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REVIEW ARTICLE

BCG vaccine: efficacy and indications for vaccination and revaccination

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Abstract

Objectives: To review the protective efficacy of the first and second doses of BCG vaccine and to assess its major indications and contraindications.

Sources of data: A systematic review of the literature was made by searching PubMed and selecting studies carried out in the last 50 years. The studies were grouped according to their design (clinical trials, case-control studies, and meta-analyses) and the results were presented separately for each type of study. Other relevant topics such as BCG and HIV/AIDS, use of tuberculin skin test, issues related to vaccine scars and to the development of new vaccines were also reviewed.

Summary of the findings: BCG vaccine has been used since 1921. However, the data concerning its use are variable and inconsistent. The protective efficacy of the first dose of BCG vaccine against miliary tuberculosis or tuberculous meningitis is remarkably important. Nevertheless, results regarding pulmonary tuberculosis have been inconsistent, either showing no efficacy or a protective efficacy rate around 80%. There is some evidence that a second dose of BCG vaccine does not increase its protective efficacy. Studies have shown that BCG vaccine protects against leprosy. The development of new vaccines to replace BCG in the future has been investigated.

Conclusions: Despite the hope that a new vaccine against tuberculosis will be available in the future, BCG vaccine, in spite of its deficiencies, is today and will be for many years to come an important tool in controlling the harmful effects of tuberculosis, especially in countries where this disease has moderate to high levels of incidence.

J Pediatr (Rio J). 2006;82(3 Suppl):S45-54: Tuberculosis, BCG vaccine, tuberculin skin test, protective efficacy, BCG scar.

Introduction

Tuberculosis (TB) is a major public health problem worldwide. One third of the world's population is believed to be infected with *Mycobacterium tuberculosis* (MT). Approximately 8.8 million new cases of TB are notified around the world every year. Of these cases, 3.9 million are smear-positive and approximately 1.7 million die from TB. Nearly two billion people have latent tuberculosis infection (LTBI), and a small number develops clinical TB, depending on factors such as the development of immunodeficiency or other unknown conditions. Pulmonary TB is the most frequent clinical form, and is responsible for the transmission of the TB bacillus. Although there has been a sharp decrease in the occurrence of TB in most industrialized countries, its incidence has remained high in regions such as Africa and Eastern Europe. In general, TB has shown an upward trend in countries with a high incidence of AIDS.[1,2] In industrialized countries, the increase in TB cases has been correlated with higher levels of poverty and with social inequalities.[3]

Countries with a low incidence of TB have focused their attention on the identification and treatment of infected individuals, in order to prevent new cases from occurring. In some of these countries, the use of BCG vaccine has been discontinued in order to safeguard the diagnostic value of purified protein derivative (PPD) as an indicator of previous MT infection. In other countries, such as Brazil, BCG vaccine is given at birth. Other control measures include early diagnosis, treatment of TB cases, and chemoprophylaxis of contacts.[2]

The aim of the present study is to review the most important studies focused on the protective efficacy of the first and second doses of BCG vaccine against TB, and to evaluate the main indications and contraindications of this vaccine. Therefore, a systematic review was made by searching PubMed using the following keywords: BCG,

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vaccine, tuberculosis, BCG scar, BCG and TST, BCG and PPD, either separately or combined. The review covered a time span of approximately 50 years. The studies were grouped according to their design (clinical trials, case-control studies, descriptive studies, and meta-analyses), and the results were presented accordingly. Some recent studies on new vaccines, PPD test and vaccine scar, among other aspects, were also included in the review.

