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Pereira, Susan M; Souza Dantas, Odimariles Maria; Ximenes, Ricardo; Barreto, Mauricio
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Vacina BCG contra tuberculose: efeito protetor e políticas de vacinação

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Susan M Pereira^I

Odimariles Maria Souza
Dantas^{II}

Ricardo Ximenes^{II}

Mauricio L Barreto^I

BCG vaccine against tuberculosis: its protective effect and vaccination policies

ABSTRACT

OBJECTIVE: The BCG vaccine has been in use since 1921, but still arouses controversy and uncertainties. The objective was to analyze the protective effect of the BCG vaccine in its first and second doses and the accompanying vaccination policies.

METHODS: A systematic review of the literature in both English and Spanish was carried out, covering the period 1948 to 2006, using the PubMed database. The main search terms used included BCG vaccine, BCG efficacy, BCG and tuberculosis. The studies were grouped by design, with the main results from the clinic tests, case-control studies and meta-analyses presented separately.

RESULTS: The protective effect of the first dose of the BCG vaccine against tuberculosis in its miliary and meningeal forms is high. However, the results vary in relation to the pulmonary form of the disease, with some indicating zero effect and others levels of nearly 80%. Research is being carried out to develop new vaccines that could substitute the BCG or be used as a booster.

CONCLUSIONS: There are evidences that the protective effect of the BCG vaccine does not increase with a second dose. In spite of its limitations and the expectation that a new tuberculosis vaccine will be developed in the future, the BCG vaccine remains an important tool in controlling the harmful effects of tuberculosis, particularly in countries with medium or high incidence levels of the disease.

KEY WORDS: Tuberculosis, prevention & control. BCG Vaccine, supply & distribution. BCG vaccine, history. Immunization programs. Review [Publication Type].

INTRODUCTION

Of the 8.9 million new cases of tuberculosis (TB) in the world in 2004, 3.9 million related to its pulmonary form with a positive basilloscopy,⁴⁸ which is the main clinical form responsible for the transmission of the disease. In Brazil, approximately 80,000 TB cases are recorded annually, but it is estimated that the true incidence could be as much as 100,000 cases. More recently, a rise in the number of TB cases has been recorded in countries with high incidence rates of HIV, most notably in sub-Saharan Africa. In these countries, around 30% of TB cases in adults are due to HIV and 7% of HIV positive cases are responsible for transmitting TB. In addition, TB is related to social inequalities.^{18,43,48}

Among the available control methods are early diagnosis and treatment, treatment of the latent infection and the BCG vaccination. The BCG vaccine was developed between 1906 and 1919 in Paris, by Camille Calmett and Albert Guérin at the Pasteur Institute in Paris. The researchers managed to obtain an

^I Instituto de Saúde Coletiva. Universidade Federal da Bahia. Salvador, BA, Brasil

^{II} Centro de Ciências da Saúde. Universidade Federal de Pernambuco. Recife, PE, Brasil

Correspondence:

Susan M Pereira
Instituto de Saúde Coletiva – UFBA
Rua Basílio da Gama s/nº
Campus Universitário do Canela
40110-040 Salvador, BA, Brasil
E-mail: susanmp@ufba.br

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attenuated strain of the original *Mycobacterium bovis* after passing it through a culture every three weeks over a 13-year period, a total of 231 times. In 1921 the vaccine produced with the weakened *M. bovis* strain began to be used in humans, under the name BCG (Bacillus Calmette Guérin).^{17,39} From 1920 onwards, the BCG vaccine was adopted widely, thanks to the work of the World Health Organization (WHO) and, beginning in 1948, of the United Nations Children's Fund (Unicef). In 1974, the WHO's Expanded Program on Immunization (EPI) included it in its calendar. From the 1970s onwards, coverage of the BCG vaccine began to grow around the world, and reached approximately 80% by 1990. In some African countries, coverage below 80% can be found while most WHO regions have coverage levels above this figure.⁵⁰

