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# REPORT OF THE ASM TASK FORCE ON ANTIBIOTIC RESISTANCE

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AMERICAN SOCIETY FOR MICROBIOLOGY
PUBLIC AND SCIENTIFIC AFFAIRS BOARD
1325 MASSACHUSETTS AVENUE, N.W.
WASHINGTON, D.C. 20005-4171
(202) 737-3600

# EXECUTIVE SUMMARY

The American Society for Microbiology (ASM), the oldest life science society in the world, represents over 40,000 members. ASM members include scientists in medical microbiology (infectious and immunological diseases), molecular biology and genetics, industrial and food microbiology, biotechnology and public health, agriculture, water purification and waste treatment, environmental science, dental microbiology, veterinary medicine, as well as education and regulatory activities.

The membership of ASM is gravely concerned about the national and global increase in antibiotic resistance and the complex issues surrounding this public health threat. Infections caused by resistant pathogens result in morbidity and mortality from treatment failures and increased health care costs as newer, more expensive antibiotics are needed to treat common infections. As resistance spreads involving more antibiotics and more pathogens, infections may occur which cannot be treated effectively with antibiotics. Due to increasing drug resistance in animal pathogens and changes in food production practices there is a growing threat to food the food industry and hence the U. S. economy. Due to increased foreign trade, travel, and immigration the threat of global spread of antibiotic resistance has never been greater.

Because of these concerns, the Public and Scientific Affairs Board of ASM convened a Task Force composed of expert scientists (see Appendix A) from the academic, government and industrial sectors. The Task Force considered the current prevalence of antibiotic resistance, major factors affecting the emergence of antibiotic resistance, future research needs and future surveillance strategies for monitoring resistance. The conclusions and recommendations of this group are as follows:

## FINDINGS AND CONCLUSIONS

- Although defining the precise public health risk of emergent antibiotic resistance is not a simple undertaking, there is little doubt the problem is global in scope and very serious. Some of the more striking examples include the following:

  Today, in the U. S., more than 90% of strains of *Staphylococcus aureus* (one of the most common disease-producing organisms in humans) are resistant to penicillin and other beta-lactam antibiotics (1).

  According to the National Centers for Disease Control and Prevention (CDC) the incidence of vancomycin resistant enterococci in the U. S. increased 20 times from January 1989 to March

1993 (2). Enterococci are the most common cause of hospital acquired infections and vancomycin is often the last weapon available against these potentially deadly microbes.

Before 1987, antibiotic resistant *Streptococcus pneumoniae* "pneumococci)" were uncommon in the U.S. Recent reports document an alarming increase in pneumococcal infections resistant to commonly used antibiotics (3). Pneumococci are the leading cause of pneumonia, meningitis, and blood stream infections in the elderly and the leading cause of middle ear infections in children. These infections are treated empirically, during the critically important initial days of therapy. In order to choose the most optimal antimicrobial drug for initial therapy, physicians need to know the pattern of drug resistance of pneumococci circulating in their community.

Medical care costs associated with treating infections in humans due to antibiotic resistant microorganisms is estimated to be over $4 billion annually in the U.S. (CDC, unpublished data).

- While appropriate antimicrobial drug use has unquestionable benefit, often these agents are used inappropriately by physicians and the public. Inappropriate use results from physicians providing antimicrobials to treat viral infections, using inadequate criteria for diagnosis of infections that potentially have a bacterial etiology, unnecessarily prescribing expensive, broad spectrum agents, and not following established recommendations for using chemoprophylaxis. It is also likely that patients or in the case of children, their parents contribute to antimicrobial misuse by pressuring physicians to provide treatment.

- Fueling the excessive use of broad spectrum antimicrobial drugs is an absence of reliable diagnostic tests that enable physicians to accurately discern when antimicrobial drugs are not needed. When antimicrobial drug therapy is needed, improved diagnostic tests would lead to use of more targeted antimicrobial drugs, resulting in a reduction in the widespread administration of broad spectrum drugs.

- Selective pressure exerted by widespread antimicrobial use is the driving force in the development of antibiotic resistance. The association between increased rates of antimicrobial use and resistance has been documented for nosocomial infections in hospital-based studies (4), and for resistant community-acquired infections in studies associating rates of drug use on a regional or national basis with resistance patterns (5). In addition, case-control studies have shown antimicrobial use as a significant risk factor for infection with a resistant pathogen (6,7).

- According to the CDC, most antimicrobial use in humans is for treatment of outpatient infections. In 1992, an estimated 110 million courses of antimicrobial therapy were prescribed by office-based physicians in the U. S., a 28% increase over 1980 (8).

- While antimicrobials are provided to persons of all ages to treat a variety of conditions, the best data are available for the pediatric population. Data from the National Center for Health Statistics (NCHS) indicates that the rate of antimicrobial use in children (less than age 15) is more than 3-times greater than any other age group within the population (8). In addition, the leading diagnoses resulting in antimicrobial prescriptions in 1990 were all common pediatric infections including otitis media, upper respiratory infection, bronchitis, sinusitis, and pharyngitis.

- Otitis media is the second leading cause of office visits to physicians (24.5 million visits in 1990 (9), and the leading cause of emergency room visits (10). This diagnosis accounts for over 40% of all outpatient antimicrobial use in children (11).

- As the leading bacterial causes of otitis have developed resistance to "first line" antibiotics, therapy with new, broader-spectrum, more expensive antibiotics has increased. The significance of the resulting selective pressure extends far beyond its potential impact on resistance in otitis media. Resistance among pathogens such as *S. pneumoniae*, affects persons of all ages who have pneumococcal infections including pneumonia, bacteremia, and meningitis. Antimicrobial use for otitis media and other upper respiratory infections also exerts selective pressure on other bacterial species that colonize the respiratory and gastrointestinal tracts which are not etiologies of otitis media, such as *Staphylococcus*, Gram negative enteric organisms, and enterococcus.

- In 1988, the National Academy of Sciences/Institute of Medicine estimated that nearly half of the total annual production of antibiotics is directed to use in farm animals (12).

- Due to changes in management practices (i.e. consolidation of animal production in very large facilities instead of small-scale family farms), there is also a growing concern related to animal health, antibiotic resistance, and therefore food production in this country. Conditions are such that diseases can spread rapidly through a large number of animals in a herd or flock, sometimes with dire economic consequences. As is the case for diseases in humans, the number of therapeutic options for treatment of diseases in animals (both farm and domestic) is diminishing.

- Increasing reliance on aquaculture for food production, the increasing problems associated with infectious diseases in fish, the limited number of drugs available for treatment and

prevention of these diseases, and the rapid increase in resistance to these antibiotics, represent major challenges for production of this food source world wide.

- Resistance factors in human and animal pathogens, particularly those carried on mobile elements, can spread rapidly within human and animal populations and from animals to humans, particularly in contaminated food products.

- Resistance to antimicrobial drugs is a global problem. Multidrug resistant pathogens travel not only locally but also traverse wide parts of the globe. Due to increased international travel and increased foreign trade of fresh food products, the threat of global spread of antibiotic resistance is greater than ever before.

- The relative utility of available antibiotics is eroding, tipping the balance in favor of multidrug resistant pathogens and there appear to be few new drugs in the pipe lines of the U. S. pharmaceutical companies. These developments amount to an incipient public health "emergency," albeit one that is poorly appreciated or recognized.

- Currently there is no national or global surveillance system for monitoring of antibiotic resistance in animals or humans. In fact the amount being expended is totally inadequate. The last survey which was conducted in 1992 indicates that less than a total of $55,000 is spent in the U.S. for antibiotic resistance monitoring in human pathogens at the federal, state, and local levels (13). The Task Force concluded that due to the lack of a national surveillance system that current data related to the incidence of antibiotic resistance represent only the tip of the iceberg. There are even fewer data available on the incidence of antibiotic resistance in animal pathogens. Therefore, the magnitude of the problem has likely been underestimated.

- Emphasis in developed countries should be placed on the availability of safe and effective antibiotics and the enforcement of more responsible national drug policies. Success will require the collective action of governments, the pharmaceutical industry, health care providers, and consumers.

# RECOMMENDATIONS

1. **A national surveillance system should be established immediately.**

- Federal funding should be immediately allocated for the establishment of a national antibiotic resistance surveillance system in animals, humans, and food products. The lead agency should be the National Center for Infectious Diseases of the National Centers for Disease Control and Prevention. Other agencies, specifically the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, the United States Department of Agriculture, the Environmental Protection Agency, and the Food and Drug Administration should be involved in establishing priorities, implementation of regulatory policies related to antibiotic resistance. These agencies should receive additional funding for this purpose. None of these federal agencies have adequate funding to address the magnitude of current problems related to antibiotic resistance.

2. **Professional and public education should be strengthened in the area of infectious diseases and antibiotics to reduce inappropriate usage of antibiotics.**

- An urgent need exists for more appropriate selection and use of antimicrobial drugs. The curriculum of health professional (medical, dental, nursing and veterinary) schools and postgraduate educational programs should be strengthened in the areas of sterilization, disinfection, hazards of inappropriate antimicrobial drug use, and appropriate diagnosis and treatment of infectious diseases, and antibiotic resistance. These efforts should result in reduction of spread of infectious agents and more prudent use of antibiotics.

- Better guidelines should be established and enforced to reduce the spread of infectious agents and antibiotic resistance in the hospital environment, nursing homes, day care facilities, and food production industries.

- Educational materials should be developed and widely distributed to patients and food producers . The need for partnerships in improving antimicrobial use for cost effective treatment of infections and to preserve the effectiveness of antimicrobials for the future should be emphasized.

3. There is an urgent need for more basic research directed toward development of new antimicrobial compounds, effective vaccines, and other prevention measures.

- In FY 1994 allocations to the National Institute of Allergy and Infectious Diseases of the NIH for funding of non-AIDS infectious disease research were reduced by $20 million. Increased appropriations are urgently needed to fund areas of research directly related to new and re-emerging infections and antibiotic resistance.

- More basic research is needed to delineate the genetic and metabolic pathways, including essential regulatory factors, that determine virulence as well as antibiotic susceptibility or resistance in pathogens of human and veterinary importance. To conduct this research, better, more consistent measures of antibiotic resistance are needed, and a culture collection containing representative antibiotic resistant biotypes and genotypes should be developed and made available for researchers worldwide. Such studies are expected to help in identifying novel targets for molecules that interfere specifically with essential physiological steps of pathogens.

- More resources should be devoted to the sequencing of the entire genome of microbial pathogens in an attempt to identify common antimicrobial targets.

- More basic research is needed to determine the mechanisms of spread of pathogens particularly in closed populations (i.e. hospitals, child care facilities, and food production facilities).

- More basic research is needed to better understand the genetics of microorganisms and the development of antibiotic resistance, particularly in fungi and newly described pathogens.

- Research is needed for development of rapid, reliable diagnostic techniques for identifying specific infectious causes of illnesses. More clinical and epidemiologic research is needed to determine the clinical impact of infection with drug resistant pathogens and to identify the most optimal therapeutic options in the setting of infection with a drug resistant strain. More clinical research is needed to clarify the etiology of otitis and respiratory infections in all age groups.

- The laws of evolution dictate that microbes will eventually develop resistance to nearly every antibiotic. Thus, more basic research is needed to facilitate development of effective vaccines and other prevention measures. Vaccines are the most cost effective method of disease control and prevention for many diseases.

# I. FINDINGS AND CONCLUSIONS

## A. Definition of the Problem of Antibiotic Resistance

Although defining the precise public health risk of emergent antibiotic resistance is not a simple undertaking, there is little doubt the problem is global in scope and very serious.

Antibiotic resistance results in morbidity and mortality from treatment failures and increased health care costs. Current costs related to treatment of infections with antibiotic resistant organisms are estimated by the National Centers for Disease Control and Prevention (CDC) to be over $4 billion annually. As resistance spreads involving more and more infectious agents, the concern is that infections may occur which cannot be effectively treated with antimicrobials. Also, of growing concern is the impact of antimicrobial resistance upon the food production industry and food safety in the U.S.

When penicillin was introduced in 1940, virtually all strains of *Staphylococcus aureus*--bacteria associated with pneumonia, bronchitis, abscesses, osteomyelitis--were susceptible to this antibiotic. Today, more than 90% of strains of this organism are resistant to penicillin and other beta-lactam antibiotics (1). In addition, enterococci--the second leading cause of hospital acquired infections have developed resistance to vancomycin The incidence of vancomycin-resistant enterococci associated with hospital acquired infections increased 20 times from January 1989 to March 1993, according to the CDC. Increasing resistance to vancomycin is alarming, since this antibiotic is often the last weapon the physician has against this potentially deadly microbe (2). A great fear is that these microorganisms will transfer the resistance factor for vancomycin, which represents the last effective antibiotic for many common infectious diseases, to other more frankly virulent bacterial pathogens such as *S. aureus*. Due to resistance to penicillin, aminoglycosides, and other agents vancomycin resistant strains are essentially untreatable (2). There are other parts of the world where treatment of some forms of bacterial intestinal infections and gonorrhea is now limited to a single effective antibiotic.

Medical experts duly noted the appearance of antibiotic resistant *Streptococcus pneumoniae* in New Guinea as early as 1967 but concluded that the microorganisms were not likely to spread and thus posed little threat to the general population. This prediction was erroneous. Drug resistant pneumococcal infections became prevalent in South Africa in the 1970s and in Europe in the 1980s. These strains are becoming increasingly prevalent in the United States in the 1990s (3). This is of major concern because *S. pneumoniae* infections are among the leading causes of illness and death among young children, persons with debilitating medical conditions, and the elderly worldwide.

Although the infections caused by antibiotic resistant pathogens cause serious problems in the general population, such infections can be particularly devastating for the very young, the elderly,

and the immunocompromised. With respect to these patient populations, antimicrobial resistance is becoming a major concern in treating fungal infections. Currently, 10% of all nosocomial bloodstream infections are caused by Candida species, with an attributable mortality of 38%. The overall rate of candidemia is 5 to 10 per 10,000 hospital admissions; the rate is much higher in high-risk patients (14). High-risk patients include those who are immunosuppressed such as those with leukemia, solid tumors, and neutropenia, bone marrow transplant patients, premature infants, and burn patients.

It was recently reported that 23% of 157 orthotopic liver transplant patients experienced disseminated fungal infections and that these infections contributed to the deaths of 13% of the 157 (58% of those infected) (15). The excess length of hospital stay due to Candida infections can be greater than 30 days at an average cost of $1,200 per hospital day per patient. Resistance to fluconazole has been increasing for *Candida albicans* from mucocutaneous disease in HIV positive patients in France for the past four years. There appears to be both clinical and microbiological resistance.

Antibiotic resistance is not only a threat to human health from the standpoint of treatment of infectious diseases but also to our economic health because of the emerging threat to food production. During the past two decades, U. S. production of poultry, beef, and swine has consolidated under corporate direction, with animals typically concentrated in very large facilities instead of on small-scale family farms. For instance, a typical farm with a corporate affiliation may house 100,000 chickens. In such settings, strong management techniques are emphasized as a way of minimizing and controlling infectious diseases. However, conditions are such that diseases can spread rapidly through a large number of animals in a herd or flock, sometimes with dire economic consequences. As is the case for diseases in humans, the number of therapeutic options for treatment of diseases in animals (both farm and domestic) is diminishing. The increasing reliance on aquaculture for food production in this country, the increasing problems associated with infectious agents and the limited number of drugs available for treatment and prevention of infectious diseases in fish represent some of the most difficult challenges in antibiotic resistance and food production.

Antibiotic resistant pathogens in animals is not only a concern with respect to animal health but it is a growing concern because of possible transmission to humans as foodborne pathogens. The role of animals as primary sources of human disease has now been documented (e.g. campylobacters in contaminated poultry, salmonella serotype enteritidis from eggs, and vibrios in fish) (16,17). Foodborne illness associated with fruits and vegetables is also increasing in this country.

Ironically, as disease related to bacterial pathogens and antibiotic resistance is increasing, the search for new drugs or other novel agents to combat bacterial pathogens has lost much of its momentum in recent years. Advances in chemistry and biochemistry as well as the availability of

rapid screening methods mean that tens of thousands of chemical derivatives can now be looked at rather quickly and at least superficially evaluated in large numbers. Significant effort has been expended to understand mechanisms of action of resistance to identify new targets based on understanding of fundamental cellular/virulence properties to design screens to specifically address those targets. Despite the availability of such new screening methods, this approach has not uncovered a new and widely useful family of antibiotic drugs since the fluroquinolones came into clinical use a number of years ago.

Given these forces, the relative utility of available antibiotics is eroding, tipping the balance in favor of multidrug resistant pathogens. These developments amount to an incipient public health "emergency," albeit one that is poorly appreciated or recognized. Early successes during the antibiotic era helped to foster widely held beliefs among researchers, the medical community, and the general population, that infectious diseases would soon be conquered and that research and public health attention could safely shift to other problems. Reversing that general perception and overcoming the complacency that has grown up around it are not easy undertakings but must occur.

B. Emergence and Spread of Antibiotic Resistance

The laws of evolution dictate that microbes will eventually develop resistance to nearly any antibiotic. Selective pressure exerted by widespread antimicrobial use is a driving force for the development of antibiotic resistance. The association between increased rates of antimicrobial use and resistance has now been documented for nosocomial infections in hospital-based studies (4), and for resistant community-acquired infections in studies associating rates of drug use on a local or national basis with resistance patterns (5). In addition, case-control studies have shown antimicrobial use as a significant risk factor for infection with a resistant pathogen (6,7).

According to CDC, most antimicrobial use in humans is for treatment of outpatient infections. In 1992, an estimated 110 million courses of antimicrobial therapy were prescribed by office-based physicians in the U. S., a 28% increase over 1980 (8).

Factors contributing to the emergence of antibiotic resistance differ depending upon the geographic location. Over-the-counter use of antibiotics and their use as "folk" remedies have contributed to antibiotic resistance in developing countries. In other areas, abuse in prophylactic and empiric therapy and misuse of the newest drugs for questionable indications in the community have been major contributors.

Due to a number of factors, including the critical state of the patient, physicians are often forced to use antibiotics empirically, prior to receiving test results which routinely take several days to process. Predicting the cause of disease without laboratory test results is risky because one or

more organisms may be involved. Such use of antibiotics contributes to development of resistance. There is concern that new cost containment pressures may also impede appropriate management of infections if physicians must select antibiotics that are on a hospital's "formulary". Widespread use of oral antibiotics for treatment of acne and other mild conditions are of growing concern.

Inappropriate use of antibiotics results from application of inadequate criteria for diagnosis of infections that potentially have a bacterial etiology, unnecessarily prescribing expensive, broad spectrum agents, and not, following established recommendations for using chemoprophylaxis. It is also likely that patients or in the case of children, their parents contribute to antimicrobial misuse by pressuring physicians to provide treatment. The reduced time in the medical school curriculum devoted to basic microbiology and principals of infectious diseases has undoubtedly contributed to these problems.

While antimicrobials are provided to persons of all ages to treat a variety of conditions, the best data are available for the pediatric population. Data from the National Center for Health Statistics indicates that the rate of antimicrobial use in children less than age 15 is more than 3-times greater than any other age group within the population (8). In addition, the leading diagnoses resulting in antimicrobial prescriptions in 1990 were all common pediatric respiratory infections including otitis media, upper respiratory infection, bronchitis, sinusitis, and pharyngitis.

Otitis media (ear infections) is the second leading cause of office visits to physicians (24.5 million visits in 1990 (9), and the leading cause of emergency room visits (10). This diagnosis accounts for over 40% of all outpatient antimicrobial use in children (11). As resistance to "first line" antibiotics has developed in the leading bacterial pathogens that cause otitis media, therapy with new, more expensive, broader-spectrum cephalosporins and combination agents has increased. Pharmacy records of two Health Maintenance Organization practice plans indicate that, in 1993-94, 24% and 17% of children with otitis media had been treated with cephalosporins and combination agents. The significance of the resulting selective pressure extends far beyond its potential impact on resistance in otitis media. Resistance among pathogens such as *S. pneumoniae*, affect both children and adults with other pneumococcal infections including pneumonia, bacteremia, and meningitis. Selective pressure also would be exerted on other colonizing bacterial species that are not etiologies of otitis media, such as Gram negative enteric organisms and enterococcus.

Resistance factors, particularly those carried on mobile elements, can spread rapidly within human and animal populations and to a certain extent the environment. Multidrug resistant pathogens travel not only locally but also traverse wide parts of the globe. For example, a specific strain of *S.. pneumoniae*, resistant to multiple antimicrobial drugs, was observed first in South Africa in 1977. Since then, as evidenced by its molecular signature, it has become the commonly identified

multidrug resistant form of *S. pneumoniae* in a variety of distant settings, including Spain, the United Kingdom, and Iceland (3).

In various regions of the world, one area may become overrun with multi-drug resistant pathogens, whereas a neighboring area may be relatively unaffected or, at least temporarily, spared. On the Iberian Peninsula, for instance, Portugal is relatively free of penicillin resistant forms of pneumococci, whereas such pathogens are common in neighboring Spain. Similarly, within Hungary, the overall prevalence of these penicillin resistant *S. pneumoniae* is moderate to high at 35-40%, but that average varies considerably from county to county, with far higher rates in regions bordering Ukraine where poverty is common. Within the U.S. the prevalence of antibiotic resistance can even vary tremendously within hospitals within the same city.

Increased travel "both foreign and domestic" fosters spread of organisms, disease, and spread of antibiotic resistance (18). Over 100 million people currently live outside the countries in which they were born (19).

Commercial movement of fruits and vegetables from one country to another, also redistribute microorganisms and their resistance factors. There is a rapid increase in foodborne diseases in this country. In 1992, there were over 9,000 deaths attributable to foodborne bacteria (CDC, unpublished data).

Many unanswered questions surround the role of animals and the microbiota and the contribution to the problem of antibiotic resistance. However, the need for increased production of fish and the increasing use of aquaculture represents one of the biggest concerns. First, this commercial activity is growing in volume but practices are far from standardized or regulated. Second, when antibiotics are used in aquaculture settings, the drugs typically remain in the open environment and may flow out of growth ponds into open waterways or sewage systems to become widely disseminated environmental contaminants. Third, the antibiotics used are the same as those used to treat human infection. Antibiotics specific for fish have not been considered economical to produce. The impact of all these factors on the overall emergence of antibiotic resistance is unknown. However, recent studies indicate that the level of resistant bacteria in the gut of wild fish in nearby ponds is affected during antimicrobial treatment of farmed fish. Furthermore, these studies convincingly demonstrate an increase in resistant bacteria in the intestine of fish receiving antimicrobial drugs. Seventy-four to 100% of wild fish in close proximity to treated ponds contained quinolone residues (20). Furthermore, prior to medication 0.6 to 1.0% of the fecal bacteria in wild fish were resistant to oxacillin and oxytetracycline, respectively. After termination of medication with oxacillin, 46% of the fecal flora were resistant to oxacillin and 20% were resistant to oxytetracycline.

C. Current Surveillance and Status of U. S. Public Health Infrastructure

At the national level, the CDC in collaboration with local, state, and territorial public health departments currently track a number of reportable infectious diseases in humans. However, even when infectious diseases are reported, drug resistance patterns of the pathogenic organisms involved may not be, meaning that special studies are often needed to discern those patterns.

Although local, county, state and territorial health departments bear the chief responsibility for monitoring the incidence of infectious diseases and antibiotic resistance, budget cutbacks over the past decade have reduced those surveillance efforts substantially (13, 21). Most federal resources are now channeled into meeting concerns raised by the HIV epidemic as well as the recent upsurge of multidrug resistant mycobacteria. In addition, there are continuing needs to monitor the incidence of sexually transmitted diseases (STDs) and vaccine-preventable diseases. The surveillance efforts for the above four categories of diseases account for about 85% of the total, annual CDC budget. These budgetary mandates leave very little in the way of resources for monitoring other infectious diseases or for tracking the emergence of antibiotic resistance.

State and local resources that might help to extend surveillance to diseases that lie outside the federally specified areas of AIDS, TB, and STDs, have been reduced and are not likely to be forthcoming, particularly because states are prohibited from deficit budgeting. At the state and territorial level, these reductions in surveillance budgets have led to personnel shortages and mean that there are typically no full-time personnel and perhaps even part-time individuals doing routine surveillance of these additional infectious diseases, including food- and water-borne illnesses, that fall outside federal mandates. In 1992, less than $55,000 was spent on the federal, state, and local levels for monitoring of antibiotic resistance through the national notifiable disease reporting system (13). The amount has not increased substantially over the past two years.

Several other somewhat limited and underfunded forms of infectious disease surveillance are in place. They include the National Nosocomial Infection Surveillance System (NNIS), which is a voluntary program for tracking the incidence of infections in standard and intensive care units at selected hospitals as well as a nosocomial network within the Veterans Administration Hospital. However, the NNIS program is not representative of all geographic areas or hospital types, and it does not provide information on antibiotic resistant bacteria in the community.

Because antibiotic resistance patterns may vary locally and regionally, surveillance data need to be gathered locally, at least from selected sentinel sources. Patterns can change very rapidly and they need to be monitored closely because of their important implications for how individual physicians practice medicine as well as for public health in general. Thus, recognition of these changing patterns of antibiotic resistance can affect how physicians treat patients, which for many routine (or seemingly routine) infections is done empirically.

Most hospitals in the public sector are facing budgeting cutbacks that threaten their quality of work, decrease their ability to screen for resistance, and decrease their incentive to send resistant strains to local and state public health laboratories as well as to CDC. Health care networks in the private sector, including large-scale health maintenance organizations, and many private practices tend to use large commercial laboratories whose main goal is profit. Thus far, these laboratories have done little to summarize and report antibiotic resistance data and it is generally felt that such data, even if it were available, is not suited for the purpose of monitoring the emergence of antibiotic resistance.

Other impending economic factors could make these problems worse. For example, as regional and global trade barriers are lowered, imported meats, fruits, vegetables, and other foods could become an important source of antibiotic resistant infectious diseases--particularly from developing countries. In developing countries, antibiotic resistance is even higher due to over-the-counter sale of antibiotics and almost total lack of antibiotic resistance screening. Several recent outbreaks of foodborne illness in Minnesota involving imported fruit and vegetables lend support to this assertion that greater rather than reduced surveillance is urgently needed.

In addition, surveillance of disease and antibiotic resistance in animals is under the auspices of the Animal Plant Health Inspection Service (APHIS) within the U.S. Department of Agriculture. Current activities by the American Association of Veterinary Laboratory Diagnosticians (AAVLD) and National Committee for Clinical Laboratory Standards (NCCLS) include a program to develop standardized procedures for antibiotic sensitivity testing in agriculturally relevant pathogens following guidelines comparable for those used for human pathogens. However, this is a very limited program.

In summary, there are no national surveillance programs for either human or veterinary pathogens, thus available data on the incidence of antibiotic resistance in this country probably represents only the tip of the iceberg.

## II. RECOMMENDATIONS

There is an urgent need for effective, domestic and global surveillance of antibiotic resistance in animals and humans. There is also an urgent need for more prudent use of antibiotics in both human and veterinary medicine, particularly as it relates to food production. Of equal urgency is the need for better hospital infection control and implementation of guidelines to reduce spread of infection and antibiotic resistant pathogens in the hospital environment. There is a great need for strengthening the curriculum of human and veterinary health care professionals in the areas of sterilization and disinfection, mechanisms of antibiotic resistance and factors contributing to its

spread including inappropriate usage. There is also a need for patient education regarding appropriate uses of antibiotics. More basic research is needed to more clearly delineate mechanisms of antibiotic resistance and to identify new antimicrobial targets. Lastly, greater emphasis must be placed upon research related to rapid, reliable diagnostic tests and vaccines for prevention and control of infectious diseases.

## A. National Antimicrobial Surveillance System

### 1. Indications

The most compelling indication for a national surveillance system is that no such system currently exists. Recent advances now make it possible for clinical and reference laboratories to accurately assess the susceptibility of a wide variety of bacterial and fungal pathogens via standardized methods. Medical informatics and computer technology are now available for accurate collection, efficient transmission, and analysis of surveillance data in a timely manner which will allow the information to be disseminated in a site specific manner. Implementation of a surveillance system with necessary quality assurances and fiscal supports will allow the generation of antimicrobial resistance data needed for decision-making in therapeutics and/or prophylaxis. Data will be forthcoming to predict emerging resistances among available therapeutic drugs leading to effective interventions that could control dissemination of resistance.

### 2. Considerations

#### a. National surveillance system should include the following:

1). Focus on the most prevalent "bacterial" and fungal pathogens (not viral) that concern human health. This will assess isolates from "clinical" disease cases and routine isolates so that no bias results from one center testing only the "problem" or more resistant isolates compromises the results. Attention will be given to the trend in upward "creep" of MIC values.

There is also a need to monitor food sources such as animal products at the supermarket level as well as imported fruits, vegetables, and other products that may carry colonizing, drug-resistant bacterial and colonizing fecal flora in some patient populations. Salmonella and Shigella both should be monitored. Salmonella gives the best window into the impact of uses of antibiotics in the animal world, and the fraction of Shigella that is imported gives us an excellent view of the impact of antibiotic uses in the developing world (20). Monitoring of soil waste in farms should also be considered.

2). Establish a base line of antimicrobial in vitro efficacy to which the following can be compared: earlier data from similar surveillance studies found in medical literature reviews, especially if these studies utilized comparable methodologies and surveillance techniques; subsequent surveillance data resulting from the establishment of a national surveillance system analyzed in a longitudinal manner; non-USA data to assess the international risks of resistance.

3). Accumulate concurrent demographic profile information to allow the inter-relationships of organisms emerging in hospitals of various size or disease therapy focus, and those pathogens prevalent among ambulatory patients in the community and animals housed in various environments. The role of drug-use in these environments shall be addressed.

4). Establish a mechanism where by organisms possessing certain phenotypic and genotypic resistance patterns will be referred to adequately funded laboratories for detailed study. Various molecular typing and investigative procedures can lead to earlier understanding of developing resistance mechanisms and spread of epidemic clones.

5). Allow for the future assessment of the encountered resistant pathogens' effect on patient outcomes, general community health, and the costs of the health care delivery. Surveillance will target areas for specific intensive interventions for prevention (like vaccine campaigns and antimicrobial use reduction programs). Surveillance will also identify areas where epidemiologic investigations are needed to improve understanding of spread of drug-resistant strains and to identify ways to interfere with spread.

6). Maximize the possibility that data will lead to significant professional, health care "interventions" to reduce the probability that the drug's resistance will be spread widely and have an adverse impact on the national quality of health care outcomes. Interventions ideally should be focused at the local level but regional and national interventions could also provide great benefits.

7). Provide expert federal agencies and societies the information to modify recommendations of therapy or prophylaxis of diseases or procedures. These can be implemented at various levels related to patient or institutional demographics or by geography (local, regional, national).

8). Provide a compatible system in which subsets of participants could be grouped for common benefits. Examples include Federal hospitals (VA, Military, etc.), animal care facilities (University-based, USDA, etc.), recognized HMO-like programs, and academic institutions such as university-teaching hospitals.

9). Provide the data accumulated to be available to pharmaceutical manufacturers thus providing the validations of contemporary drug spectrums. This will be valuable in establishing meaningful organism coverage indications in antimicrobial agent package inserts.

10). Provide a system that can be modified to address any discovered area of concern related to the effective therapy of infectious organisms. This could allow expansion to cover fungi, viruses, cell-associated organisms, and some parasites.

**b. Organisms to be monitored:**

1). Bacterial pathogens considered important in human and animal infections should be monitored. Suggestions are included in Appendix B. The choices should be selected and updated periodically based on: the frequency that these agents cause disease; the human or animal morbidity/economic impact of resistance in that species if it occurs or increases; the perceived threat of genomic mutation; and the need to confirm the continued efficacy of important therapeutic antimicrobial agents.

2). Some strains/species shall be tested on a regular schedule (quarterly) and others as dictated by the needs of the surveillance "oversight panel" or requirements for spectrum validations as part of the interaction with industry colleagues (pharmaceutical drug package insert spectrum data).

3). The numbers of organisms tested should be significant (final counts depending on number/species/site, and the numbers of participant sites) and should be finalized with input from medical statisticians.

4). Some isolates will require the choice of participants that routinely test unusual species (referral centers) or in the case of some animal pathogens, those geographic specialty laboratories having expertise with a single or a group of pathogens specific for a single animal species e.g. swine, cattle, sheep.

5). Some species may be added that represent unusual organisms from which documented resistance genomes have been transferred to prevalent human pathogens (Examples: viridans gr. streptococci, and oral Neisseria spp.).

**c. Geographic locations of participants:**

1). A representative sample of organisms can only be achieved by a broad sampling of geographically dispersed laboratory isolates. Preliminary ideas for selection include:

i. USA population density-driven choices of laboratories by state. Local and state public health laboratories should be involved in data collection but should not be the sole participants.

ii. Grouping of states into regions in a manner that should not be significantly different than those used in the CDC-Morbidity and Mortality Weekly Report.

iii Participants should represent demographic populations of patients and organisms within their states or regions. Examples would include laboratories from large and small (<= 250 beds) hospitals plus samples from microbiology laboratories servicing outpatient clinic practices. Distribution of centers based on hospital bed size should be encouraged.

2). The above ideas will focus toward human pathogen surveillance. Smaller numbers of locations will contribute the animal pathogens also geographically diverse and hopefully representative for the animal species/pathogen population data.

3). In general there is a need for one monitoring site per 1,000,000 to 2,000,000 people, supplemented by animal pathogen participants and important demographic subsets (VA Medical Centers, etc.). Distribution of centers based upon hospital bed size should be encouraged with regional centers being considered in more geographically dispersed areas. Not all locations will have to be recruited in the first year, but representative participants from each region should be sought as early as possible.

d. Populations to be monitored:

1). Demographic profiles of the hospital/laboratory will be required for participation (updated each year). This would allow initial classification of participants by various parameters such as hospital size, services offered, formulary practices, antimicrobial use patterns, infection control practices, teaching status, etc.

2). Particularly important surveillance groups will be by:

i. Hospital size.

ii. Services or teaching offered.

iii. Health care delivery classification (HMO, federal, VA, private, etc.).

iv. Clinic practice.

v. Hospital-acquired versus other sources of the pathogen.

vi. Prior antimicrobial therapy and type.

vii. Others.

3). Given the limited testing done by commercial laboratories, a systematic approach for measuring community acquired antibiotic resistant bacteria must

be established. This niche might best be served by the local and state health departments

e. **Methods to be used:**

1). All methods used should be of reference-quality and should closely follow the documents published by the NCCLS.

2). Where possible, initial screening should use the disk diffusion method (NCCLS M2-A5) for those pathogen/antimicrobial combinations that can be accurately tested.

3). A subset of organism/antimicrobial combinations will require special tests that will need referral to a reference laboratory or laboratories. Alternatively, these generally fastidious species can be tested at each location by some newer technologies, if costs and reagent availability dictate.

4). Method choices should be focused through an "advisory panel" of experts in the field of antimicrobial susceptibility testing.

5). Rigid quality controls (QC) should be necessary for each participant (local) laboratory, monitoring reference laboratory and any laboratory used for special contracted tests or molecular studies. Only data from accepted methods accompanied by validating QC should be entered into the antimicrobial surveillance data base. Participants regularly not complying with QC guidelines should be replaced.

f. **Locations of pathogen testing:**

1). The dominant, quarterly testing schedule should be performed at the laboratory participant locations.

2). Specific pathogens (identified by species, resistance phenotype, isolate origin, etc.) should be routinely forwarded to secondary, reference (monitor) laboratories. These centers should perform contracted studies by specified methods (protocol) and report results to the USA antimicrobial surveillance data processing location (i.e. CDC see below).

3). Molecular typing, resistance mechanism studies and other molecular-level techniques will be necessary on an annual basis. These studies should be issued to appropriate reference laboratories as required by the surveillance administrators.

g. Format for data:

1). All data should be expressed as quantitative endpoints regardless of method. This dictates measurement of disk diffusion tests by calipers to the nearest whole mm and the use of ug/ml MIC endpoints for dilution methods. Such measurements will facilitate the recognition of susceptibility changes within categories (qualitative) established by the NCCLS.

2). Qualitative interpretations shall be applied objectively by computer programs based on current NCCLS Tables. Similarly QC guidelines found in the NCCLS tables should also establish the validity of each participant's/referee's data.

h. Data entry and analyses:

1). Surveillance studies of all types can greatly benefit from well-structured computer systems. Prior studies performed by the CDC [NNIS and Public Health Laboratory Information System (PHLIS)], WHO (WHONET), and private parties have effectively utilized relatively simple data input programs. Such software is available and/or programmable without the significant risk of problems. Timeliness, flexibility, and the ease of expanding the pyramidal reporting structure are important considerations.

2). All input should be simplified to include minimal transcriptions via digital reading or bar-coding or disk transfers or modem networking.

3). A single data analysis location would be preferred. Programming would be under the direction of the surveillance "oversight panel" that should also periodically review the analysis results.

4). Simple in-laboratory work forms should also be standardized for all locations as a hard-copy backup. These forms should not greatly differ from the clinically used forms at each location.

5). Previously organized, computerized networks can be used as models. Possible collaborations might include: CDC-NNIS, CDC-STD regional surveillance in *N. gonorrhoea*, VA networks, SCOPE (University of Iowa Program), and international programs through various medical specialty societies.

i. Frequency of analysis and access:

1). Preliminary guidelines for the surveillance are as follows:

i. Surveillance of basic pathogen group by each participant at the local site-QUARTERLY.

ii. Special (usually fastidious) pathogens performed by a selected number of reference or special skill laboratories-QUARTERLY.

iii. Expanded list of antimicrobial agents and pathogens that will satisfy annual validation of drug package insert spectrum-YEARLY (Winter quarter).

iv. Special studies as directed by the "oversight panel"-VARIABLE.

2). The program must establish the perception that participation is a benefit. To accomplish this goal the following items might be considered:

i. Quarterly reports to all participants.

ii. Annual newsletter summary of results.

iii. Publications generated from surveillance data should acknowledge the participation of all sites.

iv. Participant interaction with the data base should be developed. Confidentiality should be maintained by coding locations and limiting laboratory defined access to the participant-center only. However, data would otherwise be available but audited by the "oversight panel" or study administrators.

v. Periodic meeting of the surveillance participants should be encouraged, at a national meeting or as a free standing annual symposium.

j. Organization of the surveillance system:

1). Funding should be sought from all parties that would derive a significant benefit from the system. These include, but would not be limited to (a consortium approach):

i. Federal and state agencies

a). CDC

b). FDA (several components)

c). NIH

d). USDA

e). State health departments

f). VA

g). Department of Defense

ii. Industry

a). Pharmaceutical manufacturers

b). Reagent manufacturers

1. Antimicrobial tests

2. Microbiology media

c). Drug delivery systems

d). Health care delivery corporations/hospital corporations

e). Contract research organizations

iii. Academic institutions, professional societies and university medical centers

2). An "oversight-panel" should be established for the surveillance study network. This panel should include representatives from the principal federal agencies, members of the scientific community at large who are experts in antimicrobial resistance, specialists in infectious disease and in vitro antimicrobial testing in animals and humans, experienced personnel in multi-laboratory surveillance, hospital/health care epidemiologists, computer and statistical analysis conversant with antimicrobial issues, and representatives of industry as dictated by consortium participation. The "Antimicrobial Resistance Surveillance Program" should be located within the National Center for Infectious Diseases at CDC. This would allow integration with other surveillance activities for infectious diseases by experts in microbiology and epidemiology. Because of the CDC's track record and proven expertise this is the logical location for a national surveillance system.

3). If this program is successful in meeting the cited goals and objectives, cost savings could easily be in the hundreds-of-millions of dollars to the national health care system. A few areas of greatest impact are i) the focusing of pharmaceutical research as early as possible on emerging drug resistance problems; ii) the reduction of drug development costs by placing new compounds into the system to establish in vitro spectrums (cost rates would be less than the multiple individual grants to independent investigators); iii) like ii, current compound spectrums would be annually validated reducing manufacturers costs for independent vendor contracts; iv) federal and state agencies would have contemporary, localized data to address emerging resistances or pathogen frequencies that would allow early interventions and selections of affective therapeutic regimens or prophylactic modalities; and v) other interventions stimulated by the data derived from the surveillance should lead to greater cooperation among government, industry, and professional components of the health care system at large.

**k. Immediate recommendations**

1). Convene an expert panel to develop surveillance protocol and establish an annual budget. The above outline could be used as a preliminary or tentative plan.

b). Federal funding should be immediately identified for the national surveillance system and several agencies (CDC, FDA, NIH, VA, USDA, etc.) as well as other sources should be involved in funding decisions.

c). Seek appropriate expertise in statistical analysis for determination of organism sample sizes, population-based participant selection, and computer support for analyses.

d). Initiate an extensive search for earlier surveillance data bases on resistance generated from USA multi-center investigations performed with NCCLS or compatible methods. Also expand that literature search to world-wide surveillance data, if available.

B. Recommendations Related to Emergence of Resistance

Many unanswered questions surround the role of animals and the microbiota. The use of subtherapeutic levels of antibiotics for prophylaxis and as growth promoters continue to be a concern. Current aquaculture practices also raise concerns. Systematic studies are needed to determine how much of our clinical problem of antibiotic resistance traces to these phenomena.

At the health care level, community- and hospital based practices should be studied from a behavioral standpoint to determine what practices may contribute to emergence and spread of antibiotic resistance and how they might be modified.

Professional and public education should be strengthened in the area of infectious diseases and antibiotics so as to reduce inappropriate usage of antibiotics. The curriculum of health professional (medical, dental, nursing and veterinary) school and postgraduate educational programs should be strengthened in the areas of sterilization, disinfection and antibiotic resistance. This should result in reduction of spread of infectious agents and more prudent use of antibiotics.

Educational materials should be developed and widely distributed to patients and to food producers. The need for partnerships in improving antimicrobial use for cost effective treatment of infections and to preserve the effectiveness of antimicrobials for the future should be emphasized.

Key federal agencies, including the NIH, CDC, and the USDA should develop more information on the impact of infectious diseases and better means for conveying information to representatives

from pharmaceutical and biotechnology companies, health care organizations, elected officials, and the general public.

To preserve the extraordinary gains made by antimicrobials against the battle of infectious diseases will require more imaginative, collective action by governments, the pharmaceutical industry, health care providers, and consumers. No one group or country can accomplish this goal alone. Resistant microorganisms do not recognize geographic boundaries. Inappropriate or excessive use of antimicrobial drugs by any person or practitioner can affect the entire ecologic system and cannot be condoned. Attention must be focused on societal issues that determine how these drugs are used and establishment to policies that will result in more selective and rational use of antimicrobial drugs.

### C. Research and Drug Development Needs

There is an urgent need for more basic research directed toward development of new antimicrobial compounds but also toward development of effective vaccines and other prevention measures. In FY 1994 allocations to the National Institute of Allergy and Infectious Diseases of the NIH for funding of non-AIDS infectious disease research were reduced by $20 million (21). Increased appropriations are urgently needed to fund areas of research directly related to new and re-emerging infections and antibiotic resistance.

More basic research is needed to delineate the genetic and metabolic pathways, including essential regulatory factors, that determine virulence as well as antibiotic susceptibility or resistance in pathogens of human and veterinary importance. To conduct this research, better, more consistent measures of antibiotic resistance are needed, and a culture collection containing representative antibiotic resistant biotypes and genotypes should be developed. More resources should be devoted to the sequencing of the entire genome of microbial pathogens in an attempt to identify common antimicrobial targets. Such studies are expected to help in identifying novel targets for molecules that interfere specifically with essential physiological steps of pathogens. Traditional empirically based screening of potential inhibitors of pathogens is believed to be too crude to unveil such targets.

Screening procedures have been modernized so that tens of thousands of compounds can be tested on a daily basis. Eventually, such strategies for drug development taken together with better, quicker, and more precise diagnostic technologies could lead to a new more highly focused approach for dealing with infectious diseases that could be associated with economically attractive niche markets.

Nonetheless, conservative marketing projections have led many companies to reduce--or, in some cases, disband--their antibiotic drug discovery and development programs in this country but not in other countries like Japan. Because such projections are misleading, if not outright wrong, company marketing specialists should participate in discussions of the problem of emergent antibiotic resistance and they should be involved in efforts to identify incentives for basic and applied research in this area that would contribute to the development of new antibiotics or other novel entities to inhibit pathogens. It is also recommended that representatives from national and regional health maintenance organizations be consulted on such matters because of the increasing cost of treating antibiotic resistant infections and the escalating use of the most expensive, recently introduced agents for prophylaxis or empiric therapy.

Other efforts to encourage antibiotic drug research and development that involve federal agencies, universities, and companies in the private sector should be encouraged. Other factors which may be considered to encourage discovery of new agents may be tax benefits for companies engaged in such research and development and the issue of litigation problems. Existing efforts in other health-related areas, such as the National Cooperative Drug Discovery Development Groups for the development of anticancer drugs and the National Vaccine Program, should be reviewed. Potential models for a new program to coordinate research on new drug development should be explored, including extending the useful patent life of drugs. An orphan drug-like concept for novel narrow-spectrum drugs for treating specific pathogens, and perhaps using a treatment-IND approach to allow licensing and sale of new anti-infective products at an earlier stage of development than is now permitted should be considered.

The need for partnerships in order to make drugs more readily available, to improve usage, and to develop new products cannot be over emphasized. For example, it should be to the advantage of the pharmaceutical industry to support national policies that require better quality control, proof of safety and efficacy, and assurance of patent protection (22). Likewise, it should be realized that the research -intensive pharmaceutical industry is the source for most new drugs and that industry need to profit from their investments in order to pay for the research.

In return for help from the government in providing a more stable market for their products, industry should help support national efforts (scientific organizations, foundations, educational institutions) whose role it is to educate people about the appropriate use of antibiotics, to improve the availability and distribution of effective drugs, to monitor the emergence of resistant strains, and to train young investigators in therapeutics (22).

The laws of evolution dictate that microbes will eventually develop resistance to nearly any antibiotic. Thus more basic research is needed to facilitate development of effective vaccines. For other infectious diseases, better non-vaccine prevention measures are needed that target environmental or behavioral factors that contribute to pathogen transmission. Support for more

research is needed to facilitate development of better infection control technologies in several arenas, for example, water treatment, food production, hospital hygiene, and vector control.

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# APPENDIX A
## TASK FORCE ON ANTIBIOTIC RESISTANCE

Gail H. Cassell, Ph.D. - Chairman
Immediate Past President, American Society for Microbiology
Department of Microbiology
University of Alabama at Birmingham/University Station
Birmingham, AL 35294

Gordon L. Archer, M.D.
Professor of Medicine
Medical College of Virginia/ID Division
1504 Hearthglow Lane
Richmond, VA 23233-4612

Thomas R. Beam, M.D.
Associate Professor of Medicine and Microbiology
Buffalo Veterans Administration Hospital
3495 Bailey Avenue
Buffalo, NY 14215-1129

Mary J. Gilchrist, Ph.D.
Director Microbiology Laboratory / MC113
Veterans Administration Medical Center
3200 Vine Street

Donald Goldmann, M.D.
Professor of Pediatrics, Harvard Medical School
Hospital Epidemiogist, Medical Director of Quality Improvement
Director, Microbiology Laboratory / Infectious Disease Division
Children's Hospital
300 Longwood Ave.
Boston, MA 02115-5737

David C. Hooper, M.D.
Associate Professor of Medicine/Infectious Disease Unit
Massachusetts General Hospital
Fruit Street

Ronald N. Jones, M.D.
Department of Pathology
5232 RCP
University of Iowa
Iowa City, IA 52242

Stanley H. Kleven, D.V.M., Ph.D.
Head, Department of Avian Medicine
University of Georgia
953 College Station Road

Joshua Lederberg, Ph.D.
The Rockefeller University
New York, NY 120021-6399

Stuart B. Levy, M.D. (by telephone)
Tuft University Medical School
136 Harrison Avenue

Donald H. Lein, D.V.M., Ph.D.
College of Veterinary Medicine/Diagnostic Laboratory
Cornell University
Upper Tower Road
Ithaca, NY 14852-5786

Robert C. Moellering, M.D.
Physician-In-Chief
NE Deaconess Hospital
Department of Medicine/Room 6A
110 Francis Street

Thomas F. O'Brien, M.D.
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115

Bennie Osburn, D.V.M., Ph.D.
Associate Dean, Research and Graduate Education Programs
School of Veterinary Medicine
University of California, Davis
1018 Haring Hall
Davis, CA 95616

Michael Osterholm, Ph.D.
State Epidemiologist
Acute Disease Epidemiology Section
Minnesota Department of Health
717 SE Delaware Street
Minneapolis, MN 55440

David M. Shlaes, M.D., Ph.D.
Division of Infectious Diseases
Cleveland VA Medical Center
10701 East Boulevard
Cleveland, OH 44106

Martin Terry, D.V.M.
Animal Health Institute
501 Wythe Street
Alexandra, VA 22314

Sue A. Tolin, Ph.D.
Professor, Department of Plant Pathology and Weed Science
Virginia Polytechnic Institute and State University
Blacksburg, VA 24061-0330

Alexander Tomasz, Ph.D.
Professor and Head / Laboratory of Microbiology
The Rockefeller University
1230 York Avenue / Box 152
New York, NY 10021-6399

Government Liaisons

Robert F. Breiman, M.D.
Respiratory Diseases Branch / Bacterial and Mycotic Diseases Division
Centers for Disease Control and Prevention
Atlanta, GA 30333

Mitchell Cohen, M.D.
Director, Bacterial and Mycotic Diseases Division
Centers for Disease Control and Prevention / Room 4065
1600 Clifton Rd, NE

Jean Cooper, Ph.D.
Center for Veterinary Medicine
U.S. Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

James M. Hughes, M.D.
Director, Center for Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Road NE - Mailstop C-12
Atlanta, GA 30333

John La Montagne, Ph.D.
Director, Division of Microbiology and Infectious Diseases, NIAID
National Institutes of Health
3A18 Solar Building
9000 Rockville Pike

Edward McSweegan, Ph.D.
National Institute of Allergy and Infectious Diseases, NIH
CDB, Room 3A-35
Bethesda, MD 20892

Albert T. Sheldon, Ph.D.
Division Anti-Infective Drugs
U.S. Food and Drug Administration
HFD-520, Room 12B17
5600 Fishers Lane

Fred Tenover, Ph.D.
Chief, Nosocomial Pathogen's Laboratory
Centers for Disease Control and Prevention
1600 Clifton Road NE 3389-CDC1

Industrial Liaisons

Jerry Boscia, M.D.
Vice President - Research and Development
SmithKline Beecham Animal Health
1600 Paoli Pike
West Chester, PA 19380

Carl J. Craft, M.D.
Abbott Laboratory
1 Abbott Park Road / Dept 48V
Abbott Park, IL 60064

Susan Froshauer, Ph.D.
Senior Research Scientist
Pfizer Central Research
Eastern Point Road
Groton, CT 06340

Michael McCabe, D.V.M.
Field Study Coordinator
Abbott Laboratories
1401 Sheridan Road / Dept. 32 P
North Chicago, IL 60064-4000

Catherine Reese, Ph.D.
Senior Research Scientist
Pfizer Central Research
Eastern Point Road
Groton, CT 06340

Ray Testa, Ph.D.
Lederle Laboratories / Infectious Disease Section
Middletown Road
Pearl River, NY 10965

Office of Technology Assessment

Sean Tunis, M.D.
Director, Health Program,
Office of Technology Assessment (OTA), U.S. Congress
Washington DC 20510-8025

Justin Latus, M.PP.
Health Program, OTA
Washington DC 20510-8025

# Appendix B
## Suggested Organisms to be Included in Antibiotic Resistance Surveillance Program

| Organisms | | Antimicrobial agents[b] | Method preferred (screening) | Frequency/ scope[c] |
|---|---|---|---|---|
| Primary[a] | Secondary[a] | | | |
| Enterococcus* (E. faecalla, E. faeclum) | | Vancomycin<br>Ampicillin<br>Gentamicin-HLR<br>Streptomycin-HLR<br>(Telcoplanin)[d]<br>(Chloramphenicol)<br>(Doxycycline)<br>(Fluoroquinolones)<br>(β-lactamase test) | Disk | 4/All |
| Streptococci (Pneumococcus*, Serogr. A, B, and viridans gr.) | | Penicillin<br>Macrolide<br>Trim/Sulfa<br>Cephalosporin (3rd)<br>Vancomycin<br>Chloramphenicol<br>(Cephalosporin [2nd]) | Dilution | 4/All (referred) |
| Staphylococcous (S. aureus*, CNS) | | Oxacillin<br>Macrolide<br>Vancomycin<br>(Fluoroquinolone)<br>(Rifampin) | Disk | 4/All |
| Enterobacteriaceae (E. cloacae*, E. coli, K. pneumoniae*, P. mirabilis, P. rettgeri, S. marcescens, Shigella spp, Salmonella typhi, Salmonella non-typhi*) | | Cephalosporin - 1st<br>Cephalosporin - 3rd(2)<br>Ceftazidime<br>Cefotaxime<br>Aminoglycosides<br>Carbapenem<br>Fluoroquinolone<br>BLIC[b]<br>Ampicillin<br>Piperacillin<br>Trim/Sulfa<br>(Chloramphenicol) | Disk | 4/All |

| Organisms | | Antimicrobial agents[b] | Method preferred (screening) | Frequency/ scope[c] |
|---|---|---|---|---|
| Primary[a] | Secondary[a] | | | |
| Neisseria gonorrhorea | | Penicillin<br>Tetracycline<br>Cephalosporin (3rd)<br>Fluoroquinolone<br>Trim/Sulfa<br>(β-lactamase test) | Dilution | CDC-STD Monitoring System |
| | Xanthomonas maltophilla | Trim/Sulfa<br>BLIC<br>Fluoroquinolone<br>Tetracycline<br>Cephalosporin (3rd) | Dilution | 1/All (referred) |
| | Campylobacter spp, Helicobacter pylori, Vibrio spp. | Pending species-dependent selection | Dilution | 1/Focused, (referred) |
| Bacteroides fragilis gr. | | Metronidazole<br>Carbapenem<br>BLIC<br>Cilndamycin<br>Cephamycin<br>Cephalosporin (3rd)<br>(Chloramphenicol)<br>(β-lactamase test) | Dilution | 4/Focused, (referred) |
| | Clostridium difficile | Metronidazole<br>Vancomycin<br>(Teicoplanin) | Dilution | 1/Focused, (referred) |
| | Bacterial vaginosis-assoc. pathogens (Peptostrepto-coccus spp., G. vaginalis, Mobiluncus spp. Prevotella spp.) | Metronidazole<br>Clindamycin<br>Ampicillin<br>Trim/Sulfa<br>(Cephamycin)<br>[Cephalosporin(3rd)]<br>(Carbapenem)<br>(BLIC) | Dilution | 1/Focused, (referred) |

| Organisms | | Antimicrobial agents[b] | Method preferred (screening) | Frequency/ scope[c] |
|---|---|---|---|---|
| Primary[a] | Secondary[a] | | | |
| Veterinary pathogens (H.sominus*, A. pleuropneumoniae*, B. bronchiseptica, Pasteurella spp., etc.) | | (list dictated by Federal regulation if food animals or by vet prescription availability) | Dilution | 1/Focused, (referred) |
| Mycobacteria*,[e] | | (Pending species selection) | Dilution and species dependent | 4/Focused, (referred) |
| Neisseria meningitidis* | | Penicillin<br>Cephalosporin (3rd)<br>Fluoroquinolone<br>Rifampin<br>Trim/Sulfa<br>(β-lactamase test) | Dilution (E) | 4/All (referred) |
| Haemophilus influenzae* (may be grouped by serogroup B and others) | | β-lactamase test<br>Ampicillin<br>Chloramphenicol<br>Trim/Sulfa<br>Cephalosporin (3rd)<br>Macrolide<br>Fluoroquinolone<br>BLIC<br>(Cephalosporin [1st, 2nd,oral]) | Disk or Dilution | 4/All |
| Pseudomonas aeruginosa* | | Aminoglycosides<br>Penicillins (3rd)<br>Trim/Sulfa<br>Fluoroquinolone<br>Carbapenem | Disk | 4/All |
| Aeromonas hydrophila | | Ampicillin<br>Aminoglycoside<br>Cephalosporin (3rd)<br>Fluoroquinolone<br>Trim/Sulfa<br>(Penicillin [3rd])<br>(Carbapenem) | Disk | 1/All |

| Organisms | | Antimicrobial agents[b] | Method preferred (screening) | Frequency/ scope[c] |
|---|---|---|---|---|
| Primary[a] | Secondary[a] | | | |
| | Moraxella catarrhalis | Ampicillin<br>Macrolide<br>Cephalosporin (1st, 2nd, 3rd)<br>Tetracycline<br>Trim/Sulfa<br>BLIC<br>Fluoroquinolone | Disk | 4/All |
| | Acinetobacter spp. | Ampicillin<br>Aminoglycoside<br>Cephalosporin (3rd)<br>BLIC<br>Fluoroquinolone<br>Carbapenem<br>Trim/Sulfa | Disk | 4/All |

## Footnotes:

* Highest priority.

a. Primary indicates the need for routine susceptibility surveillance because of high medical care impact of antimicrobial resistance changes. Secondary indicates a reduced impact or the current frequency of that pathogen (real incidence or low isolation rates) in human or animal disease is minimal.

b. Some agents are listed by class because a marker compound could be selected to represent a group of drugs sharing high levels of cross-resistance (Examples: fluoroquinolones, generations of cephalosporins, aminoglycosides, etc.). BLIC = beta-lactamase inhibitor combinations and penicillin (3rd) defines either meziocillin or piperacillin.

c. Frequency specifies the number of times that a pathogen is audited per year e.g. 4 = quarterly, 1 = once annually. Scope indicates the breadth of participants on their isolates that will be sampled (Example: 4/All = quarterly by all participant laboratories or 1/Focused = once yearly by a selected subset of laboratories.

d. () = secondary drugs that could be added to screen for resistance phenotypes or to provide data on alternative therapeutic regimens.

Screened mycobacteria would include: M. tuberculosis, M. avium-intracellulare complex, M. bovis, and rapid-growers (M. chalonae, M. fortultim).