BCG vaccine was first developed by Albert Calmette and Camille Guerin in 1921, after 13 years of successive subcultures of a strain isolated by Nocard in 1908, known as "Lait Nocard,"[4] which caused bovine tuberculous mastitis. Successive subcultures were made until 1921, when the strain was lyophilized at the Pasteur Institute. The sequential subcultures caused eight genetic mutations over a 40-year period; therefore, the strain brought by Julio Elvio Moreau to Uruguay in 1925 had already undergone two mutations.[5] BCG vaccine was brought to Brazil by Arlindo de Assis in 1927. It was actually a daughter strain of the BCG vaccine brought by Moreau, which was then denominated BCG Moreau - Rio de Janeiro.[4] Despite the genetic mutations, the originally described protective efficacy[6] was not reduced, and the Brazilian strain is regarded as one of the most immunogenic among the 12 vaccine preparations that are currently available.[7]

BCG vaccine is produced by several laboratories around the world. Although the preparations were made from attenuated *M. bovis*, they may not be bacteriologically identical, due to the biological variability of the strains, with different genotypic and phenotypic characteristics. As a result, depending on the strain, they have different viability, immunogenicity, reactogenicity, and residual virulence. Recent genome studies have shown that BCG vaccine differs in some genetic aspects.[4]

BCG vaccine was first used in 1921 in a newborn infant whose mother had TB. The infant did not develop the disease and did not have any adverse events. The vaccine was largely used in Europe between 1920 and 1930. In 1929/30, in Lubek, Germany, the use of an oral BCG vaccine lot unintentionally contaminated with the virulent TB bacillus caused 72 deaths among 251 vaccinated children, producing a negative impact on BCG vaccination; however, this was later regarded as an isolated event, and there have been no similar occurrences.[8] Intradermal BCG vaccination was introduced in 1927, whereas multiple puncture vaccination[2] began to be used in 1939. In Brazil, intradermal BCG was introduced only in 1968; before that, the vaccine was given orally. After 1930, the first clinical trials evaluating the protective efficacy of the first dose of BCG began. Due to the favorable results obtained after 1948, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) encouraged vaccination campaigns all over the world. Approximately 1.5 billion people[2] were vaccinated between 1948 and 1974. In 1974, the WHO launched the Expanded Program on Immunization. Currently, BCG vaccination covers 85% of newborn infants. It has been estimated that nearly 100 million children are vaccinated with BCG vaccine every year, with lower vaccination rates in Africa, Southeast Asia, and the Western Pacific.[8,9]

In addition to its effects on TB, the protective efficacy of BCG vaccine has also been described for the treatment of other mycobacterial infections, such as leprosy and Buruli ulcer.[10] Efficacy has also been demonstrated for immunotherapy of some types of cancer, especially bladder cancer.[11] Also, there have been reports about the efficacy of BCG vaccine against ancylostomiasis[12] and other helminth infections.[13] The decrease in the frequency of atopy among children vaccinated with BCG has also been described.[14,15]

Protective efficacy of the first dose of BCG against pulmonary tuberculosis

Several studies were carried out to assess the protective efficacy of BCG vaccine against pulmonary TB. These studies show large discrepancies in protective efficacy, depending on the study design or on the geographic areas where they were performed, among other aspects. This has fueled uncertainties about the protection afforded by the vaccine, making the subject highly controversial. There is common agreement in the literature about the protection provided by the first dose of BCG vaccine against severe and disseminated forms of TB among children, especially with regard to tuberculous meningitis and miliary tuberculosis. However, controversy still exists over the protective efficacy of BCG vaccine against pulmonary TB, a clinical form that has a major impact on TB control.

Several clinical trials assessing the protection of BCG vaccine against pulmonary TB, carried out after 1930, show an efficacy rate between 0 and 80%.[16-22] The largest clinical trial undertaken to assess the efficacy of BCG vaccine was carried out in Madras, India, and showed no protection against TB. This discrepancy in efficacy leads to uncertainty about the protective role of the first dose of BCG vaccine against pulmonary TB, with possible consequences on TB control in the community.[9,23]