In spite of having the same name, the BCG vaccines used around the globe come from different strains that have been cultivated over years in different laboratories around the world. They display a similar genotype to the *M. bovis*, but have different genotype and phenotype characteristics, with different forms relating to their viability, immunogenicity, reactogenicity and remaining virulence. The number of particles cultivated per dose, for example, varies from 37,500 to 500,000 in the Pasteur sub-strain and from between 200,000 and 3,200,000 in the Copenhagen sub-strain.^{10,29,39}

The aim of the present study was to review the protective effect of the first and second doses of the BCG vaccine and the accompanying vaccination policies. In addition, the main issues related to the development of potential new vaccines for the control of TB will be discussed.

METHODOLOGICAL PROCEDURES

A literature review was carried out using the National Library of Medicine's database, PubMed, covering the period 1948 to 2006. To be included in the review, publications must have been in the form of articles and the following search terms were used: BCG vaccine, BCG efficacy, BCG and tuberculosis, candidate vaccines and tuberculosis. Articles written in English, Portuguese and Spanish were considered. The chosen studies were grouped by design, with the main results from the clinical tests, case-control studies and meta-analyses presented separately. Other relevant subjects were also included, such as the use of BCG and HIV/Aids and the development of new vaccines.

STRATEGIES FOR BCG VACCINATION AROUND THE WORLD: FIRST DOSE

The first dose of the BCG vaccine for new-born babies is not recommended in seven European countries: Andorra, Austria, Germany, Luxemburg, Spain, Belgium

and Denmark. In the last two countries of this group, the vaccine is recommended for children who move to countries with high incidences of TB. European countries that do provide the BCG vaccine to new-born babies are: Estonia, Finland, Hungary, Ireland, Latvia, Lithuania, Portugal, Romania, Slovakia, the Czech Republic, Bulgaria and Poland. The last four from this group have a policy for revaccinating school-age or older children who test negative in the purified protein derivative (PPD) tuberculin test. Other countries such as Malta, France, Norway, the United Kingdom, Greece, Holland and Slovenia vaccinate children when they are older, and some are in the process of discontinuing with BCG.²³ Countries with low incidences of TB, including England, Sweden and Canada vaccinate risk groups;^{35,50} The BCG vaccine is not a routine vaccine in the USA or in Holland, but is available to high risk groups such as health professionals working in endemic areas, children who have been exposed to multi-resistant TB and homeless people.

The majority of countries, however, recommend a single dose of the BCG for new-born babies, as per recommendations from the WHO which considers there to be a lack of evidence to support the use of additional doses.⁴⁷ Studies considered below point out that strategies which include additional doses have mainly been adopted in regions with high incidences of TB, in order to protect against the spread of very serious forms of the infection principally in children.

Protective effect against serious forms (meningeal and miliary tuberculosis)

Clinical and case-control studies carried out in different countries to measure the protective effect of the first dose of the BCG vaccine against clinical forms of meningeal and miliary tuberculosis indicated protection levels above 80% for the different strains of the vaccine (Copenhagen, Moreau, Glaxo).^{7,11,12,27} Meta-analyses also point out an average protective effect of the first dose of the BCG vaccine of between 73% and 86%.^{9,44} In Brazil, three case-control studies in different cities also report a high level of protection of the first dose of the BCG vaccine: 84.5, 93.3 and 99.5% (Table).^{7,11,12,27}

Protective effect against pulmonary tuberculosis

The protective effect of the BCG vaccine for pulmonary tuberculosis was found to be between zero and 80%, in clinical and case-control studies carried out in various countries since the 1940s.^{2,11,19,28,34,45} The protective effect that was observed in meta-analyses was also quite heterogeneous, ranging from -88% to 79%.³² While some studies present a summary average of results, Rodrigues (1993) argues that such a figure is of little value due to the heterogeneity of the observed effect.^{8,32}

Table. Data from the Brazilian case-control studies in the evaluation of the efficacy of the first dose of the BCG vaccine against meningeal tuberculosis.

