BCG vaccines: Selected references for the WHO Position Paper published in WER 23 Jan 2004

TB epidemiology

Raviglione MC, Snider DE Jr, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. JAMA. 1995 Jan 18;273(3):220-6.

This article describes the global epidemiology of tuberculosis and reviews recent estimates of tuberculosis incidence and mortality in the world. The highest prevalence of tuberculosis infection and estimated annual risk of tuberculosis infection are in sub-Saharan Africa and Southeast Asia. Overall, almost 3.8 million cases of tuberculosis were reported in the world in 1990, of which 49% were in Southeast Asia. From the period 1984 through 1986 to the period 1989 through 1991, notification rates increased in all World Health Organization regions, except the American and the European regions. In 1990, there were an estimated 7.5 million cases of tuberculosis and 2.5 million deaths worldwide. The human immunodeficiency virus epidemic is causing increases in the number of tuberculosis cases, particularly in Africa, although increases are also expected in Southeast Asia. In many industrialized countries, tuberculosis has recently failed to decline, and in eastern Europe and the former Soviet Union, cases and deaths are increasing. Drug resistance is a serious problem, especially in the United States. If worldwide control of tuberculosis does not improve, 90 million new cases and 30 million deaths are expected in the decade 1990 through 1999.

Farmer P, Kim JY. Community based approaches to the control of multidrug resistant tuberculosis: introducing "DOTS-plus". BMJ. 1998 Sep 5;317(7159):671-4.

Tuberculosis remains the world's leading infectious cause of adult deaths, most of which are due not to multidrug resistant tuberculosis but to lack of access to effective treatment for drug susceptible tuberculous disease.[1] New data suggest, however, that multidrug resistant tuberculosis is emerging as an increasingly important cause of morbidity and death. In the United States, Europe, and Latin America, highly resistant strains of tuberculosis have caused explosive institutional outbreaks (in hospitals, prisons, and homeless shelters) with high case fatality rates among immunosuppressed people and high rates of transmission to other patients and to caregivers and their families.[2-8]
These outbreaks are not restricted to certain regions. The WHO/International Union Against Tuberculosis and Lung Disease's global survey of resistance to antituberculous drugs now reveals that multidrug resistant tuberculosis has already become established worldwide. In several countries—including Russia, Estonia, Latvia, Côte d'Ivoire, and the Dominican Republic—"hot zones" of ongoing transmission have been identified. Failure to follow the World Health Organisation's guidelines was clearly associated with high rates of multidrug resistant tuberculosis; the survey was thus able to identify countries in which an increase in multidrug resistant tuberculosis was likely, given the current programme conditions.

Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003 May 12;163(9):1009-21.

BACKGROUND: The increasing global burden of tuberculosis (TB) is linked to human immunodeficiency virus (HIV) infection. METHODS: We reviewed data from notifications of TB cases, cohort treatment outcomes, surveys of Mycobacterium tuberculosis infection, and HIV prevalence in patients with TB and other subgroups. Information was collated from published literature and databases held by the World Health Organization (WHO), the Joint United Nations Programme on HIV/Acquired Immunodeficiency Syndrome (UNAIDS), the US Census Bureau, and the US Centers for Disease Control and Prevention. RESULTS: There were an estimated 8.3 million (5th-95th centiles, 7.3-9.2 million) new TB cases in 2000 (137/100,000 population; range, 121/100,000-151/100,000). Tuberculosis incidence rates were highest in the WHO African Region (290/100,000 per year; range, 265/100,000-331/100,000), as was the annual rate of increase in the number of cases (6%). Nine percent (7%-12%) of all new TB cases in adults (aged 15-49 years) were attributable to HIV infection, but the proportion was much greater in the WHO African Region (31%) and some industrialized countries, notably the United States (26%). There were an estimated 1.8 million (5th-95th centiles, 1.6-2.2 million) deaths from TB, of which 12% (226 000) were attributable to HIV. Tuberculosis was the cause of 11% of all adult AIDS deaths. The prevalence of M tuberculosis-HIV coinfection in adults was 0.36% (11 million people). Coinfection prevalence rates equaled or exceeded 5% in 8 African countries. In South Africa alone there were 2 million coinfected adults. CONCLUSIONS: The HIV pandemic presents a massive challenge to global TB control. The prevention of HIV and TB, the extension of WHO DOTS programs, and a focused effort to control HIV-related TB in areas of high HIV prevalence are matters of great urgency.

Mycobacterial agents and immune response

Mostowy S, Behr MA. Comparative genomics in the fight against tuberculosis: diagnostics, epidemiology, and BCG vaccination. Am J Pharmacogenomics. 2002;2(3):189-96.

Although the causative agent of tuberculosis, Mycobacterium tuberculosis, has been known for some 120 years, the disease continues to plague humanity. In 1998, the sequencing of M. tuberculosis H37Rv enabled tuberculosis researchers to draw comparisons between it and other species of the closely-related M. tuberculosis complex, including bacillus Calmette-Guerin (BCG), the vaccine administered to prevent human tuberculosis. These efforts have uncovered genomic variability that potentially encodes the discrepant phenotypes displayed by species. Due to the infrequency of single nucleotide polymorphisms (SNPs) and other modes of genomic change, large sequence polymorphisms (LSPs) have presented themselves as the most obvious form of genomic variability among species. This review discusses genomic polymorphism among species of the M. tuberculosis complex as revealed through comparative genomics. Attention is drawn towards the impact of comparative genomics in generating several exciting hypotheses towards diagnosis, epidemiology, and prevention of tuberculosis disease.

Boom WH, Canaday DH, Fulton SA, Gehring AJ, Rojas RE, Torres M. Human immunity to M. tuberculosis: T cell subsets and antigen processing. Tuberculosis (Edinb). 2003;83(1-3):98-106.

A hallmark of M. tuberculosis infection is the ability of most (90-95%) healthy adults to control infection through acquired immunity, in which antigen specific T cells and macrophages arrest growth of M. tuberculosis bacilli and maintain control over persistent bacilli. In addition to CD4+ T cells, other T cell subsets such as, gammadelta, CD8+ and CD1-restricted T cells have roles in the immune response to M. tuberculosis. A diverse T cell response allows the host to recognize a wider range of mycobacterial antigens presented by different families of antigen-presenting molecules, and thus greater ability to detect the pathogen. Macrophages are key antigen presenting cells for T cells, and M. tuberculosis survives and persists in this central immune cell. This is likely an important factor in generating this T cell diversity. Furthermore, the slow growth and chronic nature of M. tuberculosis infection results in prolonged exposure to antigens, and hence further T cell sensitization. The effector mechanisms used by T cells to control M. tuberculosis are poorly understood. To survive in macrophages, M. tuberculosis has evolved mechanisms to block immune responses. These include modulation of phagosomes, neutralization of macrophage effector molecules, stimulating the secretion of inhibitory cytokines, and interfering with processing of antigens for T cells. The relative importance of these blocking mechanisms likely depends on the stage of M. tuberculosis infection: primary infection, persistence, reactivation or active tuberculosis. The balance of the host-pathogen interaction in M. tuberculosis infection is determined by the interaction of T cells and infected macrophages. The outcome of this interaction results either in control of M. tuberculosis infection or active disease. A better understanding of this interaction will result in improved approaches to treatment and prevention of tuberculosis.

Fine PE, Floyd S, Stanford JL, Nkhosa P, Kasunga A, Chaguluka S, Warndorff DK, Jenkins PA, Yates M, Ponnighaus JM. Environmental mycobacteria in northern Malawi: implications for the epidemiology of tuberculosis and leprosy. Epidemiol Infect. 2001 Jun;126(3):379-87.

More than 36000 individuals living in rural Malawi were skin tested with antigens derived from 12 different species of environmental mycobacteria. Most were simultaneously tested with RT23 tuberculin, and all were followed up for both tuberculosis and leprosy incidence. Skin test results indicated widespread sensitivity to the environmental antigens, in particular to Mycobacterium scrofulaceum, M. intracellulare and one strain of M. fortuitum. Individuals with evidence of exposure to 'fast growers' (i.e. with induration to antigens from fast growers which exceeded their sensitivity to tuberculin), but not those exposed to 'slow growers', were at reduced risk of contracting both tuberculosis and leprosy, compared to individuals whose indurations to the environmental antigen were less than that to tuberculin. This evidence for cross protection from natural exposure to certain environmental mycobacteria may explain geographic distributions of mycobacterial disease and has important implications for the mechanisms and measurement of protection by mycobacterial vaccines.

Vaccine efficacy

Milstien JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. Bull World Health Organ. 1990;68(1):93-108.

WHO oversees the quality control of BCG vaccine via a system that includes regular testing of products by in vitro methods and clinical trials. Three parent strains of BCG (Glaxo-1077, Tokyo-172, and Pasteur-1173P2) account for over 90% of the vaccines currently in use worldwide. Important characteristics of the vaccine preparations are summarized here, along with their physical-chemical properties. In instances where diagnostic criteria for tuberculosis are stringent, there is no evidence that when administered to newborns different preparations of BCG vaccine exhibit different efficacies; however, the incidence of BCG-associated adverse reactions does correlate with the type of preparation. Other factors, including dose, administration technique, and recipient characteristics are also important in determining vaccine-associated reactions.

Wilson ME, Fineberg HV, Colditz GA. Geographic latitude and the efficacy of bacillus Calmette-Guerin vaccine. Clin Infect Dis. 1995 Apr;20(4):982-91.

In a meta-analysis of the efficacy of BCG vaccine for preventing tuberculosis, study sites at a greater distance from the equator were associated with a higher efficacy. In a random-effects regression analysis of prospective studies, geographic latitude alone accounted for 41% of the between-study variance. Many factors that vary with latitude may influence the effectiveness of BCG vaccine by modifying the susceptibility of human hosts, the pathogenecity of the organism, or host-agent interactions. These factors include socioeconomic conditions, genetic composition of the population, climate, exposure to sunlight, diet and nutrition, presence of nontuberculous mycobacteria in the environment, completeness of surveillance and follow-up in studies of BCG vaccine, virulence of locally prevalent strains of Mycobacterium tuberculosis, and storage and viability of BCG vaccine. This paper describes the biological plausibility, epidemiologic evidence, and other scientific data bearing on the influence of these factors on the efficacy of BCG vaccine.

Fine PE. BCG: the challenge continues. Scand J Infect Dis. 2001;33(4):243-5.

It is widely recognized that BCG provides inconsistent and often inadequate protection against tuberculosis; however, simple estimates of efficacy fail to reflect the complexity of protection within, let alone between, populations. A decline in protection with an increase in age at vaccination has been seen in many studies. This may reflect 2 things: (i) that as people age they are exposed to a variety of mycobacterial challenges which may interfere with, or mask, the protection of BCG; and/or (ii) that the vaccine is better at protecting against primary disease than against either reactivation- or reinfection-type disease. These factors need to be taken into consideration when interpreting the results obtained with screening vaccines in animal models, as most of these models mimic acute primary-type disease. In addition, we have no evidence that the protection induced by BCG lasts for > 15 y, in any population. Recent data from South India indicate a complex interaction of age and time effects: BCG imparted consistent protection in children, but no

protection for subjects > 15 y old, and may even have imparted negative protection among these older individuals. If true, these findings have important implications for efforts to develop a vaccine against adult pulmonary tuberculosis.

Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. Int J Epidemiol. 1993 Dec;22(6):1154-8.

The protective effect of BCG against tuberculosis (TB) estimated in randomized controlled trials and observational studies ranges from negative to close to a 100%. One of the many explanations offered for this is that different immunological mechanisms may be associated with protective effect against different forms and sites of disease. In this investigation, we recalculated vaccine protective effect separately for pulmonary disease and for meningeal/miliary disease in randomized controlled trials and case-control studies, tested for heterogeneity in site-specific estimates of protective effect and calculated a summary measure when appropriate. We found protective effect against pulmonary disease to be heterogeneous to a statistically significant degree, and thus we did not calculate a summary measure of protection. Protective effect against meningeal and miliary TB was higher than against pulmonary disease and, except for a single study with two cases only, appeared to be homogenous. Summary BCG protective effect against miliary or meningeal TB in randomized controlled trials was 86% (95% confidence interval [CI] 65, 95) and in case-control studies 75% (95% CI: 61, 84). The fact that protective effect appeared to be homogeneous against meningitis and miliary TB but not against pulmonary disease may result from the fact that patients with meningitis are on average younger and thus less likely to have been exposed to atypical bacteria; to a waning of the protective effect of BCG; or from the diversity of mechanisms of pathogenesis of pulmonary disease, which can originate from reinfection, reactivation or primary progression.

Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, Fineberg HV. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. Pediatrics. 1995 Jul;96(1 Pt 1):29-35.

OBJECTIVE. To quantify the efficacy of vaccination of infants with bacillus Calmette-Guerin (BCG) against tuberculosis. DATA SOURCES. MEDLINE with index terms BCG vaccine, tuberculosis, and human; lists of all known studies provided by experts at the Centers for Disease Control and Prevention, the World Health Organization, and other organizations. STUDY SELECTION. A total of 1264 articles and abstracts were reviewed for details on BCG vaccination, the availability of concurrent vaccinated and unvaccinated groups, and a tuberculosis outcome. Seventy articles were reviewed in depth for method of vaccine allocation used to create comparable groups, age at vaccination of study participants, comparability of surveillance and follow-up of recipient and concurrent control groups in trials, an appropriately defined control group in case-control studies, and outcome measures (tuberculosis cases and/or deaths). Five prospective trials and eleven case-control studies of vaccination during infancy were included in the present analyses. DATA EXTRACTION. We recorded study design, age range of study population, number of patients enrolled, efficacy of vaccine, location of the study, and a series of items to assess the potential for bias in study design, follow-up, and diagnosis.

We extracted or computed vaccine efficacy by years since vaccination wherever possible. At least two readers independently extracted data and evaluated data validity. DATA SYNTHESIS. The relative risk (RR) or odds ratio (OR) for tuberculosis in vaccinated versus unvaccinated infants was the measure of vaccine efficacy analyzed. A random-effects method estimated a weighted average RR or OR from data extracted from the trials and case-control studies. The protective effect was then computed by 1-RR or 1-OR. Overall, the protective effect of vaccination against cases of tuberculosis was 0.74 (95% confidence interval [95% CI], 0.62 to 0.83) when estimated from four randomized controlled trials, and 0.52 (95% CI, 0.38 to 0.64) when estimated from nine case-control studies. Five trials reporting deaths from tuberculosis showed a BCG protective effect of 0.65 (95% CI, 0.12 to 0.86), five studies reporting on meningitis showed a protective effect of 0.64 (95% CI, 0.30 to 0.82), and three studies of disseminated tuberculosis showed a protective effect of 0.78 (95% CI, 0.58 to 0.88). Three case-control studies included separate results for laboratory-confirmed cases of tuberculosis. These studies documented a protective effect of 0.83 (95% CI, 0.58 to 0.93). In a random-effects regression model of the nine case-control studies, study validity score explained 15% of the heterogeneity among study-estimated protective effects, suggesting that better studies reported greater efficacy. Three trials and six case-control studies provided some age-specific information that allowed us to examine the duration of BCG efficacy. Most of this evidence suggested that BCG efficacy may persist through 10 years after infant vaccination. CONCLUSION. BCG vaccination of newborns and infants significantly reduces the risk of tuberculosis--by over 50%, on average. Protection has been observed across many populations, study designs, and forms of tuberculosis. Rates of protection against cases that are confirmed by laboratory tests, reflecting reduced error in disease classification and consequently more accurate estimates of BCG efficacy, are highest at 83%.

Felten MK, Leichsenring M.Use of BCG in high prevalence areas for HIV. Trop Med Parasitol. 1995 Jun;46(2):69-71.

Recommendations state that, where the risk of tuberculosis is high, BCG should be administered to infants as early in life as possible, even if the mother is known to be HIV-infected. BCG should be withheld from individuals with symptomatic HIV infections. However, continuing reports from sub-Saharan Africa and elsewhere of BCG complications in HIV-infected persons call for a re-assessment of current vaccination policies. For HIV-infected infants any benefit of BCG vaccination may be marginal because the prognosis is very poor. It is however not possible to exclude HIV-infected children from BCG vaccination at birth. HIV-uninfected infants born to HIV-infected mothers are at great risk of tuberculosis infection, which justifies routine vaccination. BCG rarely causes serious complications. Theoretically, persons with asymptomatic HIV infection may be at greater risk of complications from BCG vaccines, but available data are inconclusive in that respect. To vaccinate children with BCG at one year of age does not seem feasible and would increase the risk of tuberculosis especially for uninfected infants of HIV seropositive mothers. Available data seem to indicate that routine vaccination of newborns is indeed safe, even in areas with high prevalence of HIV infection.

Correlates of protection

al-Kassimi FA, al-Hajjaj MS, al-Orainey IO, Bamgboye EA. Does the protective effect of neonatal BCG correlate with vaccine-induced tuberculin reaction? Am J Respir Crit Care Med. 1995 Nov;152(5 Pt 1):1575-8.

A case-control study was conducted in Saudi Arabia, where the same strain of BCG has been used and surveys had shown that up to 88% of vaccinated children remain tuberculin negative. Active cases were obtained by surveying the seven tuberculosis centers in 1 yr. Control subjects were obtained from a nationwide survey of normal individuals. Vaccination in both groups was ascertained by history and BCG scar. Relative risk of contracting active tuberculosis in the vaccinated versus unvaccinated and protection was calculated. Protection was as follows: age group 5 to 14 yr, 82% (55 to 93%); age group 15 to 24 yr, 67% (55 to 77%); and age group 25 to 34 yr, 20% (-6 to 37%). We document the uninterrupted record of protection by BCG administered in the neonatal period and discuss the significance of vaccination timing. We concur with other studies that protection lapsed after about 20 yr. More importantly, this is the first large study that documents a lack of tuberculin sensitivity despite protection. This challenges the view that sensitization is essential for protection and supports the "two-pathway" theory that BCG vaccination could trigger either protective (Lister type) or antagonistic (tuberculin or Koch type) reactions and that the most protective vaccines would have little tuberculin-sensitizing effect because the two pathways are competitive.

Stanford JL, Shield MJ, Rook GA. How environmental mycobacteria may predetermine the protective efficacy of BCG. Tubercle. 1981 Mar;62(1):55-62.

A proposal is made that there are 2 mechanisms of cell mediated response to mycobacteria, both of which produce positive tuberculin tests and that one of them is more protective against mycobacterial infection than is the other. These are referred to respectively as the Listeria-type and the Koch-type of responses. Contact with environmental mycobacteria will induce one or other of these types of response and BCG vaccination will enhance it. Thus in those places where the environmental species prime for the Listeria-type of response subsequent BCG vaccination will afford good protection from both tuberculosis and leprosy. Where the Koch-type of response frequently results from environmental contact BCG will be ineffective. Evidence if presented that a large contact with Mycobacterium scrofulaceum is prejudicial to at least one marker of BCG efficacy in Burma.

Vaccine adverse events

Grange JM. Complications of bacille Calmette-Guerin (BCG) vaccination and immunotherapy and their management. Commun Dis Public Health. 1998 Jun;1(2):84-8.

Complications of bacille Calmette-Guerin (BCG) vaccination are uncommon. Fewer than one in 1000 people vaccinated develop significant local reactions, and serious disseminated disease develops in fewer than one in a million. Localised complications--

which include hypersensitivity reactions, abscesses at the injection site, and localised lymphadenopathy--are usually self limiting. They usually result from faulty technique, including the accidental intracutaneous injection of the stronger percutaneous vaccine, or poor selection of subjects for vaccination. Abscesses at the injection site usually respond to drainage and chemotherapy with isoniazid or erythromycin. Lymphadenopathy responds poorly to antimicrobial treatment and surgery may be needed for suppurating or discharging lesions to hasten recovery and give a good cosmetic result. Disseminated disease usually occurs in people with impaired immunity, in whom it is often fatal. BCG should never be given to people who are known to be infected with HIV, but the risk of complications in children born to HIV infected mothers is low. Disseminated disease can also result from intravesical instillation of BCG to treat bladder cancer, but this responds to antituberculosis chemotherapy.

Talbot EA, Perkins MD, Silva SF, Frothingham R. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. Clin Infect Dis. 1997 Jun;24(6):1139-46

The attenuated bacille Calmette-Guerin (BCG) vaccine is administered to prevent tuberculosis. Complications of vaccination are uncommon. We report a new case of disseminated BCG disease and review 27 additional cases identified from a review of > 5,000 reports published between 1980 and 1996. Twenty-four of the 28 total cases were associated with an immune deficiency, including nine cases of AIDS. Seventy-one percent of the cases occurred in children younger than 2 years old. Sixty-eight percent of the patients were male. About one-half of the patients were vaccinated in a developed nation, but 85% of the cases were reported from a developed nation. Response to therapy was poor, with an overall mortality rate of 71%. We made two new observations. Disseminated BCG disease has historically been a disease of infants, but cases now occur in adults and older children coinfected with human immunodeficiency virus. Cases also occur after revaccination of individuals who were anergic following the initial administration of BCG vaccine. Disseminated BCG disease is an uncommon but devastating complication of vaccination that should be considered in the appropriate clinical setting. Immunocompromised infants and patients with late-stage AIDS are at greatest risk and respond poorly to standard therapies.

Future vaccines against tuberculosis

Okkels LM, Doherty TM, Andersen P. Selecting the components for a safe and efficient tuberculosis subunit vaccine--recent progress and post-genomic insights. Curr Pharm Biotechnol. 2003 Feb;4(1):69-83.

Prophylactic vaccination against tuberculosis with BCG gained much of the credit for the decline of TB in Europe. However, with TB resurgent in many parts of the world, better vaccines are urgently needed. To improve on BCG, a rapid, rational approach to vaccine discovery is needed. Fortunately, advances in the fields of molecular biology and computer science have spawned new disciplines: Genomics, Proteomics and Transcriptomics are transforming the ways in which candidate vaccine antigens are discovered. In this review, we discuss how these new approaches have accelerated the

pace of antigen discovery and vaccine development, and highlight some of the most promising new candidate vaccines and vaccine targets.

Relevant unpublished WHO document:

The Immunological Basis for Immunization Series. Module 5: Tuberculosis. (WHO/EPI/GEN/93.15)