Several case-control studies were carried out to assess the protection provided by the first dose of BCG vaccine against all forms of TB. Altogether, these studies show an efficacy rate between 16 and 73%. Protection against pulmonary tuberculosis ranged from 10 to 66%, whereas protection against tuberculous meningitis and miliary tuberculosis was consistently high (greater than 50%) in all studies. These studies differ in some aspects, for instance, as to the age of the cases included in the analysis, proportion of different clinical forms of TB,

source of controls, selection criteria for controls, and sample size, which may influence the levels of protection obtained.[24-39] Case-control studies performed with HIV-positive children did not provide any evidence of the protective efficacy of BCG vaccine against pulmonary and extrapulmonary TB.[40,41]

Meta-analyses were also carried out to analyze the different results obtained. The results were homogeneous for the protective efficacy of BCG vaccine against tuberculous meningitis and miliary TB, ranging between 72 and 100%, with a summary estimate of 86%.[42] Summary estimates of the protection afforded by BCG vaccine against all forms of TB were similar for randomized clinical trials (RCT) and case-control studies (51 and 50%, respectively).[43] Nevertheless, the protective efficacy of BCG vaccine against pulmonary TB was quite heterogeneous, as several RCTs revealed rates between -88 and 79%. By admitting that such differences result from factors that are not always known (see next topic), the attempts to provide a summary and overall estimate that represents the protective efficacy of BCG vaccine uniformly in different contexts have been criticized.[44]

Heterogeneity in the protective efficacy of BCG

The heterogeneity in the protective efficacy of BCG, especially with regard to pulmonary TB, has been ascribed to several factors, as follows:

Biological variability of BCG vaccine due to different strains

This occurs due to possible mutations and immunogenic differences between the strains cultured in different laboratories and in successive cultures for years. This may interfere with the efficacy of the vaccine, but there is no consensus about this. Studies using the same BCG strain in different countries report discrepant levels of protection.[23,45,46]

Exposure to environmental mycobacteria (EM)

Exposure of populations to other mycobacteria may influence the recipient's immune response, interfering with the efficacy of BCG vaccine. Clinical trials carried out with populations from countries located far away from the equator, with low or no prevalence of EM, had high efficacy rates (greater than 70%). The low protective efficacy observed in a study conducted in southern India is consistent with the heterologous immunity acquired through previous environmental exposure to mycobacteria. A meta-analysis revealed that 41% of the discrepancy in the estimated efficacy is due to latitude, which may represent exposure to EM.[23,46-48]

Route of infection

Differences in the natural history of infection and disease have also been considered to influence the protective efficacy of the vaccine. The vaccine can have a protective effect if the disease results from primary infection (e.g., meningitis and disseminated TB). There would be low protective efficacy against TB caused by exogenous reinfection. If this hypothesis were true, there would be low protective efficacy in those populations at high risk for infection and a high incidence of exogenous reinfection.[22]

Other factors

Other factors related to the use of the vaccine, such as viability, dose used, route of vaccine administration; host-related factors, such as nutritional status, other infections, and genetic aspects, could also interfere with the estimates of vaccine efficacy.[22,48,49]

In short, although there is some evidence that the occurrence of EM is a more consistent factor for explaining different protective efficacy rates, this is just a hypothesis, without any conclusive proof.

Length of the protective efficacy of BCG

The length of the protective efficacy of BCG vaccine plays an important role in the establishment of vaccination policies.[11] According to the literature, the protection provided by BCG vaccine decreases with time.[50] In Great Britain, the Medical Research Council conducted a study between 1950 and 1970, including 54,239 participants aged 14 and 15 years,[21] to assess the protective efficacy of BCG vaccine. The average annual incidence for the entire follow-up period corresponded to 0.98/1,000 among unvaccinated non-reactive individuals and to 0.23/1,000 in the two groups that received the vaccine, with a protection of 77% for the period. However, the analysis carried out every five years revealed that protection decreased from 84% in the first five years to 59% between 10 and 15 years, showing a reduction in protective efficacy.[21]

A study based on a placebo-controlled clinical trial including American Indians and Alaska Natives has been recently published. The protective efficacy of BCG vaccine at the beginning of the follow-up period (1935 to 1947) amounted to 77%.[20,51] A new evaluation, encompassing the period from 1948 to 1998, revealed a protective efficacy of 52% during a six-decade follow-up, with an initial reduction during this period. A study of the RCT control group on the efficacy of the second dose of BCG vaccine in Brazilian school-aged children demonstrated that the protective efficacy of neonatal BCG against all forms of TB lasts for 15 to 20 years.[52] These findings, if

confirmed, suggest that the length of protection of neonatal BCG is longer than previously described in the literature, although there is some evidence that this protective efficacy is higher in those years close to vaccination.[30,53-55]

BCG revaccination

The WHO recommends the use of one dose of BCG vaccine against TB, given the lack of evidence supporting the use of additional doses.[56] Some countries, such as Russia, Portugal, Chile and Hungary, use repeated doses of BCG vaccine against pulmonary TB, based on the assumption that the protection provided by the vaccine decreases with time. Most of the evidence regarding the second dose of BCG vaccine is based on observational studies. In Hungary, after 1959, they adopted BCG revaccination in individuals younger than 20 years who were nonreactive to PPD. In subsequent years, there was a sharp decrease in the incidence of TB among revaccinated children, compared to the adult population, which was attributed to the revaccination policies used.[57] In Chile, a case-control study did not find protective efficacy after additional doses of BCG vaccine.[58] In Finland, after 1990, after the second dose of BCG vaccine was discontinued in PPD-nonreactive children, the number of cases did not increase, compared to the cohort of children revaccinated with BCG vaccine.[59] An RCT carried out in Malawi to assess the efficacy of the second dose of BCG vaccine against TB did not show any protective effect, despite a 50% reduction in the incidence of leprosy.[60] In Brazil, the results of an RCT of revaccination of school-aged children in two capital cities, Salvador and Manaus, showed that the second dose of BCG vaccine had no protective efficacy against pulmonary TB and, consequently, this practice was contraindicated.[61,62] In Japan, a study on the second dose of BCG vaccine concluded that the Japanese revaccination policy was inefficient as a preventive measure, given the low prevalence of TB, the estimated costs, and the lack of protection provided by the second dose.[63]

BCG scar

BCG vaccine leaves a typical scar, which indicates previous BCG vaccination.[64] Studies conducted in two Brazilian cities revealed a high sensitivity and specificity of the scar as an indicator of BCG vaccination.[65,66] However, other studies have shown that 17 to 25% of children previously vaccinated with BCG do not have a scar.[67,68] The presence of a vaccine scar indicates previous BCG vaccination, but there is no evidence in the literature of an association between vaccine scar and protection or immunity against TB. In spite of this, the Ministry of Health, by means of the *Programa Nacional de Imunizações* (Brazilian National Immunization Program), recommends that children who do not have a vaccine scar be vaccinated, even if they have a positive history of BCG vaccination, due to the theoretical possibility that unviable units of the vaccine might have been used, resulting in lack of a skin test response.

When BCG vaccine is applied to newborns and infants, local reaction occurs later, in the second week, with an induration of 3 to 9 mm at the vaccination site, followed by softening of the central zone between the fifth and eighth weeks, with crust formation. After it falls off, this crust leaves an ulcer of 2 to 6 mm in diameter at the puncture site, which heals slowly between the eighth and tenth weeks.[69,70]

The size of the vaccine scar bears a correlation with PPD response before vaccination. Individuals with greater tuberculin skin test reactivity before vaccination have a vaccine scar approximately 2.8 mm larger.[71] Moreover, a smaller vaccine scar associated with the use of a smaller dose of BCG vaccine (0.05 mL) has been reported.[72] The size of the vaccine scar is also associated with the number of doses of BCG vaccine, being larger with the increase in the number of doses.[68,73] Nevertheless, a study of Brazilian revaccinated school-aged children showed that the second scar was smaller than the first one, which resulted from the vaccine given in the neonatal period.[70]

Skin reaction to BCG vaccine, when given intradermally, is different when the first vaccination is compared with revaccination. Revaccination of school-aged children using the same dose of BCG vaccine given in the first year of life produces strong and early vaccine reaction, compatible with Koch's reaction. This means that hyperemia and induration are observed within the first 72 hours, and that an ulcer develops at the site from the second week onwards. However, total healing takes longer. It has been described that nearly two thirds of revaccinated school-aged children show total healing of the scar in the tenth week; therefore, there is no rapid healing as described in Koch's experimental model.[70]

Intradermal tuberculin test and BCG vaccine

In 1890, Robert Koch developed the first tuberculin, referred to as *old-tuberculin*. It was not until the 1920s that tuberculin was regarded as a definitive method for detecting *M. tuberculosis* infection. In 1955, the WHO standardized the readings of the intradermal tuberculin skin test (ID-TST) in 48 to 72 hours after its application.[74] In 1958, the Statens Seruminstitut, in Denmark, produced a large lot of "Renset Tuberculin (Purified Tuberculin) RT23"(PPD-RT23), with the aim of storing a standardized preparation.[75] This test has been used to investigate the contact of individuals with active TB, especially children.[76] The Brazilian Ministry of Health recommends the tuberculin skin test with 0.1 mL of PPD RT23, given intradermally, preferably in the anterior medial third of the forearm, according to the Mantoux technique.[77]

PPD response gauges the reaction to tuberculin. In general, a response greater than 10 mm is considered positive. In populations vaccinated with BCG, PPD response is difficult to interpret, since recency of vaccination (before 15 years) can interfere with this response. The tuberculin response is lower (RR 2.4; 95%CI 2.00-2.97) after the use of neonatal BCG vaccine, and higher after postneonatal vaccination (RR 10; 95%CI 5.29-18.89). When interpreting the PPD response, one should consider the prevalence of tuberculosis infection, in addition to the patient's vaccine history. In countries with low incidence of tuberculosis infection, this response is related to the use of BCG vaccine.[78]

In Brazil, infants who were vaccinated in the neonatal period showed tuberculin skin test conversion greater than 80%.[79,80] In school-aged children, strong ID-TST reaction was detected in 60 to 80% of the children tested up to 10 months after vaccination.[81-83] There is some evidence in the literature that tuberculin reactivity after vaccination decreases over time. In São Paulo, out of 11,455 school-aged children vaccinated in their first year of life, only 6.4% presented induration equal to or greater than 10 mm.[84] A positive tuberculin skin test (strong ID-TST reaction) two years after the first vaccination, in young children, should not be ascribed to the use of the vaccine in the neonatal period.

Even in countries with a wide vaccine coverage, the tuberculin skin test is used as an adjuvant in the indication of chemoprophylaxis for contacts of patients with active TB. Based on the response to the test, the Brazilian Ministry of Health recommends the use of isoniazid in the following situations: individuals younger than 15 years, those without clinical signs of active TB, individuals who had some contact with the TB bacillus, unvaccinated individuals whose ID-TST reaction is greater than 10 mm, or vaccinated individuals with ID-TST reaction greater than 15 mm; individuals with recent tuberculin skin test conversion, i.e., with an increase of at least 10 mm in ID-TST reaction in the past 12 months; in the indigenous population, in all those who had some contact with the bacillus, those with strong ID-TST reaction, regardless of age or vaccine status, after TB-disease has been ruled out; in case of immunosuppression, resulting either from drug use or from disease, household contact with active TB; individuals with strong tuberculin reactivity, without signs of active TB, but with clinical conditions associated with greater risk for diseases such as diabetes, severe nephropathies, sarcoidosis, lymphoma, alcoholism, and silicosis.[85]

There is some evidence in the literature that a positive tuberculin test does not mean that immunity is induced by the vaccine, i.e., the presence of delayed-type hypersensitivity is not associated with protective efficacy.[6,73,78] In general, indurations greater than 15 mm are more related to infection by the TB bacillus than to skin hypersensitivity caused by the vaccine. Other tests have been developed so as to distinguish between the infection caused by the TB bacillus and that one caused by BCG vaccine.[86] Recently, the Food and Drug Administration (FDA) has allowed the use of an *in vitro* test (QuantiFERON® TB Gold Test - QTF-G, Cellestis, Limited, Carnegie, Victoria, Australia). This test is based on the fact that MT produces specific antigens, namely Early Secretory Antigen Target-6 (ESAT-6) and Culture Filtrate Protein-10 (CFP-10), which are not produced by BCG or by other EM. The blood of an infected individual (with active or latent TB), when incubated with the two antigens, will cause sensitized lymphocytes to produce interferon gamma (IFN-γ). The positive result yielded by ELISA indicates MT infection. The use of this test is restricted, due to its high cost, necessity of a specialized laboratory, and also because it has not been tested in individuals younger than 17 years.[87]

BCG and leprosy

Although BCG vaccine was initially developed to provide protection against TB, it also protects against leprosy. Starting in 1960, controlled clinical trials have been performed in six countries.[9] With regard to the protection provided by the second dose of BCG vaccine in the general population, efficacy ranged from 0 to 50%,[9,88] in Brazil and Malawi, respectively. The protective efficacy of the first dose of BCG vaccine corresponded to 14% in India, in the general population, and to 80% in individuals in contact with leprosy patients. Several case-control studies were carried out to assess the protective efficacy of BCG vaccine against leprosy; 12 of them to assess the first dose of the vaccine.[9,89-92] Most of these studies were conducted in populations covered by TB control programs. One of them was carried out with contacts of leprosy patients, at routine healthcare services. General protection ranged between 36 and 90% in these studies.[89,92-95] In short, it has been demonstrated that the first dose of BCG vaccine protects against leprosy and that an additional dose confers additional protection.[60,93,96,97] However, as estimates vary, it is not possible to obtain a summary estimate, and therefore, the high protective efficacy observed in some studies cannot be generalized.[15,98] Issues related to when, for whom and how often the vaccine should be given have not been totally clarified yet.[99]

In Brazil, vaccination/revaccination is recommended by the Brazilian Ministry of Health for contacts of patients with leprosy. In spite of this, the impact of this strategy on the incidence of leprosy in the community and its cost effectiveness have not been shown yet.[100]

Adverse events of BCG vaccination

In general, BCG vaccination is followed by a local reaction that is short-term and benign, with infrequent occurrence of adverse events. The Moreau strain, in particular, has proved very safe.[101,102] The occurrence of adverse events associated with the use of BCG vaccine is related to the concentration of bacilli in the vaccine, child's age, strain, and vaccination method. These events range from slow-healing ulcers at the vaccination site, hypertrophy and/or suppuration of satellite lymph nodes, to hematogenous dissemination, especially when applied to a deeper skin layer or to immunocompromised patients.

The most frequent adverse events are ulcers at the vaccination site, resulting from inappropriate application (e.g., given subcutaneously instead of intradermally), excessive dose or secondary contamination at the puncture site. A rare adverse event is regional suppurative lymphadenitis. An incidence of 0.1 per 1,000 vaccinated children was observed in Denmark, and in some developing countries up to five of 1,000 children are affected.[101] Most of these adverse events occur in the first five months after vaccination. Disseminated infection caused by the BCG bacillus is rare, and may result in death. The incidence rate for this event ranges from 0.19 to 1.56 per one million vaccinees. Recently, in Canada, the occurrence of this adverse event was estimated in 205 cases per one million doses, a number that is much larger than that which had been previously reported. Its occurrence has been reported six months after vaccination, usually in children with congenital or acquired immunodeficiency who are mistakenly vaccinated.[103] Development of progressive immunosuppression may lead to the reactivation of latent BCG organisms, causing local or disseminated adverse events. BCG dissemination has been described in AIDS patients. The number of cases reported among AIDS patients is low, possibly due to underreported cases, since the diagnosis depends on the availability of a laboratory for the procedure.[104] Another rare adverse event is osteitis, with an incidence of 0.6 to 46 cases per one million vaccinated children.[101]