Variable	Study		
	Wunsch Filho, ⁵¹ 1990	Camargos, ⁷ 1988	Costa et al, ¹² 1991
Location	Sao Paulo	Minas Gerais	Bahia
Year of the Study	1981-1983	1975-1981	1986
Size of population studied	72/520 v 72/83 h	64/128	16/64
Age of population studied (years)	0-4	0-12	0-14
Source of control data	Neighboring/Hospital	Hospital	Surrounding area
Clinical form	Meningitis	Meningitis	Meningitis
Pairing	Residential area, SEL*	Age, date interned, nutritional status	Age (± 6 months)
Efficacy (CI 95%)	84.5 (66.7-92.8)	93.3 -	99.5 -

SEL: Socioeconomic level

BCG VACCINATION STRATEGIES AROUND THE WORLD: SECOND DOSE

Some European countries (Hungary and Russia, for example) administer multiples doses of BCG, on the basis that the protection that it offers to new-born babies diminishes over time. In other countries, such as Thailand and Japan, school children who do not develop a scar receive a second vaccine, while in still others, such as Turkey, a second dose is recommended for school children, irrespective of scarring or PPD. In Slovakia, the Czech Republic, Poland and Bulgaria, school children are revaccinated when the result of their PPD test is negative.²³ Brazil is one of the countries that recently suspended the use of the second dose of the BCG vaccine in school children.* This was decided after discussions held by the technical support committee of the national immunization program at the Ministry of Health, and was based on the reasoning given below.

Protection provided

Revaccination was given to children and adolescents in Hungary from 1959, when high incidences of TB were found, at levels that were comparable to a serious epidemic. Revaccination was administered to tuberculin-negative children at the ages of seven, 11, 17 and 20. The first dose of BCG was given to new-born babies in maternity wards. As a result of these measures, a decline in the incidence of pulmonary TB was recorded, from 83 per 100,000 inhabitants in 1953 to 21 per 100,000 by 1983. The incidence levels of all forms of TB dropped from 368 per 100,000 to 47 per 100,000. Infection rates in children who had been revaccinated declined four times more quickly than those who had not, and this was attributed to the

vaccination and revaccination policies (on average three doses).²⁶ During this period, efforts were made to diagnose and treat TB, which may also explain this result. In Finland, the incidence of TB did not increase in adolescents after the BCG revaccination program was suspended.⁴¹ In Malawi, the second dose of the BCG vaccine was found to provide no protection, although its protective effect on Hansen's disease was 50%.²⁴ In Chile, BCG revaccination was found to give no protection in a case-control study.³⁶ In Brazil, a random clinical control study carried out in Salvador and Manaus also found that the second dose of BCG gave no protection³³, and a case-control study of the BCG second dose in Recife had similar findings.¹³ These results acted in support of the decision to suspend the Brazilian revaccination program against TB.

Why does efficacy vary?

Variations in the protective effect of the BCG vaccine have been attributed to different factors including differences in exposure to mycobacteria in the environment, the genetic characteristics of the population, differences in the virulence of the *M. tuberculosis*, high risk of re-infection, differences in the BCG strains and nutritional differences. The different methodologies used in the studies have also been identified as a contributing factor to the variations.^{16,38,39,42,46}

Protective effect of BCG against infection

In addition to the protective effect against serious forms of TB, it is generally accepted in the literature that the BCG vaccine can prevent the infection from becoming an active illness. The results from a recent study carried out on children exposed to domestic contact with TB cases in Turkey suggested a protec-

* Brazil. Technical note number 66 CGPNI/DVEP/SVS/MS. 2006.

tive effect of 40% against infection. These results were gathered using the ELISpot test which serves as a much better indicator of infection from the *M. tuberculosis* than the tests used previously, such as the PPD.³⁷ These results offer a new perspective on the extent of the protective effect of BCG to prevent infection, but should be interpreted with some caution, since the immunological markers for TB infection still require further study.

Length of protection

The literature presents evidences of a decline in the protective effect of BCG over time.^{19,40} A recent clinical control study reported that the general protective effect of BCG was 55% (31% - 77%) after 60 years of compliance among American Indians and Alaska Natives.³ In Brazil, where the protective effect of the first dose applied after birth is considered satisfactory, the effect was 39% (9% - 58%) in adolescents aged between 15 and 20, pointing to the longevity of the first dose's effect over two decades.⁴

ADVERSE EVENTS RESULTING FROM THE BCG

Adverse events (AE) resulting from the BCG vaccine are infrequent, according to the literature. The risks of local adverse events occurring range from 0.01 to 6.0 per 1,000 live births.²⁵ Adverse events that involve the spread of the infection, six to 12 months after receipt of the vaccine, are more rare. In Brazil, the occurrence of such events were found to be one case per 5,990 for the first dose of the BCG vaccine and one case per 2,580 for the second dose. These differences were not statistically significant and all reactions were classified as local.¹⁵

In Brazil, the Ministry of Health recommends that the BCG vaccine be administered in maternity wards to the following groups: all healthy new-born babies weighing 2kg or more; HIV positive children; children born to mothers who have Aids, who are tuberculin-negative and show no symptoms; non-reactive health professionals; non-reactive military professionals; and the indigenous population. A double dose is recommended for those who have domestic contact with Hansen's disease. The contraindications are: new-born babies weighing less than 2kg; generalized infection or dermatological infection in the area where the vaccine was administered; immunosuppressants; adults who are HIV-positive, irrespective of symptoms; those with congenital immunodeficiency.*

The use of vaccines with live attenuated bacilli may pose risks to individuals who are HIV positive. Despite of this, in 1987 the WHO concluded that the benefits of

providing the BCG vaccine to all children in countries that present high incidences of TB are greater than the risks of adverse events occurring among HIV-positive groups. In these countries, vaccination is recommended as standard, but is suspended for children who are HIV positive and show symptoms. Countries with low prevalence of TB do not administer the BCG vaccine to these groups. In 2004, this recommendation was revised to include the proposal that vaccinated children whose mothers are HIV-positive should be accompanied to detect for the occurrence of possible adverse events.^{49,50}

More recent studies report on the occurrence of those events associated with the BCG vaccine in children who are infected by the HIV virus. Such events generally involve localized reaction and the occurrence of lymphadenitis, or the spread of the BCG infection.³⁰ Studies that are prospective or that use a comparative group were not found, nor ones that use a denominator to estimate risk. The protective effect of the first dose of the BCG vaccine among HIV-positive individuals was low, ranging from zero to 22% for all forms of TB.^{1,5} A review of a series of 21 cases of adverse events that occurred in Canada between 1993 and 2002 included seven deaths, one of which was an HIV-positive individual.¹⁴ In South Africa, a hospital based study reported 25 events, 17 of which were among HIV-positive patients (11 were localized events and six were remote from the area where the BCG had been administered) with 11 deaths. This was a relatively high frequency and led the authors to raise the issue of a possible relationship between the *Danish* strain and the occurrence of adverse events.²⁰ Seven of the patients who died were taking anti-retroviral therapy (HAART). Hesselting et al²⁰ propose a revision to the classification of adverse events related to BCG among children who are HIV-positive.

VACCINE CANDIDATES

The development of new vaccine candidates offers possibilities for the future control of TB. The main strategies for developing these vaccines are summarized below.^{6,21,22}

- Vaccines with live, attenuated mycobacteria – these consist of BCG vaccines that have been genetically modified to contain the protective antigens of the *M. tuberculosis*, or attenuated mutant strains obtained through genetic engineering. These may possibly be used as a booster to the BCG.
- Subunit vaccines (DNA, recombinant virus vector vaccines or recombinant protein vaccines) – capable of carrying one or more immunodominant antigen of

* Brasil. Tuberculose. Guia de Vigilância Epidemiológica, FUNASA, Editor. Ministério da Saúde: Brasília, DF. 2002.

the *M. tuberculosis*, that can have a protective effect. These may possibly be used to substitute the BCG vaccine.

Some of the vaccine candidates showed promising results in studies that were carried out using animal models. These are still at phase 1 of the clinical tests and include:^{21,22}

- MVA85A – Recombinant virus vector vaccine (attenuated vaccinia virus), expressing Ag 85 A in the *M. tuberculosis*. This is considered to be safe, and displayed good results in a population of non-infected guinea-pigs. It also displayed good results for (cellular) immunity in populations of guinea-pigs that had previously received the BCG. In 2003, phase 2 of the study began in South Africa.

- rBCG30 – recombinant vaccine (Ag 85 B). Greater protection from the BCG was found in a population of guinea-pigs. In 2004, phase 1 of the study began in the United States.

- Mtb72F – recombinant vaccine that includes polyproteins, obtained by combining two antigens (Mtb32 and Mtb39) that are recognized by the immune system of the infected patient. In 2004, phase 1 of studies began in the United States.

- ESAT6 and Ag85B – recombinant vaccines that express polyproteins. In 2005, phase 1 of studies began in Europe.

A number of challenges have been identified in the development of these vaccines,^{6,21,22,31} for example:

- The use of different animal models to test similar vaccines and use better animal models to measure the efficacy of the vaccines in more realistic situations than those currently being used: to test vaccines in animals that were previously infected with the *M. tuberculosis* or exposed to species of *Mycobacterium* in the environment, then comparing them with tests on non-infected animals or using the BCG as a transmitter;

- To develop immunological markers for protection, vaccines that prevent the infection from evolving into an illness, vaccines that are safe and effective in populations exposed to TB, HIV and BCG;

- To simulate models that are similar to human populations: HIV, *M. tuberculosis*, mycobacteria in the environment;

- The development of appropriate pre-clinical models. The experimental models must measure the occurrence of reaction after exposure, as well as consider using animals that were previously infected (Koch's phenomenon); post infection animal models.

The vaccine candidates must be safe in terms of the inoculant, with consideration given to the possibility of adverse events occurring, as was the case in DNA vaccines given to individuals who had previously been infected or who had a latent pulmonary focus which was reactivated. The potential effects of this process are not yet known.

CONCLUSIONS

While it may not be the ideal vaccine, BCG plays an important role in the control of TB, principally in areas with high levels of the disease. When a new vaccine is developed, its replacement of BCG will be slow and gradual. Since the greatest need is to develop a vaccine that works after infection has occurred, the new vaccine candidate could act as a booster to the BCG. The lack of any good "protective markers" requires that randomized tests be carried out to evaluate the efficacy of candidate vaccines. These tests require a large number of individuals and involve high costs. Regulatory issues, such as the safety and cost of the vaccine, among others, are problems that will need to be addressed.

In conclusion, if new vaccine candidates are to be developed, the following issues must be taken into consideration: will the new vaccine protect against infection or progression of the disease? What immunological markers will be used? Will the protection cover pulmonary and extrapulmonary forms? Will it cover populations who were previously exposed to mycobacteria in the environment? Will there be a booster? Will there be greater efficacy for both children and adults? Will it be safe among HIV-positive populations? What is the cost involved? These are some of the issues that will need to be addressed in future studies of the new vaccine candidates.

REFERENCES

- Arbeláez MP, Kenrad NE, Munoz A. BCG vaccine effectiveness in preventing tuberculosis and its interaction with immunodeficiency virus infection. *Int J Epidemiol*. 2000; 29: 1085-91.
- Aronson JD. