10^10-10^11 cfu/capsule , 1 capsule q.d. Lactobacillus reuteri n/a , Lyophilized, viable , 10^7 cfu/capsule , 1capsule q.d. NA **Product Name** n/a	**Direct Comparison** Dose **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** Safe.
Simren, 2007 RCT	**Genus, Species, Strain** Lactobacillus paracasei paracasei , Active , ?5*10^7 cfu/ml yogurt , 400 ml q.d. Lactobacillus acidophilus n/a , Active , ?5*10^7 cfu/ml yogurt , 400 ml /day Bifidobacterium lactis n/a , Active , ?5*10^7 cfu/ml , 400 ml /day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS	**Assessment** n/a **Result Statement** well tolerated and no serious adverse events occurred.
Sinn, 2008 RCT	**Genus, Species, Strain** Lactobacillus acidophilus SDC 2012 , Lyophilized , 2*10^9 cfu/ml , 1 capsule b.i.d. Lactobacillus acidophilus SDC 2013 , Lyophilized , 2*10^9 cfu/ml , 1 capsule b.i.d. NA **Product Name** n/a	**Direct Comparison** Genera **Subgroup Analysis** n/a **Cotreatment** n/a	1-8 yrs; Otitis media with effusion	**Assessment** Any adverse events that occurred during the treatment period was also recorded. **Result Statement** There were no adverse events reported.
Skovbjerg, 2009 RCT	**Genus, Species, Strain** Streptococcus sanguis 89a NCIMB 40104 , Lyophilized , 5*10^9 cfu/ml , 0.2 ml b.i.d. Lactobacillus rhamnosus LB21, NCIMB 40564 , Lyophilized , 5*10^9 cfu/ml , 0.2 ml /day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs Otitis Media With Effusion	**Assessment** n/a **Result Statement** No adverse events were reported.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Stansbridge, 1993 RCT	**Genus, Species, Strain** Lactobacillus casei GG , Lyophilized , 10^8 cfu/dose , b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs; Premature newborns	**Assessment** n/a **Result Statement** Clinically, there were no adverse effects.
Steeksen-Blicks, 2009 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus LB21 , n/a , 10^7 cfu/ml , 150 ml q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; day care centers	**Assessment** n/a **Result Statement** No harmful side effects were reported by any of the participants in the study.
Sugawara, 2006 RCT	**Genus, Species, Strain** Lactobacillus* casei Shirota , Live , 4*10^10 cfu/bottle , 1 bottle q.d. Bifidobacterium# breve Yakult , Live , 1*10^10 cfu/bottle , 1 bottle q.d. Lactobacillus** casei Shirota , Live , 10^8 cfu/g , 3g q.d. Bifidobacterium** breve Yakult , Live , 10^8 cfu/g , 3g q.d. NA **Product Name** *Yakult 400; #Bifiel; **Yakult BL	**Direct Comparison** Timing **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Immune compromised / critically ill	**Assessment** n/a **Result Statement** No patients had problems related to synbiotic treatment.
Sugita, 1994 CT	**Genus, Species, Strain** Lactobacillus casei n/a , n/a , 10^9-10^10 cfu , 1g NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** In two years, no adverse effects were found.
Sur, 2010 RCT	**Genus, Species, Strain** Lactobacillus casei Shirota , n/a , 6.5*10^9 cfu/bottle , 1 bottle, q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse events was observed in children of either probiotic or nutrients groups.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Surawicz, 2000 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 500 mg b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Clostridium Difficile Disease	**Assessment** The patients kept a standardized diary of… adverse reactions. **Result Statement** No significant differences in the number of adverse reactions reported by patients taking S. boulardii compared with those taking placebo. No specific type of adverse reaction was more common in patients taking S. boulardii than in those receiving placebo, … no significant adverse reactions during the 4-week followup.
Surawicz, 1989 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , Lyophilized , n/a , 250 mg b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** Disease or immunologic status **Cotreatment** n/a	Hospitalized patients	**Assessment** n/a **Result Statement** There were no side effects of either Saccharomyces boulardii or placebo.
Szajewska, 2001 RCT	**Genus, Species, Strain** Lactobacillus casei GG , n/a , n/a , 6*10^9 cfu b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** Well tolerated and no adverse effects of the treatment were noted.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Szajewska, 2007 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , n/a , 3*10^9 cfu b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; rectal bleeding	**Assessment** n/a **Result Statement** Well tolerated and no adverse effects.
Szymanski, 2006 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus 573L/1 , Lyophilized , n/a , 1.2*10^10cfu b.i.d. Lactobacillus rhamnosus 573L/2 , Lyophilized , n/a , 1.2*10^10cfu b.i.d. Lactobacillus rhamnosus 573L/3 , Lyophilized , n/a , 1.2*10^10cfu b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** Secondary outcomes were… presence of adverse events. **Result Statement** No adverse events were noted.
Szyma?ski, 2008 RCT	**Genus, Species, Strain** Lactobacillus plantarum PL02 , n/a , n/a , 10^8 cfu mixture b.i.d. Lactobacillus rhamnosus KL53a , n/a , 10^8 cfu b.i.d. , 10^8 cfu mixture b.i.d. Bifidobacterium longum PL03 , n/a , n/a , 10^8 cfu mixture b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs; 2-15 yrs	**Assessment** Secondary outcomes were…and adverse events. **Result Statement** Mixture of probiotics was well tolerated, and no adverse events associated with this therapy were reported.
Tlaskal, 2007 RCT	**Genus, Species, Strain** Lactobacillus* acidophilus Rossell-52 , n/a , n/a , 1.45*10^8 cfu q.d. Lactobacillus rhamnosus Rossell-11 , n/a , n/a , 2.755*10^9 cfu q.d. Streptococcus# faecalis n/a , n/a , n/a , n/a Lactobacillus# acidophilus n/a , n/a , n/a , n/a Lactobacillus# helveticus n/a , n/a , n/a , n/a NA **Product Name** *Lacidofil; #Hylak	**Direct Comparison** Prebiotic mix **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; Acute diarrhea	**Assessment** n/a **Result Statement** None of the participants failed to complete the 10 day course of therapy resulting from untoward effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Tubelius, 2005 RCT	**Genus, Species, Strain** Lactobacillus reuteri protectus (ATCC 55730) , n/a , n/a , 10^8 cfu q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse events reported.
Tursi, 2007 CT	**Genus, Species, Strain** Lactobacillus casei n/a , Lyophilized , n/a , 4.5*10^8 cfu/day Lactobacillus plantarum n/a , Lyophilized , n/a , 4.5*10^8 cfu/day Lactobacillus bulgaricus n/a , Lyophilized , n/a , 4.5*10^8 cfu /day Lactobacillus plantarum n/a , Lyophilized , n/a , 4.5*10^8 cfu /day Bifidobacterium longum n/a , Lyophilized , n/a , 4.5*10^8 cfu /day Bifidobacterium infantis n/a , Lyophilized , n/a , 4.5*10^8 cfu /day Bifidobacterium breve n/a , Lyophilized , n/a , 4.5*10^8 cfu /day Streptococcus salivarius thermophilus n/a , Lyophilized , n/a , 4.5*10^8 cfu /day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** All patients … were evaluated for the presence of possible side effects. **Result Statement** No side effects were recorded throughout the follow up in both groups.
Twetman, 2009 RCT	**Genus, Species, Strain** Lactobacillus reuteri ATCC 55730 , n/a , 10^8 cfu/stick of gum , 1 stick b.i.d. Lactobacillus reuteri ATPTA 5289 , n/a , 10^8 cfu/stick , 1 stick b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No harmful side effects or adverse events.
Vandenplas, 2007 RCT	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 500 mg, q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs	**Assessment** n/a **Result Statement** Side effects were not reported.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Vanderhoof, 1999 RCT	**Genus, Species, Strain** Lactobacillus casei rhamnosus GG , Live , 10^10 cfu/capsule , 1 capsule q.d. or b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	2 yrs-10 yrs	**Assessment** n/a **Result Statement** There were no failures resulting from untoward effects.
Venturi, 1999 CT	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized , 5*10^11 cfu/g mixture , 3g mixture b.i.d. Lactobacillus casei casei n/a , Lyophilized , , Lactobacillus delbrueckii Bulgaricus , Lyophilized , , Lactobacillus plantarum n/a , Lyophilized , n/a , Bifidobacterium longum n/a , Lyophilized , , Bifidobacterium infantis n/a , Lyophilized , , Bifidobacterium breve n/a , Lyophilized , , Streptococcus salivarius thermophilus , Lyophilized , n/a , NA **Product Name** VSL#3	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Ulcerative Colitis In Remission	**Assessment** n/a **Result Statement** The preparation was also safe and well tolerated by patients.
Whorwell, 2006 RCT	**Genus, Species, Strain** Bifidobacterium infantis 35624 , Live , 1*10^6/ml , q.d. Bifidobacterium infantis 35624 , Live , 1*10^8/ml , q.d. Bifidobacterium infantis 35624 , Live , 1*10^10/ml , q.d. NA **Product Name** n/a	**Direct Comparison** Dose **Subgroup Analysis** n/a **Cotreatment** n/a	IBS (women)	**Assessment** n/a **Result Statement** Only 17(
Winkler, 2005 RCT	**Genus, Species, Strain** Lactobacillus gasseri PA 16/8 , Spray-dried , 4*10^8 cfu/tablet , 1 tablet q.d. Bifidobacterium longum SP 07/3 , Spray-dried , 5*10^7 cfu/tablet , 1 tablet q.d. Bifidobacterium bifidum MF 20/5 , Spray-dried , 5*10^7 cfu/tablet , 1 tablet q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	n/a	**Assessment** n/a **Result Statement** No report of adverse events.
Woodord, 2009 RCT	**Genus, Species, Strain** Lactobacillus n/a n/a , Live , 2.4*10^9 cells/pill , 1 pill, q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** There were no probiotic-related complications.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Wullt, 2003 RCT	**Genus, Species, Strain** Lactobacillus plantarum 299 V , n/a , n/a , 5*10^10 cfu q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>18 yrs Hospitalized	**Assessment** n/a **Result Statement** No apparent side effects.
Wunderlich, 1989 RCT	**Genus, Species, Strain** Enterococcus n/a SF 68 , Lyophilized , 75*10^6 cfu/capsule , 2 capsules q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Diarrhoea	**Assessment** n/a **Result Statement** No side effects were reported.
Xiao, 2006 RCT	**Genus, Species, Strain** Bifidobacterium longum BB 536 , Lyophilized , n/a , 5*10^10 cfu b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No participants left the trial prematurely due to adverse effects.
Ya, 2010 RCT	**Genus, Species, Strain** Lactobacillus rhamnosus n/a , Lyophilized, live , 6.8x10^9 cfu , daily Lartobacillus acidophilus n/a , Lyophilized , 4x10^8 cfu , daily Streptococcus thermophilus n/a , Lyophilized , 8x10^8 cfu , daily NA **Product Name** Probaclac Vaginal	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Follow-up evaluations included… a report of adverse events **Result Statement** …no adverse events were reported in either group.
Yamamura, 2009 RCT	**Genus, Species, Strain** Lactobacillus helveticus CM4 , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>65	**Assessment** n/a **Result Statement** None of the subjects in either group developed any side effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Zeng, 2008 RCT	**Genus, Species, Strain** Streptococcus thermophilus n/a , Active , 10^8 cfu/ml , 200 ml mixture b.i.d. Lactobacillus bulgaricus n/a , Active , 10^9 cfu/ml , 200 ml mixture b.i.d. Lactobacillus acidophilus n/a , Active , 10^7 cfu/ml , 200 ml mixture b.i.d. Bifidobacterium longum n/a , Active , 10^7 cfu/ml , 200 ml mixture b.i.d. NA **Product Name** AB100	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** There were no reported adverse events related to the study drinks.
Amati, 2010 CS	**Genus, Species, Strain** Lactobacillus rhamnosus GG , n/a , 10^7 bacteria/90g , 90g b.i.d. NA **Product Name** YOMO ABC PLUS	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>65	**Assessment** n/a **Result Statement** No side effects were recorded in the individuals who terminated that trial.
Baron, 2009 CS	**Genus, Species, Strain** Bacillus coagulans GBI-30, 6086 , n/a , 2*10^9 cfu , 1 capsule /day NA **Product Name** Sustenex	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No serious adverse events were reported throughout the study.
Bennet, 1992 CS	**Genus, Species, Strain** Bifidobacterium longum BB-536 , Lyophilized , 3*10^9 cfu , t.i.d 5 days Bifidobacterium breve BB-576 , Lyophilized , 3*10^9 cfu , t.i.d Lactobacillus acidophilus LAC-343 , Lyophilized , 3*10^9 cfu , t.i.d. NA **Product Name** n/a	**Direct Comparison** Genera mix **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs	**Assessment** n/a **Result Statement** No side effects were noted.
Bennett, 1996 CS	**Genus, Species, Strain** Lactobacillus rhamnosus GG , Lyophilized , 10^9 cfu/capsule , q.d., b.i.d. or q.i.d. NA **Product Name** LGG	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>65	**Assessment** n/a **Result Statement** No side effects were associated with LGG.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Biller, 1995 CS	**Genus, Species, Strain** Lactobacillus rhamnosus GG , Lyophilized , 5*10^9cfu/g , 125 mg b.i.d. NA **Product Name** LGG	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; 5-70 mons	**Assessment** n/a **Result Statement** No side effects were noted during the course of treatment.
Bruce, 1992 CS	**Genus, Species, Strain** Lactobacillus casei GR-1 , Lyophilized , >1.6*10^9 organisms/0.5g , 1 suppository/wk Lactobacillus fermentum B-54 , Lyophilized , >1.6*10^9 organisms/0.5g , 1 suppository/wk NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** Ethnicity **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** The suppositories caused no detectable side effects. Two patients were not compliant. The reasons appropriate treatment were suffering from other types of ailments not related to UTI.
Ciprandi, 2004 CS	**Genus, Species, Strain** Bacillus clausii n/a , n/a , 2*10^9 spores /vial , 2 vials q.d. NA **Product Name** Enterogermina	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	allergic children with recurrent respiratory infections	**Assessment** n/a **Result Statement** All children assumed the prescribed treatment with B. clausii spores without any side-effect.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Drago, 2007 CS	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized , 10^9 cfu/ml , 1 douche (100 ml)/day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** The treatment kit included a questionnaire to determine whether any adverse events occurred during the treatment and in the following period. **Result Statement** The treatment kit included a questionnaire to determine whether any adverse events occurred during the treatment and in the following period.
Erzsébet, 1988 CS	**Genus, Species, Strain** Lactobacillus n/a n/a , n/a , n/a , 0.14gm tablet NA **Product Name** Lactobact	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Vaginal infection	**Assessment** n/a **Result Statement** Using the vaginal tablet did not cause subject complaints, side effect.
Fan, 2006 CS	**Genus, Species, Strain** Bifidobacterium n/a n/a , Live , 5*10^7cfu/gm , 420 mg mixture t.i.d. Lactobacillus n/a n/a , Live , 5*10^7cfu/gm , 420 mg mixture t.i.d. Enterococcus n/a n/a , Live , 5*10^7cfu/gm , 420 mg mixture t.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	IBS patients	**Assessment** Side effects were recorded at the same time as symptoms **Result Statement** All tolerated the products well; no adverse events were reported.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Federico, 2009 CS	**Genus, Species, Strain** Lactobacillus paracasei B 21060 , Lyophilized , 5*10^9 cfu/bag , 1 bag b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** The preparation was well-tolerated and well accepted, no adverse events were observed.
Ferraz, 2009 CS	**Genus, Species, Strain** Lactobacillus casei Shirota , Lyophilized , 2*10^7-10^9 cfu/50 mg , 50mg, t.i.d. Bifidobacterium breve n/a , Lyophilized , 5*10^7-10^9 cfu , 50mg, t.i.d. NA **Product Name** Yakult SA	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No adverse effects were observed while on the use of LAB.
Friedlander, 1986 CS	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , 10^8-10^9/100 ml , 100 ml, b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** In no case were side effects observed.
Fujimori, 2007 CS	**Genus, Species, Strain** Lactobacillus* casei n/a , n/a , n/a , 3*10^10 q.d. Bifidobacterium* breve n/a , n/a , n/a , 3*10^10 q.d. Bifidobacterium# longum n/a , n/a , 1.5*10^10 q.d. , NA **Product Name** *Yakult BL; #ISAGOL 5 billion	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Corticosteroid use, Diet therapies	Crohn's Disease	**Assessment** n/a **Result Statement** Synbiotic therapy can safely reduce Crohn's disease activity.
Fukushima, 1998 CS	**Genus, Species, Strain** Bifidobacterium lactis Bb-12 , Viable , n/a , 10^9cfu q.d. NA **Product Name** Nan BF	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; 15-31 mos	**Assessment** n/a **Result Statement** Well Accepted
Gee, 2010 CS	**Genus, Species, Strain** Lactobacillus paracasei NFBC 338 , Stored at 22 degree centigrade , 1*10^9 cfu/dose , 1 single dose NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No adverse effects were observed with probiotic administration.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Giacarri, 1993 CS	**Genus, Species, Strain** Lactobacillus n/a n/a , n/a , n/a , 2 capsules q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** Throughout the period of observation the appearance of any undesired effect was monitored. **Result Statement** Tolerability of the treatment was excellent; no side effects.
Gill, 2001 CS; Pre-Post	**Genus, Species, Strain** Lactobacillus rhamnosus HN 001 (DR 20) , n/a , 1.25*10^8 cfu/ml , 5*10^10 cfu q.d. NA **Product Name** DR 20 ™	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>65	**Assessment** n/a **Result Statement** No reports of adverse effects on health and no general health problems.
Gracheva, 1996 CS	**Genus, Species, Strain** Bacillus subtilis n/a , Live , n/a , 2*10^9 cfu Bacillus licheniformis n/a , Live , , 2*10^6 cfu Lactobacillus n/a n/a , n/a , n/a , NA **Product Name** Biosporin	**Direct Comparison** Dose **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Well tolerated; no adverse reactions observed.
Guandalini, 2002 CS	**Genus, Species, Strain** Lactobacillus n/a GG , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics, Corticosteroid use, Immune suppressants	Pediatric Crohn's	**Assessment** n/a **Result Statement** No patient reported any adverse effects.
Gupta, 2000 CS	**Genus, Species, Strain** Lactobacillus casei GG , n/a , n/a , 10^10 cfu b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics, Corticosteroid use, Immune suppressants	Crohn's Disease	**Assessment** n/a **Result Statement** No patient reported any adverse effects.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Guslandi, 2003 CS	**Genus, Species, Strain** Saccharomyces boulardii n/a , n/a , n/a , 250 mg t.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Adu<s 19-47 yrs Ulcerative Colitis	**Assessment** n/a **Result Statement** No side effects induced by the probiotic agent.
Kanamori, 2010 CS	**Genus, Species, Strain** Bifidobacterium breve Yakult , n/a , 10^9 - 10^10 cfu/g , 0.03g, q.i.d.-1g, t.i.d. Lactobacillus casei Shirota , n/a , 10^9 - 10^10 cfu/g , 0.03g, q.i.d.-1g, t.i.d. NA **Product Name** BiolActis, Yakult	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	severe congenital anormality	**Assessment** n/a **Result Statement** Tolerated feeding very well
Kerk, 2002 CS	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , n/a , n/a NA **Product Name** Acidosalus	**Direct Comparison** n/a **Subgroup Analysis** Age **Cotreatment** n/a	Colpitis	**Assessment** n/a **Result Statement** Proved especially tolerable since not one…experienced side effects.
Kocian, 1994 CS	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Live , 10^9 cfu/capsule , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Dyspepsia	**Assessment** n/a **Result Statement** No side effects were observed, the preparation was very well tolerated.
Laake, 2003 CS; Pre-Post	**Genus, Species, Strain** Lactobacillus acidophilus La-5 , Live , 10^8 cfu/ml , 500ml q.d. Bifidobacterium lactis Bb-12 , Live , 10^8 cfu/ml , 500 ml q.d. NA **Product Name** Cultura	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Pouchitis	**Assessment** n/a **Result Statement** No adverse effects were recorded.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Laake, 2004 CS	**Genus, Species, Strain** Lactobacillus acidophilus La-5 , Live , 10^8 cfu/ml , 500 ml q.d. Bifidobacterium lactis Bb-12 , Live , 10^8 cfu/ ml , 500 ml q.d. NA **Product Name** Cultura	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	"IPAA"(Colectomy/ileostomy)	**Assessment** n/a **Result Statement** No adverse effects were recorded.
Levy, 1997 CS	**Genus, Species, Strain** Lactobacillus plantarum 299v , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; Clostridium difficile infection	**Assessment** n/a **Result Statement** Well tolerated.
Lieske, 2005 CS	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , 2*10^11 cfu/gm , 0.4g to 1.2g q.d. Lactobacillus brevis n/a , n/a , 2*10^11cfu/gm , 0.4g to 1.2g q.d. Streptococcus thermophilus n/a , n/a , 2*10^11cfu/g , 1.6g to 4.8g q.d. Bifidobacterium infantis n/a , n/a , 2*10^11cfu/g , 1.6g to 4.8g q.d. NA **Product Name** Oxadrop	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	>65, IBD	**Assessment** n/a **Result Statement** No adverse events were noted.
Lozhardzkaya(?), 1984 CS	**Genus, Species, Strain** Lactobacillus acidophilis n/a , Live, Lyophilized , n/a , pills (powder) 2-3/day and injection 2-3 every time NA **Product Name** Acilact	**Direct Comparison** n/a **Subgroup Analysis** Disease or immunologic status **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Product is well tolerated by the patients and induces no side effects, there are no contraindications against its administration.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Matsuzaki, 2005 CS	**Genus, Species, Strain** Lactobacillus casei Shirota , Live , 4*10^10 cfu , b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Corticosteroid use	HTLV-1 associated myelopathy	**Assessment** Assessments were performed on … and adverse effects. **Result Statement** No adverse effect and laboratory findings were observed.
Monden, 2002 CS	**Genus, Species, Strain** Lactobacillus* n/a n/a , n/a , 0.5gm/vaginal suppository , n/a Lactobacillus# crispatus GAI 98322 , n/a , 10^8 cfu , n/a, NA **Product Name** *LacB, #n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** …no adverse effects in clinical examination.
Morita, 2006 CS	**Genus, Species, Strain** Lactobacillus gasseri TMC0356 , n/a , 4.3*10^8 cfu/ml , 200ml, q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No clinical problems have been observed in the medical examination during the intervention of the tested fermented milk.
Nasirova, 2007 CS	**Genus, Species, Strain** Lactobacillus n/a n/a , n/a , n/a , n/a Bifidobacterium forte n/a , n/a , n/a , NA **Product Name** n/a	**Direct Comparison** Genera **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	<2yrs	**Assessment** n/a **Result Statement** The application of probiotics did not influence on an organism negatively.
Nobuta, 2009 CS	**Genus, Species, Strain** Lactobacillus brevis KB290 , n/a , 2x10^9 cfu / tablets , per day NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** Daily questionnaire and health status. **Result Statement** No relevant adverse events were reported.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Okombo, 2010 CS	**Genus, Species, Strain** Lactobacillus acidophilus n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. Lactobacillus casei n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. Lactobacillus bulgaricus n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. Lactobacillus plantarum n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. Bifidobacterium longum n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. Bifidobacterium infantis n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. Bifidobacterium breve n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. Streptococcus salivarius thermophilus n/a , Lyophilized, live , 8*10^11 bacteria /sachet , 1 sachet, q.d. NA **Product Name** VSL#3	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** No subject reported experiencing any noticeable effects from the use of this probiotic.
Rossi, 2010 CS	**Genus, Species, Strain** Lactobacillus rhamnosus n/a , Lyophilized , >=10^6 cfu/tablet , 1 tablet, b.i.d., then reduced NA **Product Name** Normogin	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Tolerability of the local therapy was good.
Sanges, 2009 CS	**Genus, Species, Strain** Lactobacillus acidophilus n/a , n/a , 10^9 bacteria/dose , 1 dose, b.i.d. Lactobacillus salivarius n/a , n/a , 10^9 bacteria/dose , 1 dose, b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** During the study no one of the patients had a relapse of UC or relevant adverse effects.
Simenhoff, 1996 CS	**Genus, Species, Strain** Lactobacillus acidophilus NCFM , Lyophilized , 10^9 cfu/ml , 1 capsule b.i.d. Lactobacillus acidophilus BG2F04 , Lyophilized , 10^9 cfu/ml , 1 capsule b.i.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Immune compromised / critically ill	**Assessment** n/a **Result Statement** No one experienced any side effects from the LBA.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Sprunt, 1980 CS	**Genus, Species, Strain** Alpha Streptococcus n/a n/a , Active , n/a , 2*10^5-5*10^6 cfu/kg body weight NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs; newborns in neonatal ICU	**Assessment** n/a **Result Statement** There has been no evidence of disease or other adverse reaction caused by the implant strain.
Tandan, 2009 CS	**Genus, Species, Strain** Lactobacillus n/a n/a (4 strains) , Lyophilized, viable , 9*10^11 cfu/sachet , 2 sachets, b.i.d. Bifidobacterium n/a n/a (3 strains) , Lyophilized, viable , 9*10^11 cfu/sachet , 2 sachets, b.i.d Streptococcus salivarius thermophilus n/a , Lyophilized, viable , 9*10^11 , 2 sachets b.i.d. NA **Product Name** VSL#3	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	Immune compromised / critically ill	**Assessment** n/a **Result Statement** No adverse events were noted.
Thompson, 1982 CS	**Genus, Species, Strain** Streptococcus* cremoris n/a , n/a , n/a , 1L q.d. Streptococcus* lactis n/a , n/a , n/a , 1L q.d. Lactobacillus# bulgaricus n/a , n/a , n/a , 1L q.d. Streptococcus# thermophilus n/a , n/a , n/a , 1L q.d. Lactobacillus** acidophilus n/a , n/a , n/a , 1L q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** To test their tolerance, individuals were also asked to take a day's supplementation of the milk product. **Result Statement** In general, the supplements were well tolerated.
Uehara, 2006 CS	**Genus, Species, Strain** Lactobacillus crispatus GAI 98332 , Lyophilized , 1*10^8 cfu/suppository , 1 suppository on alternating days NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	recurrent urinary tract infection	**Assessment** n/a **Result Statement** Patients did not report any side effects associated with the study treatment.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Wang, 1984 CS	**Genus, Species, Strain** Bacillus cereus DM423 , n/a , n/a , 0.5g t.i.d. (NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	<2yrs	**Assessment** n/a **Result Statement** No adverse events of side effects.
Wendakoon, 2002 CS	**Genus, Species, Strain** Lactobacillus casei 03 , n/a , 1.6*10^9 cfu/g , t.i.d. Lactobacillus acidophilus 2412 , n/a , 1.6*10^9 cfu/g , t.i.d. Lactobacillus acidophilus ACDI , n/a , 1.6*10^9 cfu/g , t.i.d. Lactobacillus* bulgaricus n/a , n/a , n/a , n/a Streptococcus* thermophilus n/a , n/a , n/a , n/a Lactobacillus* acidophilus n/a , n/a , n/a , n/a NA **Product Name** n/a, *Commercial starter mix	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** n/a	n/a	**Assessment** n/a **Result Statement** Well tolerated… no adverse effects or any other complications.
Korvyakova, 2000 Coh	**Genus, Species, Strain** Bifidobacterium n/a n/a , Lyophilized , n/a , n/a NA **Product Name** Bifidumbacterin forte	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Diet therapies	n/a	**Assessment** n/a **Result Statement** Was well tolerated, no adverse drug reaction.
Marieke, 2010 Coh	**Genus, Species, Strain** Bifidobacterium bifidum n/a , n/a , 10^8 cfu/g , 5g b.i.d. Bifidobacterium lactis 2 strains , n/a , 10^8 cfu/g , 5g b.i.d Enterococcus faecium n/a , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus acidophilus 2 strains , n/a , 10^8 cfu/g each , 5g b.i.d Lactobacillus paracasei n/a , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus plantarum n/a , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus rhamnosus n/a , n/a , 10^8 cfu/g , 5g b.i.d Lactobacillus salivarius n/a , n/a , 10^8 cfu/g , 5g b.i.d NA **Product Name** Ecologic AAD	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	n/a	**Assessment** n/a **Result Statement** There was no evidence that probiotic use, given orally in addition to a normal diet, was unsafe in our population of patients who were not critically ill.

Evidence Table C6. Nonspecific safety statements (continued)

Author, Year Design	Intervention, Form, Potency, Dose	Analysis	High-Risk Population	Safety Assessment Results
Nagasaki, 2010 Case	**Genus, Species, Strain** Bifidobacterium n/a n/a , n/a , n/a , 6 mg, q.d. NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics, Corticosteroid use	>65	**Assessment** n/a **Result Statement** Bifidobacterium was used safely without any side effects.
Yangco, 2009 Case	**Genus, Species, Strain** Lactobacillus n/a n/a , n/a , n/a , n/a Saccharomyces n/a n/a , n/a , n/a , n/a NA **Product Name** n/a	**Direct Comparison** n/a **Subgroup Analysis** n/a **Cotreatment** Concomitant antibiotics	Immune compromised / critically ill	**Assessment** n/a **Result Statement** Overall the regimen was well tolerated.

*Abbreviations
b.i.d.=two times per day
Case=Case Studies
cfu: colony forming unit
Coh=Cohort
CS=Case Series
CT=Controlled Trial
g=grams
mg=milligram
ml=milliliter
q.d.=one time per day
q.i.d.=four times per day
t.i.d.=three times per day
yrs=years
RCT=Randomized Controlled Trial

Appendix D. Excluded Studies and Background Papers

Excluded Studies

Exclude-NoAE (does not address safety); Exclude-Design (lacks primary data or uncontrolled studies that are not linked to adverse events); Exclude-Duplicate (duplicates a study already reviewed); Exclude-Genus (does not address specific genera); Exclude-Intervention (does not address specific interventions); Exclude-Participants (does not address humans). Please note Rec means the reviewers had different decisions and had to reconcile.

“1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. USPHS/IDSA Prevention of Opportunistic Infections Working Group. U.S. Public Health Services/Infectious Diseases Society of America.” Clin Infect Dis 1997;25 Suppl 3: S313-335. Exclude-Intervention

Aaltonen, J., T. Ojala, et al. (2008). "Evidence of infant blood pressure programming by maternal nutrition during pregnancy: a prospective randomized controlled intervention study." J Pediatr 152(1): 79-84, 84 e71-72. Exclude-NoAE

Aas, J., C. E. Gessert, et al. (2003). "Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube." Clin Infect Dis 36(5): 580-585. Exclude-Intervention

Abbas, Z. and W. Jafri (1992). "Yoghurt (dahi): a probiotic and therapeutic view." J Pak Med Assoc 42(9): 221-224. Exclude-Design

Abd El-Atti, S., K. Wasicek, et al. (2009). "Use of probiotics in the management of chemotherapy-induced diarrhea: a case study." JPEN J Parenter Enteral Nutr 33(5): 569-570. Exclude-Genus

Abgrall, S., V. Joly, et al. (1997). "Lactobacillus casei infection in an AIDS patient." Eur J Clin Microbiol Infect Dis 16(2): 180-182. Exclude-Intervention

Abrams, S. A., I. J. Griffin, et al. (2007). "Effect of prebiotic supplementation and calcium intake on body mass index." J Pediatr 151(3): 293-298. Exclude-Intervention

Adam, J., A. Barret, et al. (1977). "Essais cliniques controles en double insu de l'ultra-levure lyphilisee: etude multicentrique par 25 medicins de 388 cas." Gaz Med Fr 84: 2072-2078. Exclude-NoAE (French)

Adam, J., C. Barret, et al. (1977). "Controlled doubleblind clinical trials of Ultra-Levure: Multicentre study by 25 physicians in 388 cases. ." Gaz Med Fr 84: 2072–2078. Exclude-NoAE(French)

Adams, M. R. and P. Marteau (1995). "On the safety of lactic acid bacteria from food." Int J Food Microbiol 27(2-3): 263-264. Exclude-Rec NoAE

Adawi, D., S. Ahrne, et al. (2001). "Effects of different probiotic strains of Lactobacillus and Bifidobacterium on bacterial translocation and liver injury in an acute liver injury model." Int J Food Microbiol 70(3): 213-220. Exclude-Participants

Adler, S. N. (2006). "The probiotic agent Escherichia coli M-17 has a healing effect in patients with IBS with proximal inflammation of the small bowel." Dig Liver Dis 38(9): 713. Exclude-Genus

Agadjanyan, M., V. Vasilevko, et al. (2003). "Nutritional Supplement (NT Factor(TM)) Restores Mitochondrial Function and Reduces Moderately Severe Fatigue in Aged Subjects." Journal of Chronic Fatigue Syndrome 11(3): 23-36. Exclude-Intervention

Agarwal, R., N. Sharma, et al. (2003). "Effects of oral Lactobacillus GG on enteric microflora in low-birth-weight neonates." J Pediatr Gastroenterol Nutr 36(3): 397-402. Exclude-Intervention

Agerholm-Larsen, L., M. L. Bell, et al. (2000). "The effect of a probiotic milk product on plasma cholesterol: a meta-analysis of short-term intervention studies." Eur J Clin Nutr 54(11): 856-860. Exclude-NoAE

Agerholm-Larsen, L., A. Raben, et al. (2000). "Effect of 8 week intake of probiotic milk products on risk factors for cardiovascular diseases." Eur J Clin Nutr 54(4): 288-297. Exclude-NoAE

Aggett, P. J., J. M. Antoine, et al. (2005). "PASSCLAIM: consensus on criteria." Eur J Nutr 44 Suppl 1: i5-30. Exclude-Design

Agrawal, A., L. A. Houghton, et al. (2008). "Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173-010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation." Aliment Pharmacol Ther. Exclude-NoAE

Agrawal, A., L. A. Houghton, et al. (2009). "Clinical trial: The effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation." Alimentary Pharmacology and Therapeutics 29(1): 104-114. Exclude-Duplicates 4724

Aguirre, M. and M. Collins (1993). "Lactic acid bacteria and human clinical infection." J Appl Bacteriol 75(2): 95-107. Exclude-Rec Intervention

Ahmed, M., J. Prasad, et al. (2007). "Impact of consumption of different levels of Bifidobacterium lactis HN019 on the intestinal microflora of elderly human subjects." J Nutr Health Aging 11(1): 26-31. Exclude-NoAE

Ahola, A. J., H. Yli-Knuuttila, et al. (2002). "Short-term consumption of probiotic-containing cheese and its effect on dental caries risk factors." Arch Oral Biol 47(11): 799-804. Exclude-NoAE

Al Samaraee, A., I. J. McCallum, et al. (2010). "Nutritional strategies in severe acute pancreatitis: a systematic review of the evidence." Surgeon 8(2): 105-110. Exclude-Participants

Alander, M. and T. Mattila-Sandholm (1996). "Selection and Safety Criteria of Probiotics. Workshop Demonstration of the Nutritional Functionality of Probiotic Foods (1st).". Exclude-Rec NoAE

Alander, M., R. Satokari, et al. (1999). "Persistence of colonization of human colonic mucosa by a probiotic strain, Lactobacillus rhamnosus GG, after oral consumption." Appl Environ Microbiol 65(1): 351-354. Exclude-Participants

Aldinucci, C., L. Bellussi, et al. (2002). "Effects of dietary yoghurt on immunological and clinical parameters of rhinopathic patients." Eur J Clin Nutr 56(12): 1155-1161. Exclude-NoAE

Alenfall, J., M. Astrom, et al. (2004). "Early Enteral supply of Lactobacillus plantarum 299 reduce the incidence of infections in severely ill patients: a meta analysis of three randomized controlled trials." Clin Nutr 23: S1474. Exclude-Design

AlFaleh Khalid, M. and D. Bassler (2008). "Probiotics for prevention of necrotizing enterocolitis in preterm infants." Cochrane Database of Systematic Reviews(1). Exclude-Duplicates 4728

Allen, S. J., B. Okoko, et al. (2004). "Probiotics for treating infectious diarrhoea." Cochrane Database Syst Rev(2): CD003048. Exclude-Duplicate 6083

Alliet, P., P. Scholtens, et al. (2007). "Effect of prebiotic galacto-oligosaccharide, long-chain fructo-oligosaccharide infant formula on serum cholesterol and triacylglycerol levels." Nutrition 23(10): 719-723. Exclude-NoAE

Alm, L. (1982). "Effect of fermentation on lactose, glucose, and galactose content in milk and suitability of fermented milk products for lactose intolerant individuals." J Dairy Sci 65(3): 346-352. Exclude-Intervention

Amenta, M., M. T. Cascio, et al. (2006). "Diet and chronic constipation. Benefits of oral supplementation with symbiotic zir fos (Bifidobacterium longum W11 + FOS Actilight)." Acta Biomed 77(3): 157-162. Exclude-NoAE

Anaissie, E., G. P. Bodey, et al. (1989). "New spectrum of fungal infections in patients with cancer." Rev Infect Dis 11(3): 369-378. Exclude-Intervention

Anderson, J. W. and S. E. Gilliland (1999). "Effect of fermented milk (yogurt) containing Lactobacillus acidophilus L1 on serum cholesterol in hypercholesterolemic humans." J Am Coll Nutr 18(1): 43-50. Exclude-NoAE

Andreeva, P. M. and H. A. Omar (2002). "Effectiveness of current therapy of bacterial vaginosis." Int J Adolesc Med Health 14(2): 145-148. Exclude-Intervention

Anikhovskaia, I. A., I. Vyshegurov, et al. (2004). "[Bifidobacteria as a means of prevention or treatment of endotoxin aggression in patients with chronic diseases during remission or exacerbation]." Fiziol Cheloveka 30(6): 125-127. Exclude-NoAE

Antonio, M. A. and S. L. Hillier (2003). "DNA fingerprinting of Lactobacillus crispatus strain CTV-05 by repetitive element sequence-based PCR analysis in a pilot study of vaginal colonization." J Clin Microbiol 41(5): 1881-1887. Exclude-Participants

Antony, S. J., C. W. Stratton, et al. (1996). "Lactobacillus bacteremia: description of the clinical course in adult patients without endocarditis." Clin Infect Dis 23(4): 773-778. Exclude-Intervention

Anukam, K. C., K. Hayes, et al. (2009). "Probiotic Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 may help downregulate TNF-Alpha, IL-6, IL-8, IL-10 and IL-12 (p70) in the neurogenic bladder of spinal cord injured patient with urinary tract infections: a two-case study." Adv Urol: 680363. Exclude-NoAE

Anukam, K. C., E. Osazuwa, et al. (2006). "Clinical study comparing probiotic Lactobacillus GR-1 and RC-14 with metronidazole vaginal gel to treat symptomatic bacterial vaginosis." Microbes Infect 8(12-13): 2772-2776. Exclude-NoAE

Aponte, G. B., M. C. A. B., et al. (2008). "Probiotics for treating persistent diarrhoea in children." Cochrane Database of Systematic Reviews 4. Exclude-NoAE

Apostolou, E., P. V. Kirjavainen, et al. (2001). "Good adhesion properties of probiotics: a potential risk for bacteremia?" FEMS Immunol Med Microbiol 31(1): 35-39. Exclude-Participants

Arciero, J. C., G. B. Ermentrout, et al. (2010). "Using a mathematical model to analyze the role of probiotics and inflammation in necrotizing enterocolitis." PLoS One 5(4): e10066. Exclude-NoAE

"Are probiotics safe?" Contemporary OB/GYN 2007;52(4): 20. Exclude-Design

Armuzzi, A., F. Cremonini, et al. (2001). "The effect of oral administration of Lactobacillus GG on antibiotic-associated gastrointestinal side-effects during Helicobacter pylori eradication therapy." Aliment Pharmacol Ther 15(2): 163-169. Exclude-NoAE

Armuzzi, A., F. Cremonini, et al. (2001). "Effect of Lactobacillus GG supplementation on antibiotic-associated gastrointestinal side effects during Helicobacter pylori eradication therapy: a pilot study." Digestion 63(1): 1-7. Exclude-NoAE

Aronsson, B., P. Barany, et al. (1987). "Clostridium difficile-associated diarrhoea in uremic patients." Eur J Clin Microbiol 6(3): 352-356. Exclude-NoAE

Arpi, M., M. Vancanneyt, et al. (2003). "Six cases of Lactobacillus bacteraemia: identification of organisms and antibiotic susceptibility and therapy." Scand J Infect Dis 35(6-7): 404-408. Exclude-Intervention

Arroyo, R., V. Martin, et al. (2010). "Treatment of infectious mastitis during lactation: antibiotics versus oral administration of Lactobacilli isolated from breast milk." Clin Infect Dis 50(12): 1551-1558. Exclude-NoAE

Arshad, S., K. V. Gopalakrishna, et al. (2010). "Lactobacillus-cause of death." Infectious Diseases in Clinical Practice 18(3): 219-220. Exclude-Intervention

Arslanoglu, S., G. E. Moro, et al. (2007). "Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life." J Nutr 137(11): 2420-2424. Exclude-Intervention

Arslanoglu, S., G. E. Moro, et al. (2008). "Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life." J Nutr 138(6): 1091-1095. Exclude-Intervention

Arzumanian, V. G., A. Y. Sergeev, et al. (2009). "Antagonistic activity of Malassezia Spp. towards other clinically signifi cant yeast genera." Bulletin of Experimental Biology and Medicine 148(3): 410-415. Exclude-Participants

Asahara, T., M. Takahashi, et al. (2003). "Assessment of safety of lactobacillus strains based on resistance to host innate defense mechanisms." Clin Diagn Lab Immunol 10(1): 169-173. Exclude-Participants

Ascioglu, S., J. H. Rex, et al. (2002). "Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus." Clin Infect Dis 34(1): 7-14. Exclude-Intervention

Ataie-Jafari, A., S. Hosseini, et al. (2007). "Effects of milk replacement with regular yogurt and probiotic yogurt on blood lipid profiles of hypercholesterolemic and normocholesterolemic individuals." Iranian Journal of Diabetes and Lipid Disorders 7(2): 239-244+E224. Exclude-NoAE (Foreign Language)

Aucott, J. N., J. Fayen, et al. (1990). "Invasive infection with Saccharomyces cerevisiae: report of three cases and review." Rev Infect Dis 12(3): 406-411. Exclude-Intervention

Aureli, P., A. Fiore, et al. (2010). "National survey outcomes on commercial probiotic food supplements in Italy." Int J Food Microbiol 137(2-3): 265-273. Exclude-Participants

Avlami, A., T. Kordossis, et al. (2001). "Lactobacillus rhamnosus endocarditis complicating colonoscopy." J Infect 42(4): 283-285. Exclude-Rec Genus

Awasthi, S. (2000). "Lactobacillus GG reduced diarrhoea incidence in children treated with antibiotics." Evid Based Med(5): 113. Exclude-NoAE

Axelrod, J., G. T. Keusch, et al. (1973). "Endocarditis caused by Lactobacillus plantarum." Ann Intern Med 78(1): 33-37. Exclude-Intervention

Bahar, R. J., B. S. Collins, et al. (2008). "Double-blind placebo-controlled trial of amitriptyline for the treatment of irritable bowel syndrome in adolescents." J Pediatr 152(5): 685-689. Exclude-Intervention

Bakker-Zierikzee, A. M., E. A. Tol, et al. (2006). "Faecal SIgA secretion in infants fed on pre- or probiotic infant formula." Pediatr Allergy Immunol 17(2): 134-140. Exclude-NoAE

Baldassarre, M. E., N. Laforgia, et al. (2010). "Lactobacillus GG improves recovery in infants with blood in the stools and presumptive allergic colitis compared with extensively hydrolyzed formula alone." J Pediatr 156(3): 397-401. Exclude-NoAE

Balli, F., P. Bertolani, et al. (1992). "[High-dose oral bacteria-therapy for chronic non-specific diarrhea of infancy]." Pediatr Med Chir 14(1): 13-15. Exclude-NoAE (Italian)

Barbara, G. and R. Corinaldesi (2000). "Probiotics: could they turn out to be ineffective in irritable bowel syndrome?" Dig Liver Dis 32(4): 302-304. Exclude-Design

Barbes, C. and S. Boris (1999). "Potential role of lactobacilli as prophylactic agents against genital pathogens." AIDS Patient Care STDS 13(12): 747-751. Exclude-NoAE

Barbi, M., M. Bardare, et al. (1992). "Antibody response to inactivated polio vaccine (E-IPV) in children born to HIV positive mothers." Eur J Epidemiol 8(2): 211-216. Exclude-Intervention

Barker, P., C. McNaught, et al. (2003). "Synbiotic in irritable bowel syndrome: a double blind prospective randomised controlled trial." Gut 52: A11. Exclude-NoAE

Barreto, R., Y. Naito, et al. (2000). "Gut flora manipulation mitigates ethanol-induced liver damage and endotoxinemia: experimental comparison between a novel probiotic and metronidazole." Intern Med J 7: 121-128. Exclude-Participants

Barrett, J. F. (2006). "Potential risk of probiotic usage." Expert Opin Drug Saf 5(1): 3-4. Exclude-Intervention

Bartlett, J. G. (2006). "Narrative review: the new epidemic of Clostridium difficile-associated enteric disease." Ann Intern Med 145(10): 758-764. Exclude-Rec NoAE

Basu, S., D. K. Paul, et al. (2009). "Efficacy of high-dose Lactobacillus rhamnosus GG in controlling acute watery diarrhea in Indian children: a randomized controlled trial." J Clin Gastroenterol 43(3): 208-213. Exclude-Duplicate 4762

Batac MaCR, G. M., Caparas-de Castro C, Gutierrez-Santos K, Tondoc A (2005). "Effects of a probiotic formula on measles, mumps and rubella IgG production and on anthropometric measurements of infants aged 11-15 months in a tertiary hospital." Santo Tomas Journal of Medicine 52(4): 124-130. Exclude-NoAE

Baughan, C. A., P. A. Canney, et al. (1993). "A randomized trial to assess the efficacy of 5-aminosalicylic acid for the prevention of radiation enteritis." Clin Oncol (R Coll Radiol) 5(1): 19-24. Exclude-Intervention

Bayer, A. S., A. W. Chow, et al. (1978). "Lactobacillemia--report of nine cases. Important clinical and therapeutic considerations." Am J Med 64(5): 808-813. Exclude-Intervention

Bayona-Gonzalez, A., V. Lopez-Camara, et al. (1990). "Final results of a dental caries clinical trial using heat killed lactic bacteria (Streptococci and Lactobacilli) orally." Pract Odontol 11(6): 41-47. Exclude-Rec Genus

Bazzarre, T., S. Liu-Wu, et al. (1983). "Total and HDL-cholesterol concentrations: yogurt and calcium supplementation " Nutr Rep Int 28: 17-24. Exclude-NoAE

Bazzocchi, G., P. Gionchetti, et al. (2002). "Intestinal microflora and oral bacteriotherapy in irritable bowel syndrome." Dig Liver Dis 34 Suppl 2: S48-53. Exclude-NoAE

Beerepoot, M. A., G. ter Riet, et al. (2006). "[Non-antibiotic prophylaxis for recurrent urinary-tract infections]." Ned Tijdschr Geneeskd 150(10): 541-544. Exclude-Rec NoAE (Dutch)

Bell, M. J. (1985). "Perforation of the gastrointestinal tract and peritonitis in the neonate." Surg Gynecol Obstet 160(1): 20-26. Exclude-Intervention

Bellete, B. (2006). "Molecular confirmation of an absidiomycosis following treatment with a probiotic supplement in a child with leukemia." Exclude-Rec Genus

Bellizzi, A., V. Barucca, et al. (2010). "Early years of biological agents therapy in Crohn's disease and risk of the human polyomavirus JC reactivation." Journal of Cellular Physiology 224(2): 316-326. Exclude-NoAE

Bengmark, S. (1998). "Ecological control of the gastrointestinal tract. The role of probiotic flora." Gut 42(1): 2-7. Exclude-Design

Bennett, R., S. L. Gorbach, et al. (1993). "Treatment of relasping Clostridium difficile diarrhea with Lactobacillus GG." Nutr Today 31: 35S-42S. Exclude-Duplicate 12844

Benno, P., I. Ernberg, et al. (2010). "[Probiotics--friends or enemies of the intestine?]." Lakartidningen 107(13-14): 907-909. Exclude-Design

Benno, Y. and T. Mitsuoka (1992). "Impact of Bifidobacterium longum on human fecal microflora." Microbiol Immunol 36(7): 683-694. Exclude-NoAE

Benton, D., C. Williams, et al. (2007). "Impact of consuming a milk drink containing a probiotic on mood and cognition." Eur J Clin Nutr 61(3): 355-361. Exclude-NoAE

Berg, R. D. (1992). "Translocation of enteric bacteria in health and disease." Curr Stud Hematol Blood Transfus(59): 44-65. Exclude-Intervention

Bergogne-Berezin, E. (2000). "Treatment and prevention of antibiotic associated diarrhea." Int J Antimicrob Agents 16(4): 521-526. Exclude-NoAE

Berrada, N., J. F. Lemeland, et al. (1991). "Bifidobacterium from fermented milks: survival during gastric transit." J Dairy Sci 74(2): 409-413. Exclude-NoAE

Besirbellioglu, B. A., A. Ulcay, et al. (2006). "Saccharomyces boulardii and infection due to Giardia lamblia." Scand J Infect Dis 38(6-7): 479-481. Exclude-NoAE

Besselink, M. G., H. M. Timmerman, et al. (2004). "Probiotic prophylaxis in patients with predicted severe acute pancreatitis (PROPATRIA): design and rationale of a double-blind, placebo-controlled randomised multicenter trial [ISRCTN38327949]." BMC Surg 4: 12. Exclude-NoAE

Besselink, M. G., H. C. van Santvoort, et al. (2009). "Timing and impact of infections in acute pancreatitis." Br J Surg 96(3): 267-273. Exclude-Intervention

Besselink, M. G., H. C. van Santvoort, et al. (2008). "[Probiotic prophylaxis in patients with predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial]." Ned Tijdschr Geneeskd 152(12): 685-696. Exclude-Duplicate 4767(Dutch)

Besselink, M. G., H. C. van Santvoort, et al. (2009). "Intestinal barrier dysfunction in a randomized trial of a specific probiotic composition in acute pancreatitis." Ann Surg 250(5): 712-719. Exclude-NoAE

Bessis, D., A. Le Quellec, et al. (1995). "Lactobacillus acidophilus endocarditis after an appendectomy." Clin Infect Dis 20(3): 724-725. Exclude-Design

Betsi, G. I., E. Papadavid, et al. (2008). "Probiotics for the treatment or prevention of atopic dermatitis: a review of the evidence from randomized controlled trials." Am J Clin Dermatol 9(2): 93-103. Exclude-Rec NoAE

Bettler, J. and A. Euler (2004). "An evaluation of the growth of term infants fed formula supplemented with fructo-oligosaccharide." Exclude-Rec Intervention

Bhutta, Z. A., A. M. Molla, et al. (1994). "Nutrient absorption and weight gain in persistent diarrhea: comparison of a traditional rice-lentil/yogurt/milk diet with soy formula." J Pediatr Gastroenterol Nutr 18(1): 45-52. Exclude-Intervention

Billot-Klein, D., L. Gutmann, et al. (1994). "Modification of peptidoglycan precursors is a common feature of the low-level vancomycin-resistant VANB-type Enterococcus D366 and of the naturally glycopeptide-resistant species Lactobacillus casei, Pediococcus pentosaceus, Leuconostoc mesenteroides, and Enterococcus gallinarum." J Bacteriol 176(8): 2398-2405. Exclude-Participants

Binns, C. W., A. H. Lee, et al. (2007). "The CUPDAY Study: prebiotic-probiotic milk product in 1-3-year-old children attending childcare centres." Acta Paediatr 96(11): 1646-1650. Exclude-Rec NoAE

Birch, E. E., S. Garfield, et al. (2007). "Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula." Early Hum Dev 83(5): 279-284. Exclude-Intervention

Bisson, J. F., S. Hidalgo, et al. (2010). "Preventive effects of different probiotic formulations on travelers' diarrhea model in wistar rats : preventive effects of probiotics on TD." Dig Dis Sci 55(4): 911-919. Exclude-Participants

Bittner, A., B. Caicedo, et al. (2007). "Probiotic-prebiotic Prescript-Assist(TM) treatment for bacterial diarrhea." Prensa Medica Argentina 94(3): 195-202. Exclude-NoAE (Spanish)

Blaire, E. and B. Tull (1968). "Multiple infections among newborns resulting from colonization with Staphylococcus aureus 502a." Am J Clin Pathol 52: 42. Exclude-Genus

Bodmann, K. F. and F. Vogel (2001). "Antimikrobielle Therapie der Sepsis.": 43-55. Exclude-Intervention (German)

Boehm, G., M. Lidestri, et al. (2002). "Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants." Arch Dis Child Fetal Neonatal Ed 86(3): F178-181. Exclude-Intervention

Bongaerts, G. (2007). "Lactobacillus Fermentum Bacteremia In A Seriously Ill Premature Short Small Bowel Patient During Probiotic Lactobacillus Casei Therapy." International Journal of probiotics 1(2): 145-158. Exclude-Rec Design

Bongaerts, G., R. Severijnen, et al. (2005). "Yeast mediates lactic acidosis suppression after antibiotic cocktail treatment in short small bowel?" Scand J Gastroenterol 40(10): 1246-1250. Exclude-Intervention

Bongaerts, G., R. Severijnen, et al. (2005). "Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy." Med Hypotheses 64(1): 64-68. Exclude-NoAE

Bongaerts, G. P., J. J. Tolboom, et al. (1997). "Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia." Microb Pathog 22(5): 285-293. Exclude-Intervention

Bongers, M. E., F. de Lorijn, et al. (2007). "The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial." Nutr J 6: 8. Exclude-Intervention

Bonnay, S., J. Darchis, et al. (1991). "Saccharomyces cerevisiae septicaemia in a cancer patient " Med Malad Infect 21: 73. Exclude-Intervention (French)

Bonorden, M. J., K. A. Greany, et al. (2004). "Consumption of Lactobacillus acidophilus and Bifidobacterium longum do not alter urinary equol excretion and plasma reproductive hormones in premenopausal women." Eur J Clin Nutr 58(12): 1635-1642. Exclude-Rec NoAE

Boonyaritichaikij, S., K. Kuwabara, et al. (2009). "Long-term administration of probiotics to asymptomatic pre-school children for either the eradication or the prevention of Helicobacter pylori infection." Helicobacter 14(3): 202-207. Exclude-NoAE

Borruel, N., M. Carol, et al. (2002). "Increased mucosal tumour necrosis factor alpha production in Crohn's disease can be downregulated ex vivo by probiotic bacteria." Gut 51(5): 659-664. Exclude-Participants

Bosques-Padilla, F. J. and A. R. Flores-Rendon (2005). "[Treatment of hepatic encephalopathy with probiotics and prebiotics]." Rev Gastroenterol Mex 70(3): 372-374. Exclude-NoAE

Boudraa, G., M. Touhami, et al. (1990). "Effect of feeding yogurt versus milk in children with persistent diarrhea." J Pediatr Gastroenterol Nutr 11(4): 509-512. Exclude-NoAE

Bouhnik, Y., A. Attar, et al. (2004). "Lactulose ingestion increases faecal bifidobacterial counts: a randomised double-blind study in healthy humans." Eur J Clin Nutr 58(3): 462-466. Exclude-Rec Intervention

Bouhnik, Y., P. Marteau, et al. (1993). "[The use of probiotics in humans]." Ann Gastroenterol Hepatol (Paris) 29(5): 241-249. Exclude-Rec NoAE

Bouhnik, Y., C. Neut, et al. (2004). "Prospective, randomized, parallel-group trial to evaluate the effects of lactulose and polyethylene glycol-4000 on colonic flora in chronic idiopathic constipation." Aliment Pharmacol Ther 19(8): 889-899. Exclude-Genus

Bouilly-Gauthier, D., C. Jeannes, et al. (2010). "Clinical evidence of benefits of a dietary supplement containing probiotic and carotenoids on ultraviolet-induced skin damage." Br J Dermatol. Exclude-NoAE

Boulloche, J., O. Mouterde, et al. (1994). "Management of acute diarrhoea in infants and young children. Controlled study of the antidiarrhoeal efficacy of killed L/ acidophilus (LB strain) versus a placebo and a reference drug (Loperamide)." Ann Pediatr 41: 1-7. Exclude-Rec Genus (Foreign Language)

Bourne, K. A., J. L. Beebe, et al. (1978). "Bacteremia due to Bifidobacterium, Eubacterium or Lactobacillus; twenty-one cases and review of the literature." Yale J Biol Med 51(5): 505-512. Exclude-Intervention

Bowden, T. A., Jr., A. R. Mansberger, Jr., et al. (1981). "Pseudomembraneous enterocolitis: mechanism for restoring floral homeostasis." Am Surg 47(4): 178-183. Exclude-Intervention

Boyce, J. M., S. M. Opal, et al. (1994). "Outbreak of multidrug-resistant Enterococcus faecium with transferable vanB class vancomycin resistance." J Clin Microbiol 32(5): 1148-1153. Exclude-Intervention

Boyle, R. J., L. Mah, et al. (2009). "In vivo, in vitro and transplacental immune effects of a probiotic bacterium lactobacillus rhamnosus GG in humans." Journal of Allergy and Clinical Immunology 123(2): S200. Exclude-NoAE

Brady, L. J., D. D. Gallaher, et al. (2000). "The role of probiotic cultures in the prevention of colon cancer." J Nutr 130(2S Suppl): 410S-414S. Exclude-NoAE

Braegger, C. (2002). "Probiotics in the prevention and treatment of acute infectious diarrhea in children." (150): 824-828. Exclude-Rec Design (German)

Brand, S. and H. Reinecker (2002). "An enhanced barrier is a better defense: effects of probiotics on intestinal barrier function." Inflammatory Bowel Diseases 8: 67-69. Exclude-Participants

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Larvol, L., A. Monier, et al. (1996). "[Liver abscess caused by Lactobacillus acidophilus]." Gastroenterol Clin Biol 20(2): 193-195. Exclude-Intervention (French)

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Lata, J. and O. Stiburek (2010). "[Antibiotics and probiotics in acute pancreatitis]." Vnitr Lek 56(6): 582-584. Exclude-Design

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Lee, K., M. Lee, et al. (2008). "Safety assessment of commercial Enterococcus probiotics in Korea." J Microbiol Biotechnol 18(5): 942-945. Exclude-Participants

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Saltzman, J. R., R. M. Russell, et al. (1999). "A randomized trial of Lactobacillus acidophilus BG2FO4 to treat lactose intolerance." Am J Clin Nutr 69(1): 140-146. Exclude-NoAE

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Sandborn, W. J., R. McLeod, et al. (1999). "Medical therapy for induction and maintenance of remission in pouchitis: a systematic review." Inflamm Bowel Dis 5(1): 33-39. Exclude-NoAE

Sanders, M. E. (2006). "Summary of probiotic activities of Bifidobacterium lactis HN019." J Clin Gastroenterol 40(9): 776-783. Exclude-Rec Design

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Sawada, J., H. Morita, et al. (2007). "Ingestion of heat-treated Lactobacillus rhamnosus GG prevents development of atopic dermatitis in NC/Nga mice." Clin Exp Allergy 37(2): 296-303. Exclude-Participants

Saxelin, M. (1997). "Lactobacillus gg. a human probiotic strain with thorough clinical documentation." Food Reviews International 13(2): 293-313. Exclude-NoAE

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Saxelin, M., N. H. Chuang, et al. (1996). "Lactobacilli and bacteremia in southern Finland, 1989-1992." Clin Infect Dis 22(3): 564-566. Exclude-Rec Intervention

Saxelin, M., T. Pessi, et al. (1995). "Fecal recovery following oral administration of Lactobacillus strain GG (ATCC 53103) in gelatine capsules to healthy volunteers." Int J Food Microbiol 25(2): 199-203. Exclude-NoAE

Saxelin, M., H. Rautelin, et al. (1996). "The safety of commercial products with viable Lactobacillus strains." Infect Dis Clin Prac 5: 331-335. Exclude-Participants

Sazawal, S., U. Dhingra, et al. (2007). "Effects of fortified milk on morbidity in young children in north India: community based, randomised, double masked placebo controlled trial." BMJ 334(7585): 140. Exclude-Genus

Sazawal, S., G. Hiremath, et al. (2006). "Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials." Lancet Infect Dis 6(6): 374-382. Exclude-NoAE

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Schellenberg, D., A. Bonington, et al. (1994). "Treatment of Clostridium difficile diarrhoea with brewer's yeast." Lancet 343(8890): 171-172. Exclude-NoAE

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Schultz, M. J. (2010). "Symbiotics as a preventive measure against ventilator-associated pneumonia." Crit Care Med 38(6): 1506-1507; author reply 1507. Exclude-Design

Schwabb, J. (1993). "Phlogistic properties of peptido-glycan-polysaccharide polymers from cell walls of pathogenic and normal-flora bacteria which colonise humans." Infect Immun(61): 4535-4539. Exclude-Participants

Schwan, A., S. Sjolin, et al. (1983). "Relapsing clostridium difficile enterocolitis cured by rectal infusion of homologous faeces." Lancet 2(8354): 845. Exclude-Intervention

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Sedman, P. C., J. Macfie, et al. (1994). "The prevalence of gut translocation in humans." Gastroenterology 107(3): 643-649. Exclude-Intervention

See, J. (2006). "Lactobacillus endocarditis: Case report and literature review." Exclude-Rec Genus

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Seidel, C., V. Boehm, et al. (2007). "Influence of prebiotics and antioxidants in bread on the immune system, antioxidative status and antioxidative capacity in male smokers and non-smokers." Br J Nutr 97(2): 349-356. Exclude-Intervention

Seki, H., M. Shiohara, et al. (2003). "Prevention of antibiotic-associated diarrhea in children by Clostridium butyricum MIYAIRI." Pediatr Int 45(1): 86-90. Exclude-Genus

Semmo, N. (2007). "Probiotic drink prevents antibiotic associated diarrhea." Zeitschrift fur Gastoenterologie 45(11): 1110. Exclude-Rec Design (Foreign Language)

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Senok, A. C., V. H., et al. (2006). "Probiotics for the treatment of bacterial vaginosis." Cochrane Database of Systematic Reviews 4. Exclude-Design

Senok, A. C., A. Y. Ismaeel, et al. (2005). "Probiotics: facts and myths." Clin Microbiol Infect 11(12): 958-966. Exclude-Rec NoAE

Sensenig, J., M. Johnson, et al. (2001). "Treatment of migraine with targeted nutrition focused on improved assimilation and elimination." Altern Med Rev 6(5): 488-494. Exclude-NoAE

Sentongo, T. A., V. Cohran, et al. (2008). "Intestinal permeability and effects of Lactobacillus rhamnosus therapy in children with short bowel syndrome." J Pediatr Gastroenterol Nutr 46(1): 41-47. Exclude-NoAE

Sepp, E., K. Julge, et al. (1997). "Intestinal microflora of Estonian and Swedish infants." Acta Paediatr 86(9): 956-961. Exclude-Intervention

Sepp, E., M. Mikelsaar, et al. (1993). "Effect of administration of Lactobacillus casei strain GG on the gastrointestinal microbiota of newborns." Microbila Ecology in Health and Disease 6: 309-314. Exclude-NoAE

Sethi, N. and W. Mandell (1988). "Saccharomyces fungemia in a patient with AIDS." N Y State J Med 88(5): 278-279. Exclude-Intervention

Shadid, R., M. Haarman, et al. (2007). "Effects of galactooligosaccharide and long-chain fructooligosaccharide supplementation during pregnancy on maternal and neonatal microbiota and immunity--a randomized, double-blind, placebo-controlled study." Am J Clin Nutr 86(5): 1426-1437. Exclude-Intervention

Shah, U. and W. A. Walker (2000). "Adverse host responses to bacterial toxins in human infants." J Nutr 130(2S Suppl): 420S-425S. Exclude-Design

Shalev, E. (2002). "Ingestion of probiotics: optional treatment of bacterial vaginosis in pregnancy." Isr Med Assoc J 4(5): 357-360. Exclude-NoAE

Shamir, R., I. R. Makhoul, et al. (2005). "Evaluation of a diet containing probiotics and zinc for the treatment of mild diarrheal illness in children younger than one year of age." J Am Coll Nutr 24(5): 370-375. Exclude-NoAE

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Sharma, J., C. Chanana, et al. (2007). "Comparison of ofloxacin & ornidazole with probiotic versus doxycycline & metronidazole for the outpatient treatment of pelvic inflammatory disease." JK Science 9(2): 66-69. Exclude-NoAE

Sharma, J. K., K. K. Kapoor, et al. (1980). "Clinical trial of Sporlac in the treatment of recurrent aphthous ulceration." Uttar Pradesh State Dent J 11(1): 7-12. Exclude-NoAE

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Shaw, L. (2006). "Effects of probiotics on atopic dermatitis." Arch Dis Child 91(4): 373. Exclude-NoAE

Sheen, P., R. A. Oberhelman, et al. (1995). "Short report: a placebo-controlled study of Lactobacillus GG colonization in one-to-three-year-old Peruvian children." Am J Trop Med Hyg 52(5): 389-392. Exclude-Rec NoAE

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Shermak, M. A., J. M. Saavedra, et al. (1995). "Effect of yogurt on symptoms and kinetics of hydrogen production in lactose-malabsorbing children." Am J Clin Nutr 62(5): 1003-1006. Exclude-NoAE

Sherman, M. E., M. Albrecht, et al. (1987). "An unusual case of splenic abscess and sepsis in an immunocompromised host." Am J Clin Pathol 88(5): 659-662. Exclude-Design

Sheu, B., J. Wu, et al. (2002). "Impact of supplement with Lactobacillus and Bifidobacteria - containing yogurt on triple therapy for Helicobacter pylori eradication." Aliment Pharmacol Ther 16: 1669-1675. Exclude-Duplicate 1749

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Shiau, S. L., B. H. Su, et al. (2007). "Possible effect of probiotics and breast milk in short bowel syndrome: report of one case." Acta Paediatr Taiwan 48(2): 89-92. Exclude-NoAE

Shibolet, O., F. Karmeli, et al. (1999). "Probiotics ameliorates iodoacetamide induced colitis." Gastroenterology 116: A818. Exclude-Participants

Shimizu, R. and H. Haruna (2002). "Effects of Lactobacillus gasseri OLL 2716 (LG21) on Helicobacter pylori infection in children [5]." J Antimicrob Chemother 50(4): 617-618. Exclude-NoAE

Shinefield, H. R., J. C. Ribble, et al. (1971). "Bacterial interference between strains of Staphylococcus aureus, 1960 to 1970." Am J Dis Child 121(2): 148-152. Exclude-Genus

Shlaes, D. M., J. Levy, et al. (1981). "Enterococcal bacteremia without endocarditis." Arch Intern Med 141(5): 578-581. Exclude-Intervention

Shornikova, A. V., I. A. Casas, et al. (1997). "Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children." J Pediatr Gastroenterol Nutr 24(4): 399-404. Exclude-NoAE

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Shteyer, E. and M. Wilschanski (2008). "Novel therapeutic modalities in pediatric inflammatory bowel disease." Isr Med Assoc J 10(11): 816-820. Exclude-NoAE

Sicherer, S. H. and L. S. Ford (2009). "Probiotic supplementation in the first 6 months of life in at risk Asian infants: Effects on eczema and atopic sensitization at the age of 1 year." Pediatrics 124(SUPPL. 2): S112. Exclude-Duplicate 5858

Siegman-Igra, Y., J. Lavochkin, et al. (1983). "Meningitis and bacteremia due to Bacillus cereus. A case report and a review of Bacillus infections." Isr J Med Sci 19(6): 546-551. Exclude-Intervention

Siitonen, S., H. Vapaatalo, et al. (1990). "Effect of Lactobacillus GG yoghurt in prevention of antibiotic associated diarrhoea." Ann Med 22(1): 57-59. Exclude-NoAE

Silk, D. B., A. Davis, et al. (2009). "Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome." Aliment Pharmacol Ther 29(5): 508-518. Exclude-Intervention

Silva, M. R., G. Dias, et al. (2008). "Growth of preschool children was improved when fed an iron-fortified fermented milk beverage supplemented with Lactobacillus acidophilus." Nutr Res 28(4): 226-232. Exclude-NoAE

Simakachorn, N., V. Pichaipat, et al. (2000). "Clinical evaluation of the addition of lyophilized, heat-killed Lactobacillus acidophilus LB to oral rehydration therapy in the treatment of acute diarrhea in children." J Pediatr Gastroenterol Nutr 30(1): 68-72. Exclude-Rec NoAE

Simark-Mattsson, C., C. G. Emilson, et al. (2007). "Lactobacillus-mediated interference of mutans streptococci in caries-free vs. caries-active subjects." Eur J Oral Sci 115(4): 308-314. Exclude-Design

Simren, M., A. Syrous, et al. (2006). "Effects of Lactobacillus Plantarum 299V on symptoms and rectal sensitivity in patients with irritable bowel syndrome (IBS) - a randomized double blind controlled trial." Gastroenterology 130(Suppl 2): A600. Exclude-Rec NoAE

Singh, T. (1987). "Yoghurt feeding during acute diarrhea." Indian Pediatr 24(6): 530. Exclude-NoAE

Sistek, D., R. Kelly, et al. (2006). "Is the effect of probiotics on atopic dermatitis confined to food sensitized children?" Clin Exp Allergy 36(5): 629-633. Exclude-NoAE

Slonim, A. E., M. Grovit, et al. (2009). "Effect of exclusion diet with nutraceutical therapy in juvenile Crohn's disease." J Am Coll Nutr 28(3): 277-285. Exclude-NoAE

Smith, D., D. Metzgar, et al. (2002). "Fatal Saccharomyces cerevisiae aortic graft infection." J Clin Microbiol 40(7): 2691-2692. Exclude-Intervention

Sobel, J. D., J. Vazquez, et al. (1993). "Vaginitis due to Saccharomyces cerevisiae: epidemiology, clinical aspects, and therapy." Clin Infect Dis 16(1): 93-99. Exclude-Intervention

Socha, J., A. Stolarczyk, et al. (2002). "Role of bifidobacteria in prophylaxis and treatment of selected diseases in children." 4(1): 47-47. Exclude-Design (Polish)

Soh, S. E., M. Aw, et al. (2009). "Probiotic supplementation in the first 6 months of life in at risk Asian infants--effects on eczema and atopic sensitization at the age of 1 year." Clin Exp Allergy 39(4): 571-578. Exclude-NoAE

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