BCG revaccination is not significantly related to the frequency of adverse events in the population.[105] However, occurrence of pain and lymphadenopathy after revaccination was greater than that observed among school-aged children who had received the first dose of the vaccine. In the first vaccination axillary lymphadenopathy is more common among newborns than among older children.[106]

BCG and HIV/AIDS

The HIV/AIDS epidemics contributed to the increase in the incidence of TB in several countries. The main explanation for this fact is that HIV/AIDS patients are immunocompromised, which favors the reactivation of LTBI. Children with immunodeficiency syndromes develop lymphadenitis or have BCG dissemination after vaccination. A study conducted with immunocompromised patients in South Africa shows that the high frequency of children with AIDS and with lymphadenitis and/or disseminated TB resulted from the use of the Danish BCG vaccine given in the neonatal period.[107] The WHO recommends BCG vaccination at birth for HIV-infected infants living in countries with a high prevalence of TB. Nevertheless, the vaccine is contraindicated for HIV-infected infants with clinical signs of the disease or with immunosuppression. In countries with a low prevalence of TB, infected individuals are usually not vaccinated.[108]

Use of BCG in routine practice

The first dose of BCG at birth is recommended in most countries, especially in those with a high incidence of TB, such as Brazil. This recommendation aims to prevent the occurrence of severe forms of TB among children.[109] In countries with a low prevalence of TB (e.g., England and other European countries), the first dose of BCG is given to school-aged children (12 and 13 years old) with a negative tuberculin skin test. Other countries apply repeated doses of BCG vaccine, such as Portugal and Switzerland (two doses). Russia and other Eastern European countries recommend the use of up to five doses of BCG vaccine. However, these strategies are arguable, since there is no evidence that corroborates additional protection with the use of more than one dose of BCG vaccine.[98,109]

Use of BCG in healthcare workers

Healthcare workers (HCW) are at risk for TB, which has a higher incidence among these professionals than that found in other workers. Recently, outbreaks of TB have been observed in hospitals, some of them caused by multidrug-resistant strains. Low-burden countries have reported outbreaks in clusters of patients and HCW.[110] Many experts assert that HCW who are nonreactive to the ID-TST should be vaccinated.[99,108]

It has been shown that individuals who are unresponsive to the ID-TST are at greater risk of becoming infected by large exposure to bacilliferous patients (as occurs with some medical students and nurses) than those with an ID-TST reaction between 5 and 15 mm.[111]

Even before the advent of streptomycin, the first effective drug for the treatment of TB, the protection of BCG vaccine against TB had been demonstrated in medical students and other HCW. These studies highlight the importance of the vaccine as an isolated element to the protection of these specific groups.

In Brazil, some medical schools opt not to vaccinate their students, but to perform an annual ID-TST instead; when tuberculin skin test conversion is confirmed, they recommend chemoprophylaxis with isoniazid (INH).[111] This strategy is efficient against the development of disease by INH-sensitive bacilli, but has some limitations due to the low compliance of HCW with the six-month INH therapy,[112] in addition to hepatotoxicity.[113,114] Furthermore, its efficacy in contacts of MDR-TB carriers has not been confirmed. In the U.S.A., the concern with the development of MDR-TB[115-117] led the Centers for Disease Control and Prevention (CDC) to recommend the vaccination of HCW who were ID-TST-negative and who were exposed to MDR-TB carriers, when physical protection measures are not totally available.[8,118]

Recommendations for BCG vaccination in Brazil

The strain used in Brazil, Moreau - Rio de Janeiro, is lyophilized and is valid for six months if stored at 2 to 8 ºC. It is available in amber flasks containing 20 doses. The vaccine dose corresponds to 0.1 mL of the vaccine reconstituted with physiological saline. It contains between 800,000 and one million viable bacilli per millimeter up to 4 to 6 hours after dilution, provided that it is not exposed to direct sunlight or that it is maintained for less than half an hour at room temperature and under indirect sunlight.[69]

By March 2006, the Brazilian Ministry of Health recommendations were as follows:

a) Immunization of children in the first month of life: the first dose of BCG vaccine should be given as close to the time of birth as possible to infants weighing more than 2,000 g,[84] and is mandatory in the first year of life.[119]

b) Revaccination of school-aged children: the Brazilian Ministry of Health recommends BCG vaccination in school-aged children, without a previous tuberculin skin test, based on factors such as: persistence of TB incidence of 50/100,000 in the last 10 years; increase of TB and HIV/AIDS epidemics, especially among adolescents and young adults; persistence of stable levels of tuberculous meningoencephalitis in individuals older than five years.[69] This policy has been reviewed, and the revaccination of school-aged children should no longer be recommended.

c) Immunization of students and HCW: the Brazilian Ministry of Health recommends the immunization of each and every HCW who attends to patients with TB and leprosy and who is initially ID-TST-negative, with or without a vaccine scar.[69,77] This policy is currently under review, and HCW involved exclusively in TB programs should be vaccinated only in cases of absence of BCG scar and negative ID-TST results.

Major contraindications to BCG vaccination

Contraindications to BCG vaccination may be either relative or temporary (weight < 2 kg; skin reactions at the vaccination site; severe diseases; use of immunosuppressants) or absolute (acquired or congenital immunodeficiencies).[85]

Prospects for new vaccines against tuberculosis

The advantages of BCG vaccine for countries with intermediate or high TB incidence certainly outweigh the disadvantages, which have already been discussed here (variable protective efficacy against pulmonary TB and, depending on geographic area, influence over skin test results, total contraindication for immunocompromised patients). However, attempts have been made to develop at least one new vaccine that can replace BCG. The ideal vaccine should provide great protective efficacy against TB and have less variation in different contexts and clinical forms, overcoming this and other previously described deficiencies of the BCG vaccine. An attempt has also been made to develop new vaccines that can be used in immunotherapy and be combined with the conventional treatment of TB. Hundreds of candidate vaccines have been developed using different concepts, and some are already in phase I or II clinical trials. Hopefully, some of them will move on to phase III soon.[120-122]

Different concepts have been used for the development of these vaccines, such as: attenuated *M. tuberculosis*;[123] subunits of BCG or *M. tuberculosis* such as ESAT 6;[124] co-immunization of BCG with plasmid-encoded IL-12;[125] DNA vaccine that encodes the expression of antigenic proteins such as Hsp 60, 85 B or Hsp 65,[125-127] all of which are still being tested. Some results are encouraging. Recently, BCG vaccine modified by genetic engineering acquired the ability to block the gene of urease produced by the original BCG when phagocytosed by the macrophage, in addition to the introduction of a gene that is responsible for the production of lysine obtained from *Listeria monocytogenes*. This resulted in the expression of new BCG antigens in the cytoplasm and on the surface of the macrophage, allowing for the stimulation of CD4+ and CD8+ cells. The result, although experimental, is that this recombinant vaccine has a larger spectrum and a more effective immune response, providing greater protection against *Mycobacterium tuberculosis* infection.[128] Animal studies using DNA vaccines have shown induction of protective efficacy against TB in uninfected animals and a therapeutic effect in infected ones. This raises the hypothesis of treating TB and also MDR-TB not only with conventional drugs, but also with an immunotherapeutic approach.[129]

The introduction and testing of new vaccines have been a reason for concern in countries with high TB incidence. In these countries, the impact of BCG vaccine

on the incidence of tuberculous meningitis or miliary tuberculosis is reason enough to recommend its use. Consequently, ethics dictates that a new vaccine against TB should only be tested in populations that have been previously vaccinated with BCG vaccine,[130] until the benefits of the new vaccine are clearly established. Only then will BCG vaccine be totally replaced.

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