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Issues relating to the use of BCG in immunization programmes

A discussion document

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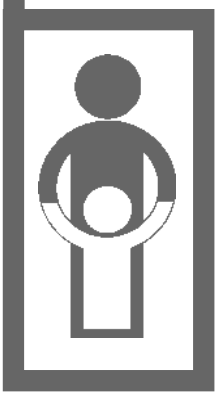

DEPARTMENT OF VACCINES AND BIOLOGICALS

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1. Introduction

Tuberculosis was declared a global emergency by the WHO in 1993, and *Mycobacterium tuberculosis* is now considered to be responsible for more adult deaths than is any other pathogen[1]. Control of this disease relies upon prevention through Bacillus Calmette-Guérin (BCG) vaccination or "preventive therapy" (chemoprophylaxis), and the ascertainment and treatment of cases, in particular employing the "directly observed therapy - short course" (DOTS) approach. Though BCG vaccines are among the most widely used vaccines in the world, policies for their use differ between countries, and there is a history of controversy concerning their efficacy and impact. This report was commissioned by the Expanding Immunization Team (EPI), the Leprosy Elimination Project (LEP/CEE), UNAIDS, and the Department of Control, Prevention and Eradication (CPE), formally the Global Programme against Tuberculosis (GTB). It summarizes the current use and utility of BCG in the world today, and comments on policy issues that deserve consideration.

2. Background

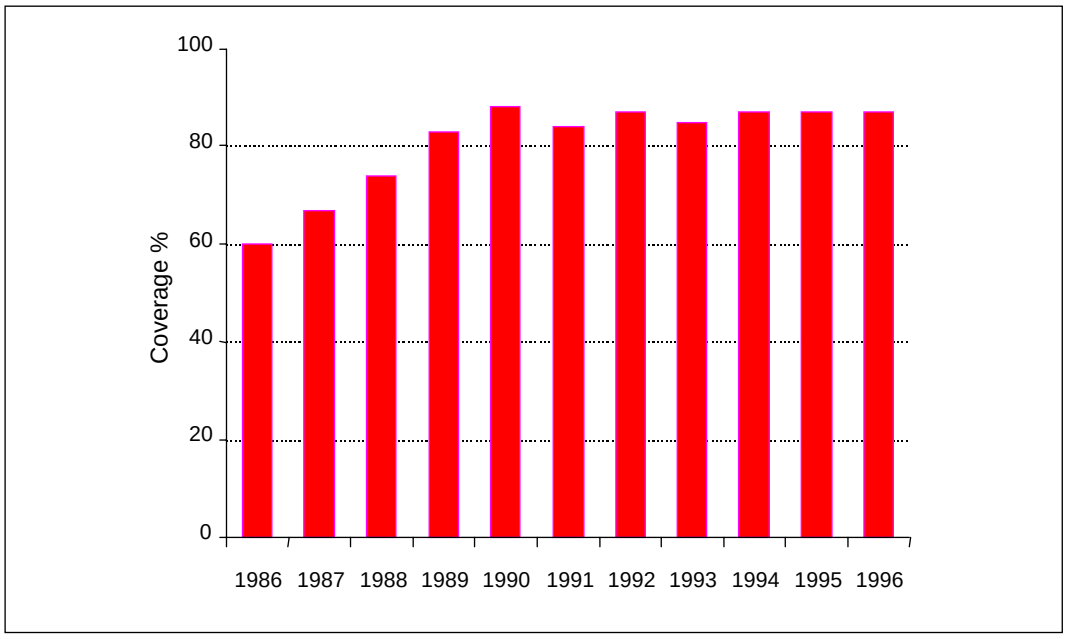
The original BCG vaccine "strain" (literally the bacillus of Calmette and Guérin) was derived from an isolate of *M. bovis* at the Institut Pasteur in Lille, and was first given to a human (per os) in 1921. The vaccine was used increasingly in Europe during the 1920s, with early evidence for its efficacy coming from studies of student nurses in Norway[2]. The first formal trials of BCG were organized among North American Indians in the 1930s[3]. By the late 1940s (by which time BCG was administered mainly by percutaneous or intradermal routes), several studies had provided evidence for the utility of BCG in protection against tuberculosis. Tuberculosis emerged as a major concern in the aftermath of World War II, and use of BCG was encouraged subsequently in many countries, stimulated in particular by UNICEF and by Scandinavian Red Cross Societies, and then by the WHO. Major trials were set up by the British Medical Research Council (BMRC) and by the United States Public Health Service (USPHS) in the early 1950s. It was soon evident that the procedure employed by the BMRC (Copenhagen strain, given to tuberculin-negative 13 year olds) provided high efficacy against tuberculosis [4,5,6]. In contrast, that used by the USPHS (Park or Tice strains given to tuberculin-negatives of various ages) provided very little protection[7]. On the basis of these results, the respective public health agencies did the logical things: BCG was recommended as a routine for tuberculin-negative adolescents in the UK, whereas BCG was not recommended for routine use in the USA, but restricted to certain high-risk populations. The majority of the world followed the lead of Europe and the WHO, and introduced BCG, first in campaigns targeted at all children, and then as a routine vaccination according to various schedules (e.g. at birth, school entry or school leaving). However, the Netherlands and the USA decided against routine BCG vaccination, and based their tuberculosis prevention strategy entirely upon reduction of sources of infection, by case finding and treatment, and including contact tracing and the use of tuberculin to identify infected individuals eligible for "preventive therapy" (typically 6 months of isoniazid).

Two hypotheses emerged early as explanations for the disparate results observed in different evaluations of BCG. One attributed the differences to variation between strains of BCG[8] and the other considered environmental factors, in particular exposure to various environmental mycobacteria[9], to be responsible for the differences. In an effort to decide between these views, a large trial, including all age groups, was organized in the Chingleput area of South India, starting in 1968, with assistance of the Indian Council of Medical Research (ICMR), the WHO and the USPHS. The aim was to compare two well-established BCG strains ("Paris/Pasteur" vs. "Danish/Copenhagen"), each in two doses, in an area known to have a very high prevalence of skin test sensitivity attributed to environmental mycobacterial exposure. A companion trial was to have been set up in an area in northern India with little

exposure to environmental mycobacteria - but unfortunately was never initiated, in part because of political unrest. The initial results of the Chingleput trial were made public in 1979, and revealed no evidence that either vaccine had imparted any convincing protection against pulmonary tuberculosis[10]. Two WHO-organized workshops reviewed the trial, and concluded that the results could not be attributed to methodological error[11]. These surprising results led to a series of observational studies aimed at evaluating BCG use in different populations of the world [12,13].

BCG was incorporated into the Expanded Programme on Immunization's (EPI) infant vaccination schedule in 1974. Given that the Chingleput trial provided no data on vaccination in infancy, its results did not influence EPI policy, and BCG use continued to increase, so that BCG vaccines are now given routinely in most countries of the world. Approximately 100 million children now receive one or another BCG vaccine, every year (Figure 1).

Figure 1: Annual global vaccination coverage of infants with BCG (%) by 12 months of age as reported to WHO, 1980-1996[128]



3. Current BCG vaccines

BCG vaccines are currently produced by 40 or more manufacturers around the world. The major commercial producers in terms of export volume are Pasteur-Merieux-Connaught, Evans-Medeva, and the Japan BCG Laboratory, which together accounted for 85 % of 217 million (infant, 0.05 ml) doses provided through UNICEF in 1996 and 1997 (Per Gjoelbo, UNICEF Supply, Copenhagen, personal communication, 1998). An estimated 25 - 30 % of the world's BCG supply is purchased by UNICEF for distribution to developing countries. Much of the remaining vaccine is produced within the countries themselves, for local use.

BCG has never been cloned, and there are now several different BCG seed strains ("sub-strains") in use in BCG manufacture (Table 1), and several different methods of BCG culture. Given the continued controversies over BCG vaccines, and the possibility that differences among vaccines may be responsible for some of the observed differences in efficacy, it is important to appreciate the variation inherent in today's BCG vaccines.

Table 1 : Sub-strains currently used in BCG manufacture, by doses produced per year*

Sub-strain	Number of manufacturers reporting	Doses/year (x 10^6, 1996 data)
Pasteur - 1173 P2	5	28.5
Copenhagen – 1331	13	127
Glaxo – 1077	2	65
Tokyo – 172	2	43
Russian	2	40
Moreau	3	32
Other or unknown	11	42.5
Total	38	378

* *Based on information provided to the WHO/VSQ Unit by national immunization programmes, UNICEF and BCG manufacturers. The table excludes manufacturers and sub-strains for which annual production figures are not available.*

Several investigators have attempted to reconstruct the derivation of the various contemporary strains from the original Institut Pasteur stock [14]. Microbiological differences have long been recognized[15], and molecular analyses have now identified particular genomic regions that are found in *M. bovis*, but appear to be absent from some or all BCG strains [16,17]. In particular, it has been found that the so-called RD-2 region, which encodes the mpt-64 gene, is present in the "primitive" BCG strains (represented by current Brazilian/ Moreau strain, Tokyo-172 and Russian sub-strains), but absent from those sub-strains derived from the original BCG Pasteur strain after 1925 (represented by today's Pasteur-1173 P2, Copenhagen-1331 and Glaxo-1077 sub-strains)[16]. The full immunological implications of these deletions, if any, are still unknown.

As it is a potential source of confusion, it is important to note that the Pasteur-Merieux-Connaught vaccine has been produced with the Glaxo 1077 strain, since the early 1990s. Evans-Medeva also uses this strain.

Aside from small quantities of liquid BCG produced for local use, all of today's BCG vaccines are provided in freeze-dried form. The freeze-drying process, in addition to the particular culture methods employed by different manufacturers, leads to considerable differences in the numbers and proportions of viable and dead organisms per dose of vaccine (see Table 2). It is recognized that this has implications both for reactogenicity (measured in terms of the size of the local lesion) and for the induction of delayed type hypersensitivity (DTH, tuberculin sensitivity)[18]. Each is correlated with the number of viable organisms in the vaccine dose; but the relationship differs between vaccine strains, reflecting different qualitative as well as quantitative reactogenicities[15]. The association is complicated further by a synergistic effect, attributable to the presence of non-viable organisms[18].

Table 2 : Some characteristics of the major BCG sub-strains in current use

Sub-strain	Number of manufacturers	Culturable particles per dose[15]	MPT-64[16]
Pasteur - 1173 P2	5	37 500 – 500 000	-
Copenhagen - 1131	13	150 000 – 300 000	-
Glaxo - 1077	2	200 000 – 1 000 000	-
Tokyo - 172	2	3 000 000	+
Russian	2	unknown	+
Moreau	3	unknown	+

Quality control

A large literature discusses the properties of different BCG vaccines[15]. The implications of these differences for protection against disease are often debated, but remain unknown. Quality control of current BCG vaccines used in national immunization programmes is the responsibility of the individual manufacturers, overseen by independent National Regulatory Authorities in the country of manufacture. Unfortunately, many countries do not have fully functional national control authorities, and the quality of much of the BCG used in national immunization programmes therefore remains doubtful or at best unknown. Until the end of 1997, WHO used a quality control system for BCG vaccines co-ordinated by the Danish State Serum Institute (WHA27.54, Quality Control of BCG vaccines, 1974); but this system has recently been ended, in part because of new WHO initiatives to strengthen National Regulatory Authorities.

UNICEF depends on the advice of WHO for assuring that systems are in place to assure the quality of the BCG vaccines it buys (WHO/VSQ/97.06, Procedures for assessing the acceptability in principle of vaccines for purchase by UN agencies). This system depends on strict National Regulatory Authority oversight including correlation of characteristics of the product with clinical study data and production consistency as ensured by compliance with Good Manufacturing Practice.

The standard quality control assays emphasize total and viable bacterial counts, thermostability and the ability to induce delayed type hypersensitivity (DTH) in guinea pigs and humans. There is a tradition to consider vaccine-induced DTH as a surrogate for efficacy [15,18,19], but no epidemiological support for this relationship exists [20, 21,22], and it is increasingly questioned by immunologists[23]. Quality control, and appropriate correlates of protection, are among the broader issues that may be addressed by a future BCG policy.

Table 3 : Summary of number of countries *reporting* on particular BCG immunization policies, by WHO Region

WHO Region (total number of countries)	Number of countries reporting by special survey (a)	First BCG given at birth	First BCG given after infancy	Recognized contra-indications (number of countries)	Special risk groups (number of countries)	Booster given	Indications for booster	Vaccine coverage in millions (%) (b)
AFR (46)	Nil	46	0	No info	No info	0	-	16.9 (66%)
AMR (44)	Nil	30	2	No info	No info	0	-	14.9 (97%)
EMR (24)	21	18	3	Mothers with AIDS (7) HIV (9) Household contacts of AIDS (2) Tuberculin pos (10) BCG scar (12) Other (4)	Medical (1) TB contacts (1) Students (1) Industrial workers (1)	7	No scar (6) Tuberculin-neg (1)	14.7 (89%)
EUR (49)	47	34	8	No info	No info	30	Risk group (2) Military (1)	9.6 (89%)
SEAR (10)	8	10	0	Mother with AIDS (1) HIV (2) Houshold contact of AIDS (1) Tuberculin-pos (2) BCG scar (5) Other (1)	None reported	3	No scar (3) Tuberculin-neg (1)	35.3 (97%)
WPR (25)	Nil	18	1	No info	No info	8	No info	26.6(94%)

Data compiled from a survey in 1995 by a WHO Regional Office[31], a special survey by EPI Geneva in 1998, and data routinely reported to EPI Geneva.

(a) Countries not reporting officially to WHO on BCG: AMRO (12); EMR (3); EUR (5); WPR (6).

(b) Vaccine coverage as reported to WHO for 1997 as a percentage of newborns, based upon an estimate of the number (millions) of infants immunized and not taking into account infant deaths. The number of doses "consumed" is much higher, due to high vaccine wastage rates in some countries. NB: the percent coverage is calculated only on those countries which report, which may not be representative of all countries in the region.

4. BCG immunization policies

BCG vaccination policies differ greatly between countries. Table 3 summarizes these policies by WHO region. The various policies may be broken down into four groups:

i) BCG only at birth (or first contact with health services): This is the current recommendation of the EPI and the Global Tuberculosis Programme (GTB)[27], and is the policy in most of the world today, in particular in developing countries. WHO has emphasized this policy in recent years, because of consistent evidence that BCG protects against serious childhood forms of tuberculosis, even where it may not protect to a high degree against adult pulmonary forms of the disease[28,29].

ii) BCG once in childhood: Some European nations have this policy, for example the United Kingdom, where BCG has been given routinely to tuberculin negative adolescents (12-13 year olds)[30]. This particular policy was initiated in 1957 as an appropriate way to deliver the vaccine at an age of low disease incidence, prior to school leaving and just before individuals move into the higher incidence period associated with young adulthood. This policy is now being discontinued in some health authorities of the UK, which have moved to selective vaccination of high risk populations (e.g. immigrants, contacts)[30].

iii) Repeated/booster BCG: Many countries have a tradition of repeated BCG vaccination[31]. For several countries (e.g. Switzerland, Portugal), this means BCG in infancy and then at school entry or leaving, but for others, in particular in Eastern Europe, BCG has been recommended up to five times, e.g. from birth to 30 years of age (as in Hungary and Russia). The criteria for revaccination differ between countries, some of which emphasize routine revaccination of everyone, and others restrict revaccination to individuals who lack a scar or who remain tuberculin "negative". Criteria for negativity differ according to the tuberculin used, the method of administration and reading, and the interpretation of the induration.

iv) No routine BCG use: Two countries (USA, the Netherlands) have never recommended routine universal BCG, and others have now moved to this policy (e.g. Sweden in 1975[24], parts of Czechoslovakia in 1986[25]). All these countries license BCG for selective use among groups considered to be at particularly high risk (e.g. household contacts unlikely to comply with preventive therapy in the USA[26], or contacts and immigrants in Sweden[24])

These four categories reflect recommendations, but countries also differ in the level of legal compulsion attached to their vaccination programmes, and as to whether formal written "informed consent" (by a parent or guardian) is required before vaccination. In those European countries recommending universal BCG vaccination, the vaccination is considered compulsory in 29 countries, and voluntary in seven others[31]. All these policy differences are based upon regional differences in patterns and perspectives of tuberculosis, regional variations in health systems (economics, relative emphasis on preventive and curative services, manpower), and local history (personalities and "schools" of opinion). Justifications for the various policies are embedded in the medical and public health teaching and traditions of the countries involved.

The International Union against Tuberculosis and Lung Disease (IUATLD) has suggested criteria under which it may be reasonable for a country to shift from routine BCG vaccination to selective vaccination of high risk groups[32]. The IUATLD recommends that BCG be discontinued only if:

- an efficient notification system is in place and either
- the average annual notification rate of smear positive pulmonary tuberculosis is less than 5 per 100,000, or
- the average annual notification rate of tuberculous meningitis in children under five years of age is less than 1 per 10 million population over the previous five years, or
- the average annual risk of tuberculous infection is less than 0.1 percent.

Whether by this criterion or another, it is likely that the trend to discontinue policies for universal BCG coverage will continue for low TB-incidence countries.

It is also important to note that BCG is generally considered to be, above all, a tuberculosis vaccine, and its policies have historically been determined with tuberculosis control in mind. However, it has been known since the 1970s that BCG vaccines are also effective against other mycobacterial diseases, in particular leprosy. At least three countries (Brazil, Cuba, Venezuela) now recommend BCG for contacts of leprosy patients. Given the continued importance of leprosy in many populations today, this benefit of BCG needs to be taken into consideration when formulating policy[33]. Although the WHO has noted that the widespread application of BCG is likely to have been a factor in the decline of leprosy incidence observed in certain populations, it has not recommended repeated doses of BCG to this end[155].

BCG vaccines are also employed as non-specific immuno-stimulants in the treatment of certain conditions, in particular bladder cancer; but such uses are on a small scale, and are irrelevant for mycobacterial disease control.

5. Contraindications

WHO/EPI has provided guidelines on contraindications and false contraindications to the use of vaccines [151]. Industrialized countries tend to have stricter guidelines on contraindications to all vaccines than do developing countries, reflecting the different abilities of their health services to ascertain relevant information and to provide alternative preventive services to individuals in particular categories. For example, BCG is contraindicated in the United Kingdom for individuals with impaired immunity (specifically on corticosteroid or other immunosuppressive therapy, or undergoing general radiation therapy), or with malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumour of the reticuloendothelial system, or who have impaired immunological mechanisms such as hypogammaglobulinaemia, and also to anyone who is HIV positive, pregnant, tuberculin positive, febrile, or with a generalized septic skin condition[30]. This contrasts with the current WHO guidelines for BCG use within the EPI, which mentions only "symptomatic HIV infection (i.e. AIDS)" as a contraindication for BCG[34]. Importantly, HIV positivity in the absence of clinical signs of impaired immunity is not considered a contraindication by the EPI.

6. Administration

Historically, BCG vaccination was first administered orally. This route was favoured by Calmette and Weill-Hallé in France in the 1920s[153], but workers in other countries soon began to experiment with intradermal administration[154]. Intradermal or percutaneous administration was ultimately favoured for four reasons:

- oral vaccination required much larger doses of BCG for conversion (e.g. from 10 to 300mg, compared with 0.1mg for intradermal injection) and hence was more expensive;
- related to this, it proved difficult to control the effective dose with oral administration, as some viable bacilli were inactivated in the stomach and many passed right through the intestinal tract;
- intradermal administration proved much more efficient at inducing tuberculin conversion;
- there were reports of cervical lymphadenopathy attributed to oral administration of vaccine.

The last country to continue oral administration of BCG was Brazil where this practice was discontinued only in 1973.

Most current BCG vaccines are given by the intradermal route, generally by injection with a 25 or 26 gauge needle, in the deltoid insertion region of the upper arm. Some countries (e.g. Japan, South Africa) have employed percutaneous administration with special multipuncture devices. Other techniques have been tried, but found inferior either because of inconsistent dose delivery or adverse reactions (e.g. with jet injectors[35]) or low tuberculin conversion rates (bifurcated needle[36]). The implications of intradermal versus percutaneous administration routes have long been debated. Percutaneous administration methods are generally simpler than intradermal methods, but are less consistent in terms of the amount of vaccine delivered.

Most manufacturers (including all who provide vaccine for UNICEF) recommend a 0.05 ml dose for infants. Children and adults generally receive twice this amount, 0.1 ml. It may be noted that these dose differences may lead to confusion in quotations of vaccine supply, if it is not stated explicitly whether figures relate to numbers of infant or adult doses. Once reconstituted, vaccine should not be kept more than one vaccination session due to the risk of contamination and loss of potency. It is estimated that more than 75% of all BCG vaccine produced is not administered.

7. Efficacy

The (clinical) efficacy of a vaccine is measured in terms of the percentage reduction in disease among vaccinated individuals that is attributable to vaccination. BCG vaccines are generally given to protect against tuberculosis. Though the WHO now emphasizes BCG's utility in prevention of severe childhood disease (e.g. tuberculous meningitis), the main public health burden of tuberculosis is associated with adult pulmonary disease. It is therefore important to consider BCG vaccine efficacy against childhood tuberculosis, separately from that against adult tuberculosis, leprosy and other mycobacterial infections.

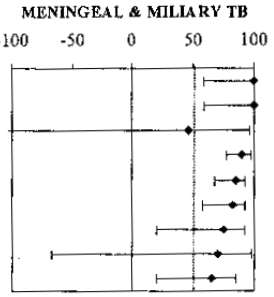
Childhood tuberculosis and tuberculous meningitis: There is evidence that BCG provides consistent and appreciable protection against tuberculous meningitis and miliary disease (Figure 2). A meta-analysis of five randomized controlled trials and eight case control studies indicated no significant heterogeneity, and an average protection on the order of 80% (86%, with 95% CI: 65% to 95% for controlled trials and 75%, with 95% CI: 61% to 84% for case control studies)[37]. This was confirmed by a meta-analysis of protection associated with vaccination in infancy[29]. Because of the rarity of these forms of tuberculosis, the bulk of the data are from observational studies. For example, no cases of tuberculous meningitis or miliary disease were recognised in the South Indian Chingleput trial, and only five cases of tuberculous meningitis and five cases of miliary disease were identified in the British MRC trial (all in the placebo group)[4]. Evidence of protection against pulmonary disease in children (which is relatively uncommon, rarely smear positive and hence difficult to diagnose) is less consistent, and appears to suggest lower protection in tropical than in temperate regions [29,38,39,40].

Adult pulmonary tuberculosis: This form of the disease has attracted the most attention, as it is responsible for the major public health burden of tuberculosis, but it is also associated with the greatest controversy relating to BCG. A wide range of efficacy estimates (0 to approximately 80%) have been provided, both by trials and observational case control and contact studies (Figure 2). The heterogeneity is highly significant ($p < 0.0001$), indicating that the variation reflects true biological differences and not just sampling errors [37,41]. The reason or reasons for the great differences remain unclear, and are discussed below.

Figure 2: Estimates of BCG efficacy against different forms of tuberculosis and leprosy, from clinical trials (CT), case controls (CC), cohort (COH) and household contact studies (HH).

BCG vaccine efficacy (%) with 95% confidence intervals

Asterisks (*) denote studies of pulmonary disease in children



Study location	Reference	Study type	Vaccine strain	Total cases
MENINGEAL & MILIARY TB				
Native Americans (Mil TB)	129	CT	Phipps	10
England (Both)	4	CT	Copenhagen	10
Puerto Rico (Both)	65	CT	Park	4
Argentina (Both)	130	CC	Mixed	18
Sao Paulo, Brazil (TBM)	131	CC	Moreau	68
Belo Horizonte, Brazil (TBM)	132	CC	Moreau	45
Indonesia (Both)	39	CC	Japan & Pasteur	15
England (Both)	79	CC	Glaxo	7
Papua New Guinea (Both)	133	CC	?	32
PULMONARY TB				
Haiti	135	CT	Frappier	18
England	4	CT	Copenhagen	203
Native Americans, USA	129	CT	Phipps	249
Puerto Rico	65	CT	Park	295
Mandanapalle, India	136	CT	Madras	80
Georgia, USA	137	CT	Tice	60
Chingleput, India	40	CT	Copen. & Pasteur	533
Georgia, USA	138	CT	Tice	7
Illinois, USA	139	CT	Tice?	19
England *	72	CC	Glaxo	33
Cameroon	140	CC	Pasteur	213
Argentina *	130	CC	Mixed	131
Indonesia *	39	CC	Japan & Pasteur	88
Kenya	45	CC	Glaxo	126
Colombia *	38	CC	Copenhagen	178
Karonga, Malawi	43	COH	Glaxo	23
TB (VARIOUS)				
Chicago, USA	134	CT	Tice	75
Korea *	141	HH	Pasteur	126
Togo *	142	HH	Glaxo	175
Thailand *	143	HH	Pasteur	218
Papua New Guinea *	133	CC	?	114
LEPROSY				
Uganda	42	CT	Glaxo	242
Papua New Guinea	144	CT	Japan	283
Chingleput, India	46	CT	Copen. & Pasteur	6219
Burma	145	CT	Glaxo	1494
Kenya	45	CC	Glaxo	69
Brazil	146	CC	Moreau	62
Indonesia	147	CC	?	115
Myanmar	58	CC	Mixed	245
Balaka, Malawi	148	CC	Glaxo	145
Venezuela	57	CC	Copenhagen	85
Karonga, Malawi	43	COH	Glaxo	137
Vietnam	149	CC	Mixed	177
Vellore, India	150	CC	Copenhagen	380

Leprosy and other mycobacterioses: Four controlled trials and approximately ten observational studies have all shown some protection against leprosy, ranging from 20 to 80%. The highest efficacy estimates have been reported from Africa (Uganda, Kenya, Malawi)[42,45]. Three different studies have evaluated protection by the same BCG vaccines against tuberculosis and leprosy in the same population, and in each case the protection was appreciably greater against leprosy[43,46]. Importantly, there is much evidence that BCG vaccines impart as much protection against lepromatous as they do against tuberculoid forms of the disease[47], though this was not observed in the Chingleput trial population[48]. Given that lepromatous disease is the most severe, and is thought to be responsible for most transmission of *M. leprae* in the community, this has important public health implications.

There is also evidence that BCG provides some protection against Buruli ulcer *(M. ulcerans* infection)[49], and against glandular disease attributable to various other "environmental" mycobacteria, in particular *M. avium-intracellulare*. This evidence is based upon observations in Sweden[50] and Czechoslovakia[51], where increases in childhood glandular mycobacterioses were identified in cohorts born after infant BCG was discontinued. The protection appeared to be on the order of 85% in Sweden, among children under five years of age[50].

Booster doses: Despite the widespread use of boosters in many countries, there has been almost no formal evaluation of their utility. Analyses of data from Hungary[52] and Poland[53] were consistent with revaccination providing some protection, but were based upon small numbers and inappropriate controls, and were not convincing. A case control study in Chile failed to find evidence for increased protection associated with increased number of BCG scars[54]. No increase in tuberculosis has been observed in Finland since that country discontinued revaccination of schoolchildren in 1990, though overall case numbers are too small for convincing analysis[55]. The only controlled trial evaluation of the efficacy of a BCG booster in protection of tuberculosis was carried out in Malawi, and found no evidence for protection[44]. On the basis of such data the WHO has not encouraged revaccination[27].

Though there is no convincing evidence that boosters are effective in preventing tuberculosis, three studies have demonstrated their utility against leprosy. The randomized trial carried out in Malawi[44], cohort analyses in Venezuela[56], and case control studies in both Venezuela[57] and Myanmar[58] have all shown an appreciable increase in protection with increasing numbers of doses of BCG (or BCG vaccine scars). The Malawi observation is of particular interest both because it was a formal trial and because no protection was observed (by either an initial or a repeated dose of BCG) against tuberculosis despite the (dose dependent) protection against leprosy. Taken together, such evidence suggests that BCG boosters may give increased protection in contexts where an initial dose is effective, but not otherwise. The question of the utility of boosters is thus referred to the more basic issue of the inconsistent behaviour of an initial BCG vaccination.

8. Reasons for variable efficacy

The variation in protection by BCG against pulmonary tuberculosis, and against leprosy, has attracted much discussion, but few clear answers. The major hypotheses are as follows:

Differences between BCG vaccines: It is well recognized that BCG vaccines differ in various properties, both in the genetics of the mycobacterial strains and in the physical properties of the vaccine preparations. Several authors have thus explored whether these differences could explain the observed pattern of protection afforded by BCG vaccines. Comstock analyzed case-control data from Indonesia and Colombia, and found evidence for possible declines in protection when the programmes shifted from Japan and Glaxo to Paris and Danish vaccines respectively[21]. A trial comparing Paris and Glaxo vaccines carried out among 300,000 infants in Hong Kong found that the Pasteur vaccine provided 40% greater protection against childhood forms of tuberculosis over the subsequent six years[59]. This was statistically significant (but in the opposite direction to the differences noted by Comstock !). A recent paper has suggested that efficacy declined with passage number of the seed substrain[60], interpreting this as evidence that manufacturers selected their strains to reduce lymphadenopathic reactions, and thereby compromised their efficacy. However, the trend was confounded by geographic area (the higher passage strains were tested at lower latitudes, where it is known that BCG vaccines perform less well). More directly, the fact that some BCG vaccine strains have been shown to perform well in some populations, but poorly in others, demonstrates that vaccine differences cannot explain all the variation: thus freeze dried Glaxo vaccine provided good protection in the UK[61], but none (against pulmonary tuberculosis) in Malawi [43,44]. Another perspective is provided by the BMRC trial, which evaluated both a Copenhagen strain BCG and a vole bacillus vaccine (*M. microti*), and found identical protection associated with the two very different vaccines[5]. A recent review of BCG strain history and protective efficacy concluded that vaccine strain "is not a significant determinant of overall efficacy"[62].

Environmental mycobacteria: Most populations in the world are exposed to various "environmental" mycobacteria. There is much evidence from animal studies that such exposure can provide some degree of protection against subsequent challenge with tubercle bacilli. Follow-up studies of humans indicate that individuals with skin test evidence of exposure (e.g. to *M. intracellulare*, as revealed by greater sensitivity to PPD-B than to PPD-S) enjoy some protection against tuberculosis[63]. Guinea pig challenge studies have shown that the observable protection imparted by BCG is reduced in animals who have already received some protection by prior exposure to *M. fortuitum*, *M. avium* or *M. kansasii* [9]. This evidence is consistent with the observation that BCG efficacy tends to be lower in populations living in warmer and

wetter regions (closer to the equator), in particular in rural areas[41], where environmental mycobacterial exposure is greater [64,65,66], than in temperate regions. All such evidence suggests that exposure to environmental mycobacteria is responsible for at least some of the variation observed in BCG's behaviour. If this depends on the sharing of various antigens between the several pathogenic and non-pathogenic species, it might also explain why BCG may protect more against leprosy than against tuberculosis.

Human genetics: There is increasing evidence that several genes which control cellular immune mechanisms (including HLA-DR, HLA-DQ, vitamin D receptor and IFNg receptor polymorphisms, and NRAMP) influence susceptibility to tuberculosis and other mycobacterial infections [67-71], and thus it has been conjectured that population genetic differences might explain the behaviour of BCG. The evidence for such a relationship is not yet convincing. Slightly (but non-significantly) higher protection against tuberculosis was observed among black compared with white participants in the USPHS trials[7]. However, appreciable protection against tuberculosis was observed among Asians in England [72,73] despite the absence of protection found in South India[10], though the fact that the UK Asians were in general not from South India weakens this comparison. Appropriate studies have yet to be done, e.g. comparing the frequency of particular genetic determinants between vaccinated and non-vaccinated cases and between populations where BCG behaves in different ways.

Differences in M. tuberculosis: This was first suggested as an explanation for the failure of BCG in Chingleput, when it was noted that many *M. tuberculosis* isolates from neighbouring Madras city were of relatively low virulence for guinea pigs[74]. Guinea pig experiments failed to confirm that this difference was relevant for BCG[75]. The hypothesis has surfaced more recently with increased interest in genetic fingerprint differences between strains of *M. tuberculosis*[76], but the appropriate comparisons have not yet been done - e.g. comparing tubercle bacilli isolated from vaccinated and unvaccinated cases.

Several other explanations have been proposed. Some investigators have wondered whether ultra violet (UV) light exposure might be relevant. It is well known that BCG bacilli are acutely sensitive to UV exposure, as are the dermal Langerhans cells which are important in antigen presentation, and this could explain the tendency for protection to be lower in tropical than temperate regions. However, it does not explain the differences in protection against tuberculosis and leprosy in the same population. Nutritional differences between populations have been discussed[77], but without good evidence, and this too, raises questions of why protection against tuberculosis and leprosy should differ.

Finally, some authors have suggested that protection might reflect the local natural history of tuberculosis, and be greater against primary infection or (endogenous) reactivation disease, than against disease attributable to exogenous reinfection[28], and therefore greater in areas of low than high infection incidence. Though such an explanation may fit the low protection observed in some developing countries, it does not easily explain the high protection observed among North American Indians, who experienced high infection risks, nor is it reflected in protection trends in England, where BCG efficacy remained high over a period of rapid decline in infection risk[61,78].

This hypothesis touches upon a continuing controversy in the tuberculosis literature over the pathogenesis of adult tuberculosis, and the relative contributions of primary, reactivation and re-infection disease in overall tuberculosis morbidity. The answer to this question involves consideration not only of immune mechanisms but also the level and temporal trend in infection risk: a declining risk of infection, as has occurred in many communities, will be associated with an increase in the average age at infection and a decrease in the probability of reinfection[79-81]. Each of these trends may have important implications for protection by BCG.

Despite a large literature discussing these various hypotheses, there is still no consensus. As a consequence, we are unable to predict confidently, based on current knowledge, just what the efficacy of a given BCG vaccine will be in any particular population.

It is important to emphasize that the variable efficacy problem relates particularly to adult, pulmonary tuberculosis (and perhaps to a lesser degree to leprosy). Evidence to date indicates consistent protection against the meningitic or miliary forms of tuberculosis, in particular in children, but very few data are available relating to other forms of tuberculosis, such as glandular, bone and joint, kidney, genitourinary, etc. The consistent protection against meningitis and miliary disease has been taken as evidence that BCG is particularly effective in preventing haematogenous spread of *M. tuberculosis* [82]. This may in turn be consistent with evidence from autopsy studies that BCG is less efficient in preventing primary lung implantation of *M. tuberculosis* than in protecting against disease [83]. In this context, it is interesting that a recent study suggested that a history of BCG vaccination may protect against *M. tuberculosis* bacteraemia in AIDS patients (based upon bacteraemia prevalence in 1 of 58 AIDS patients with previous BCG versus 7 of 68 patients without previous BCG, p=0.05)[84].

Duration of protection

In addition to the continued uncertainty over efficacy, there is uncertainty about the duration of protection. A recent analysis was unable to identify convincing evidence of a consistent pattern of protection over time, or for any evidence of protection against pulmonary disease lasting more than 15 years[85]. It is important to note that this absence of evidence for protection after 15 years does not mean absence of effect, as there are in fact very few relevant data on this issue. If observable protection does decline, as was apparently the case in the BMRC trial[5], it is unclear to what extent this might be attributable to waning of an active protective response (in which case booster doses might be effective), or to progressive exposure of the population to other immunizing infections, thereby diluting out the differential effect of BCG (in which case booster doses of BCG might not be called for) [41].

This lack of information on duration of BCG's effect has important implications for the reliability of estimates of the impact of past and current BCG vaccination on disease, as well as upon the rationale for booster doses of vaccine.

9. Adverse reactions

Though BCG vaccines are considered very safe, they are also among the most reactogenic vaccines in use today. BCG is the only commonly used vaccine to induce a local ulcer (this was more acceptable in the past, when populations were accustomed to smallpox vaccination, than it is today). The local lesion begins as a papule, two or more weeks after vaccination; it generally proceeds to ulceration, and heals after several months. A scar (typically round and slightly depressed) remains in most vaccinees, and is a useful, if imperfect, indication of past BCG vaccination in vaccine-uptake surveys and in case-control studies. The probability that BCG vaccination leaves a lasting scar is lower after vaccination in early infancy than at older ages[86]. This is due in part to the low doses of vaccine recommended in infancy, but may be influenced by the difficulty of injecting the full amount into infants, and by relatively weak local immunological response in the very young. Keloid formation on the scar site appears to be more common in some - e.g. African and Asian - populations than in others.

BCG is not easy to administer as an intradermal injection at any age, but especially to a newborn. The commonest mistake is to give the injection too deep, failing to raise the classical orange-skin appearance in the dermis. Local injection site abscesses may occur, typically as a result of improper injection technique when the vaccine is given into the subcutaneous layer of the skin.

Local reactogenicity differs between vaccines, varying with both strain and number of viable bacilli. Thus the Pasteur and Copenhagen strains have generally been found to be more reactogenic than the Tokyo, Glaxo or Brazilian (Moreau) strains[15]. There were several reports of “outbreaks” of BCG reactions, manifested as large ulcers and local lymphadenopathy or suppurative lymphadenitis, in the late 1980s, when changes in vaccine availability led many programmes to switch from the less reactogenic Glaxo1077 to the more reactogenic Pasteur 1173P2 strain vaccines[87,88]. An important lesson from this experience is the need for national immunization programme managers to be aware of the implication of changing BCG strains. They need to be able to monitor reactogenicity, and to inform peripheral staff of what to expect, what to tell parents and how to treat the various reactions that occur. Donors should respect the importance of maintaining a supply of vaccine from a single manufacturer is at all possible.

BCG must influence cellular immunity in order to provide protection, and this points to the importance of lymphatic involvement, perhaps analogous to the “primary complex” which follows a first infection with tubercle bacilli. Whether the extent of regional lymphatic involvement is a correlate of protection is unclear, but the recent trial in Hong Kong showed that the Pasteur strain, which was marginally

more protective, was appreciably more reactive than the Glaxo (all 127 complaints were associated with receipt of the Pasteur strain vaccine)[89]. The Hong Kong Department of Health ultimately favoured using the Glaxo product, despite its lower efficacy, because of its better safety record[59].

Systemic BCGosis is a recognized but rare consequence of BCG vaccination, and traditionally has been seen in children with severe immune deficiencies. A recent multicentre study has identified the syndrome in children with severe combined immune-deficiency (SCID), chronic granulomatous disease, Di George syndrome and homozygous complete or partial interferon gamma receptor deficiency [70,71,90]. Its frequency is reported as less than 5 per million vaccinees, reflecting the rarity of the underlying conditions[91]. If not properly managed, these cases may be fatal.

BCG osteitis/osteomyelitis is another of the rare and severe consequences of BCG vaccination, and has been reported in particular in Scandinavia and Eastern Europe, typically associated with changes in BCG vaccine strain. Thus there was a report of an increase in osteitis to 35 per million in Czechoslovakia after a shift from the Prague to Russian strain BCG[91]. Both Finland and Sweden reported increases in osteitis after 1971, when they shifted to a Gothenburg strain produced in Denmark. Sweden reported rates as high as 1 in 3000 vaccinees, which declined rapidly when the national programme shifted to a Danish (Copenhagen 1331) vaccine strain[91].

There has been particular concern over the implications of HIV for the safety of BCG vaccination, after early case reports of systemic BCGosis in individuals with AIDS[92]. A series of studies was initiated in Africa to compare reactogenicity in infants born to HIV positive and negative women as summarized in table 4. Only one study found a significant excess of reactions among the HIV "exposed" and positive infants, and this occurred following the mistaken administration of more than twice the recommended dose of BCG Pasteur: 4 out of 13 HIV-infected infants had "mild" (e.g. lymphadenitis, 3 infants) or "moderate" (abscess or fistula, 1 infant) reactions in comparison to 16 of 166 infants born to HIV-uninfected mothers ($p = 0.04$)[93]. In general the data available to date have supported the WHO policy of exempting only individuals with symptomatic HIV infection (AIDS) from routine BCG vaccination at birth[152].

Table 4 : Summary of adverse reactions to BCG in HIV-exposed and/or infected infants

Study	Year of vaccination	Location	Age at vaccination	Vaccine strain	Subjects and study design	Results
118	1983-85	France	Infancy	Pasteur?	18 children with clinical symptoms of HIV infection followed-up for 3-42 mos.	Disseminated BCG infections: 3 children (with no antigen-induced lymphocyte proliferation) at age 1-6 mos
119	1986	Uganda	Birth	?	Prospective monthly follow-up (1-11 mos) of 54 children of HIV(+) mothers	No local complications or evidence of disseminated BCG infections
88	1986	Zaire	Infancy	?	Outbreak investigation of post-BCG abscesses in 19 children	All the affected children were HIV(-)
120	1987	Zaire	2 days	Pasteur	Prospective follow-up (12 mos) of 48 HIV(+) children, 200 HIV(-) children of HIV(+) mothers & 440 children of HIV(-) mothers	*Regional adenitis*: 2/48 (5%) HIV(+), 10/200 (5%) HIV exposed*, 13/440 (3%) HIV(-) *fistulae*: 2/48 (5%) HIV(+), 16/200 (8%) HIV exposed, 26/440 (6%) HIV(-); ulcers: 29/48 (60%) HIV(+), 148/200 (74%) HIV exposed, 312/440 (71%) HIV(-)
121	1987	Zambia	Birth	?	Prospective follow-up (2 yrs) of 42 HIV(+) children, 67 HIV(-) children of HIV (+) mothers & 40 children of HIV(-) mothers	*BCG adenitis*: 1/42 (2%) HIV(+), 3/67 (4%) HIV exposed, 3/40 (8%) HIV(-)
122	1988?	France	<1 yr (0-3 mos)	Pasteur?	Retrospective chart review of 67 HIV(+) children with prior BCG	*Post-BCG axillary adenopathies* in 7 children

* "HIV exposed" refers to HIV-negative children of HIV positive mothers.

Management of reactions and complications

Local site lesions: It is generally considered that even large local lesions are best left untreated. Secondary infections at the site of injection are unlikely. In extreme cases, systemic treatment with erythromycin (daily, for up to one month) may be helpful.

Keloids: Keloids are difficult to treat. Simple surgical removal is likely to make them worse. A combination of surgery, irradiation, and drug treatment may be effective, but should be undertaken by a specialized practitioner.

Local gland involvement: Axillary or cervical lymphadenitis will heal spontaneously and it is best not to treat the lesion if it remains unattached to the skin. An adherent or fistulated lymph gland may be drained and an anti-tuberculosis drug may be instilled locally. Systemic treatment with anti-tuberculosis drugs is ineffective.

Rare severe complications: Rare complications, including lupus vulgaris, erythema nodosum, iritis, osteomyelitis and generalized BCGitis, should be treated systemically with antituberculosis regimens including isoniazid and rifampicin.

10. Impact

Despite the massive use of BCG vaccines for many years, it is difficult to demonstrate their effect on tuberculosis morbidity in national or population statistics. BCG differs in this regard from most other widely used vaccines (diphtheria, tetanus, pertussis, polio, measles, rubella, mumps, and *Haemophilus influenza b*), the impacts of which are readily apparent in the routine notifications of many countries. There are five reasons for these differences, and for the difficulty of demonstrating BCG's impact in this way.

First, BCG vaccines were introduced in developed countries against a background of an already declining tuberculosis incidence, and coincided with other improvements in tuberculosis case-finding and treatment. This has made it difficult to demonstrate an obvious separate effect attributable to BCG.

Second, the main burden of tuberculosis is pulmonary disease in adults, in particular older adults, whereas BCG has been administered mainly to children. This results in a delay of many years before vaccinated cohorts enter age bands at high risk of tuberculosis. It is unclear whether BCG protection lasts sufficiently long to have an impact decades after administration, and this potential lag exacerbates the problem of distinguishing BCG-attributable effects from declines attributable to other tuberculosis control measures.

Third, the fact that *M. tuberculosis* transmission is mainly from adult pulmonary cases, has meant that BCG introduction has had little impact upon infection incidence[94]. The fourth reason is the absence of good long term statistics measuring tuberculosis morbidity or mortality in most countries of the world, in particular in those where tuberculosis is most prevalent, and hence where the potential benefits of BCG should be greatest. Fifth, there have been actual increases in tuberculosis in many countries over the past decade, attributable to HIV or to other factors such as immigration, and these trends have further complicated any effort to identify a specific BCG effect.

Despite the difficulty in determining an obvious impact of BCG on global or national disease statistics, or in deriving a global estimate of the morbidity and mortality prevented by BCG to date, there are several examples of population data that do demonstrate effects of BCG. Analysis of age-specific trends of tuberculosis in the UK showed a decline in tuberculosis among young adults following introduction of the vaccine, consistent with predictions based on vaccine uptake and efficacy [61,78].

Similar analyses are available for Norway, Sweden and Denmark[95]. The discontinuation of BCG in Sweden was associated with demonstrable increases in childhood tuberculosis[24]. In addition, the rapid declines of leprosy observed in many countries of Africa have coincided with the introduction of wide-scale use of BCG there, and are consistent with the repeated observation of appreciable BCG protection against leprosy in Africa [42,44,45].

Theoretical estimation of impact

Beyond the difficulty of identifying the public health impact of past and current BCG vaccination in particular population data, the problem of estimating its impact in theory is equally difficult, because of the acknowledged yet ill-understood inconsistency in protective effects observed in different studies. Given this inconsistency, and our ignorance over the duration of any protection, we are reluctant to just assume some global protective value or pattern and to produce figures for total numbers of tuberculosis cases prevented, now, or in the past, or in the future.

This said, it is possible to make an estimate of the amount of tuberculous meningitis prevented by BCG. This is feasible for two reasons: first, because it has been shown that the incidence of tuberculous meningitis in most populations among under-fives is approximately one per cent of the annual risk of infection [96,97], and second because the protection afforded by BCG against tuberculous meningitis has been quite consistent, in all investigations[37]. Table 5 presents the argument, based upon these observations, that current infant BCG programmes are preventing 24,000 - 40,000 cases of tuberculous meningitis in the world today. This impact will be mainly in those populations where both the infection risk, and the BCG coverage, are high. On face value, this suggests one under-five TB meningitis case prevented for every 12,500 to 16,667 infant vaccinations. Extension of such argument to broader age groups and to wider case definitions is difficult, as there are no guidelines for the expected incidence of other forms of tuberculosis, such as miliary disease, for which there is evidence to believe that BCG's protection is reasonably high.

Table 5 : Estimated global impact of current infant BCG programme in prevention of tuberculous meningitis, based on the recognition that tuberculous meningitis incidence in under fives is approximately one percent of the annual risk of infection[96]

Total number of children under five years	**500 000 000**
Estimated number of tuberculous meningitis cases, assuming that the annual risk of *M tuberculosis* infection is 1 % [127], and that 1 % of infected under fives contracts tuberculous meningitis[96].	50 000
Estimated number of tuberculous meningitis cases prevented, assuming: (a) 100% BCG coverage and (b) 80% protection:	40 000 i.e. approximately 12 500 vaccinations to prevent one case of TB meningitis
Estimated number of tuberculous meningitis cases prevented, assuming: (a) 80% BCG coverage and (b) 60% protection	24 000 i.e. approximately 16 667 vaccinations to prevent one case of TB meningitis

This argument can be taken a step further, by extrapolating from a recent meta-analysis of BCG vaccination in infancy which indicated a global average protection against childhood disease of approximately 50% against all forms of tuberculosis (the estimated protection against laboratory confirmed cases was 83%, with 95% confidence limits from 58% to 93%) [29]. If we accept a 50% average figure globally (and recall that the great variability in BCG efficacy estimates relates to protection among adults, not children), we may estimate the amount of disease prevented given various simplifying assumptions of infection and disease risks. The argument is set out in Table 6. If we assume background infection risks over the range 0.5% to 1%, and risks of primary disease in the range 1% to 5% among infected individuals, then from 267 to 2667 vaccinations are required to prevent a case of childhood tuberculosis.

Table 6 : Estimated impact of BCG vaccination in infancy, based upon assumption that protection is approximately 50 % and lasts for 15 years*

	Annual risk of infection	
	0.01	**0.005**
Risk of disease, per annum, among susceptibles, assuming that 1 % *[5 %]* of infected individuals experience some form of primary tuberculosis	0.0001 *[0.0005]* (i.e. 1 *[5]* per 10 000)	0.00005 *[0.00025]* (i.e. 0.5 *[2.5]* per 10 000)
Cumulative risk of primary tuberculosis, up to age 15, assuming that 1 % *[5 %]* of infected individuals experience some form of primary tuberculosis*	15 *[75]* per 10 000	7.5 *[37.5]* per 10 0000
Number of cases preventable, up to age 5, by a vaccine which is 50 % effective, assuming that 1 % *[5 %]* of infected individuals experience some form of primary tuberculosis.	7.5 *[37.5]* per 10 000	3.75 *[18.75]* per 10 000
Number of vaccinations to prevent one case of primary tuberculosis, if vaccination given at birth and 50 % protection lasts for 15 years, assuming that 1 % *[5 %]* of infected individuals experience some form of primary tuberculosis.	i.e. 1333 *[267]* vaccinations prevent one case	i.e. 2667 *[533]* vaccinations prevent one case

* Cumulative incidence of infection to age 15 estimated crudely as simply 15 times the annual incidence.

These estimates are given as rough guidelines, and should not be over-interpreted. They suggest that current BCG programmes are preventing some tens of thousands of tuberculous meningitis cases each year, and that they are also preventing additional tens of thousands of cases of other forms of tuberculosis among children. Viewed differently, they suggest that a case of childhood tuberculosis is prevented by every one to two thousand infant BCG vaccinations administered. All this is quite aside from any protection of disease among adults. The extent of disease prevented among adults is likely to be substantial in a global context, though extremely difficult to estimate numerically. And, beyond this, it must be remembered that BCG is making an important contribution to the world-wide decline in leprosy[33].

Against these rough estimates of impact may be set the cost of BCG, currently estimated at 0.1 to 0.2 US$ per vaccination, including vaccine (0.05 - 0.09US$ / dose), needle and syringe costs (Zaffran, WHO, 1998). Among the most obvious lessons from this exercise is the importance of gaining more evidence on the long-term effects of BCG.

11. Development and evaluation of new vaccines

Despite the obvious need, there are major obstacles to development of an improved tuberculosis vaccine. First, we ask a great deal of a vaccine to protect against a disease for which there is no evidence of solid "sterile" immunity in the first place. Though individuals and animals with a history of prior infection may have an enhanced resistance to subsequent challenge, there is much evidence both for reactivation and for re-infection disease in individuals long after having first met the tubercle bacillus[98]. Tuberculosis differs from most other vaccine-preventable diseases in this respect (with the possible exception of varicella-zoster and hepatitis B, both of which are associated with chronic infections).

The second obstacle against an improved tuberculosis vaccine is our ignorance of the immunological mechanism of protection against tuberculosis, which is exemplified by the absence of any known correlate of protective immunity. It was thought for many years that BCG-induced tuberculin-sensitivity provided a measure of protective immunity, but it is now recognized that this is not so [20, 22], and that tuberculin sensitivity is a more complicated response than had previously been appreciated. Many studies have shown that strong tuberculin-sensitivity is associated with a high risk of disease[99]. Such reactivity represents ongoing aggressive immunological activity in the host, and the stronger the reactivity, the less likely it will end in victory for the host. Interestingly, several studies have suggested that a low degree of tuberculin-sensitivity is more protective than a high degree, though it is unknown whether such sensitivity reflects prior exposure to tubercle bacilli or to some cross-reacting antigens common to the tuberculin and to other mycobacteria or even other related bacteria[63]. Thus, although some authors have described tuberculin DTH as the "sine qua non" of protective immunity[19], others have argued that an effective vaccine should avoid inducing delayed type hypersensitivity at all[100]. Such confusion, on top of the recognized difficulties associated with the standardization, batch variation, administration and reading of tuberculin reactions has meant that tuberculin reactivity has provided a poor guide for the development of an effective tuberculosis vaccine. There is hope that recent advances in our understanding of cell-mediated immunity, in particular the identification of various antigen-specific (and non-specific) responses, measurable in terms of cytokine release by particular cell types, may ultimately provide a clear correlate of a protective response against mycobacterial infection, and so provide a guide for the development of improved vaccine products.

Several laboratories are pursuing the development of new tuberculosis vaccines in an international collaborative research effort coordinated by WHO's Immunology of Mycobacteria (IMMYC) task force. Different approaches are attracting attention. One is based on the identification and evaluation of subunit antigens of the tubercle bacillus. There is particular interest in secretory antigens, such as "ESAT-6" and the

"antigen 85" complex, which are thought to be released by tubercle bacilli early in the infection process. It is thus argued that an immune response to these antigens might affect tubercle bacilli early in the course of an infection [101,102]. Another approach is based upon the development of mutant or auxotropic strains of BCG or other mycobacteria in order to set up time-limited infections in the host but still induce protective immune responses[103]. Yet another approach involves the delivery of DNA, encoding various specific mycobacterial antigens within plasmid carriers. This DNA is taken-up by host muscle cells, where it is translated into foreign proteins that induce specific antibody and T cell responses[104].

There is now an active programme of evaluating such reagents in animal models, mainly guinea pigs and mice. Several reagents appear to provide as much protection as BCG in these models, but none has yet done better. The animal models themselves raise profound questions insofar as tuberculosis is an unnatural infection in all of them, and not all the models agree in their relative assessments of BCG vaccines[105]. Furthermore, the observation that at least some BCG vaccines behave differently in different human populations raises questions about the interpretability of any single animal model. There is increasing recognition of the problems inherent in these experimental systems, and in the development of models that mimic the human disease process. Thus there is increasing interest in models based upon low-dose challenge and associated with long latency[106].

The ultimate evaluation of any new vaccine product in humans poses formidable difficulties. The experience gained in previous BCG vaccine trials will be highly relevant to such evaluation, but shows that the evaluation of new vaccines is likely to be costly, time-consuming, and difficult to interpret. A particular problem is raised by the fact that the most important ultimate target for a new tuberculosis vaccine is adult pulmonary disease, especially as it occurs in developing countries. It is because of this form of the disease that tuberculosis was declared a global emergency. What is more, BCG is likely to continue to be given in most highly endemic countries, for the foreseeable future, and this vaccine appears to be providing reasonable protection against the childhood forms of tuberculosis, in particular meningitis. In addition, more than 95 percent of the world's tuberculosis is in developing countries, and developed countries are moving away from BCG vaccines, even where they appear to be effective, given their low benefit-cost ratios under conditions of low incidence.

The challenge is thus to provide a vaccine to protect against adult pulmonary disease, in populations where BCG has already been widely used, where there is a high prevalence of non-specific tuberculin sensitivity both from BCG and from environmental mycobacteria, and where a high proportion of adults have already met the tubercle bacillus. This is no easy task. In theory the best approach would be to develop a vaccine that was effective in individuals who had already been exposed to a variety of mycobacteria - BCG, environmental species, perhaps *M. tuberculosis* itself - and that could provide an appropriate boost to the immune response in such individuals. Whether such an approach is immunologically feasible is by no means clear. Animal models are currently exploring the feasibility of various approaches to booster vaccination; if any are successful, this may open a new approach to immunoprophylaxis against tuberculosis.

Several new vaccine products are now entering phase 1 trials in humans, and IMMYC has initiated preliminary discussions of phase 3 trial designs and sites. Though the pace of basic science research on mycobacterial is accelerating, with the recent sequencing of the complete genome of *M. tuberculosis*, the complexity of the problem is such that expecting a new vaccine to have proven its worth within the next five years would be optimistic. Ten years is more realistic. We will thus have to continue with BCG for the foreseeable future.

It is important to note that appropriate immunological and epidemiological studies of BCG are important both for guiding our present immunization programmes and for the development and evaluation of new vaccines. Thus research on the implications of repeated BCG, on the comparison of immunological effects of BCG in populations where BCG is known to protect differently, and on the several hypotheses for BCG's variable efficacy, are relevant not only to optimizing current BCG policies but will also provide important guidance for our understanding of induced immunity to tuberculosis and hence of new vaccines.

12. Specific BCG policy issues

Vaccines and quality control: There is continued debate, and some evidence, that BCG vaccine strains differ in their ability to protect against (at least pulmonary) tuberculosis. Unfortunately, the current system of producing and distributing vaccines does not facilitate comparative studies between vaccines. The current quality control measures emphasize viable counts and the ability to induce tuberculin sensitivity. While intuitively reasonable, there is little or no evidence that these measures are meaningful, let alone optimal, as correlates of protection. Studies are now underway to evaluate other potential correlates, such as the ability to induce cytokine secretion on exposure to mycobacterial antigens. It is hoped that these will lead to more relevant means of testing vaccines. Moreover, in addition to the shortcomings in the quality control tests being used, many BCG vaccines are still subject only to final product testing as a means of assuring quality. It should be the responsibility of each manufacturer to assure that each lot of BCG vaccine produced is as identical as possible to a lot for which clinical efficacy has been established. National Regulatory Authorities should ensure that this is the case.

Vaccine supply and distribution: 25-30% of the world's BCG is purchased on a competitive basis by UNICEF. This means that very few producers (only three in 1997, two in 1998) provide a third of the world's vaccines. Although some effort is made to supply countries with vaccine from a single source, this cannot always be achieved. UNICEF's distribution policy is based on availability of product, and assumes that vaccines which meet WHO requirements and the terms of the UNICEF tender are similar in protective efficacy and reactogenicity. It is evident that there are major differences among vaccine sub-strains, and yet there are to date no firm data that they all behave comparably.

Current distribution policies imply that there is no further need to compare the performance of different vaccines. Rationalizing the distribution of vaccines to countries would be preferable, such that vaccine types were changed infrequently, and in a controlled manner. There are two reasons for this: *first*, knowledge of which vaccines were being used, and at what time, would facilitate comparisons between vaccines (it may be unrealistic to expect that local or individual vaccination records will include reliable vaccine type information) and *second*, peripheral health workers would get to know the reactogenicity of the vaccine in use and hence be able better to inform parents about side effects and to treat adverse reactions.

Timing of infant vaccination: BCG is currently recommended at birth, or at first contact with health services. Whether it is in fact optimal to vaccinate in the first few days of life, or preferable to wait one or two months, has often been discussed but remains unresolved. It is evident from Swedish data showing increases in tuberculosis among child cohorts born after discontinuation of neonatal vaccination[24], that early neonatal vaccination can induce at least some degree of protection against childhood tuberculosis. Immunological studies are currently underway to compare the immune response to BCG when given at birth or at two or four months of age. This subject will need to be reviewed in the context of continuing research on cellular immune responses in early infancy and childhood.

Repeat vaccination: Though many countries still recommend repeat vaccination, this is not endorsed by WHO[27]. There is surprisingly little information on which to base this decision, one way or another. The only formal evaluation of repeat BCG was carried out in Malawi, and found that the second dose has no effect on (pulmonary) tuberculosis, but provided increased protection against leprosy [44]. This result should not be taken as an argument against repeat vaccination, because previous studies had shown that an initial BCG provided protection only against leprosy in this population. Thus these results could be taken as favouring repeated BCG vaccination in populations in which a first dose provides some protection. There is a need for studies to evaluate the implications of repeated vaccination. Observational studies will be difficult to perform, as revaccination is typically not allocated at random, and in fact is generally carried out on some indication (e.g. absence of tuberculin sensitivity or scar) which may itself confound the assessment.

The implications of a post-vaccination scar for protection against disease have yet to be determined, though one study found no evidence of a relationship between scar size and protection against either tuberculosis or leprosy [107]. The fact that available data show no relationship between post-vaccination tuberculin sensitivity and protection deserves to be more widely appreciated, and may in turn challenge the widespread practice of repeat vaccination on the basis of negative post-vaccination DTH.

Duration of effect: Too little is known of the duration of any protection by BCG. Such information is essential both for estimating the impact of BCG vaccination programmes and for rational decisions on the utility of repeat vaccination. Research on this important question should be encouraged.

Vaccination of health care workers: Health care workers have long been recognized as being at high risk of tuberculosis. They are also particularly likely to be exposed to drug resistant *M. tuberculosis*. A recent review of the effectiveness of BCG in nurses and physicians noted that the cumulative data were consistent in showing appreciable protection, though the studies were not always methodologically rigorous[108]. Several cost-benefit and risk-benefit models have been developed in order to address the utility of BCG in health care settings in the USA, and all have favoured BCG over measures based upon repeat tuberculin testing and chemoprophyllaxis, even assuming low levels of BCG protective efficacy[109, 157, 158]. Such arguments have been voiced to encourage a return to a policy of selective use of BCG among health care professionals in the USA (a policy abandoned in 1988). The special case of health care workers will need continued attention as additional countries give up routine BCG, particularly if the incidence of drug-resistant infection increases.

Implications of HIV: Evidence to date still supports the current policy of only withholding BCG from those with clinical evidence of immuno-suppression, and not on grounds of HIV sero-positivity alone[34]. This situation needs to be monitored closely as the HIV epidemic evolves. A requirement to HIV test infants before vaccination would not be feasible. In addition, the current policy has the advantage of providing protection to HIV positive and negative children who are at high risk of exposure to tuberculosis because their mothers have HIV. Whether prior BCG can reduce the risk of tuberculosis or other mycobacterioses in AIDS patients is unclear, and requires further study[84]. On the other hand, the extreme rarity of reports of systemic BCG-osis in adult AIDS patients[110] is itself an interesting observation, suggesting that viable BCG does not remain long in vaccinated individuals.

Criteria for discontinuation: It is likely that more and more developed countries will shift from routine to selective BCG vaccination during the next decade. The IUATLD's criteria provide a rough guide for this decision[32], but further work is needed on the benefit-cost ratio of BCG as opposed to other approaches to tuberculosis control [109-112]. One argument favouring discontinuation of BCG is based on the advantages inherent in the absence of non-specific BCG-induced tuberculin sensitivity. This would facilitate the use of tuberculin testing for contact tracing, source identification and selection of individuals for preventive therapy. This is a valid argument, but many years must pass after discontinuation of routine BCG vaccination to replace a vaccinated population with unvaccinated individuals completely.

BCG as a vaccine delivery vehicle: There is much interest in the potential use of BCG as a live vector to deliver a variety of recombinant antigens, and hence as a "super vaccine"[113]. Thus antigens from HIV, *Borrelia burgdorferi* and pneumococcus have been expressed in BCG in such a way as to induce immune responses in experimental animals [114-117]. The fact that BCG can be delivered at birth, that it has a good safety record (despite its local reactogenicity), and that it has general adjuvant activity, enhances the attractiveness of this approach. Among the implications of this research is the need to consider the possibility of broader uses of BCG in the future, and hence to maintain the acceptance of BCG in the immunization community.

13. References

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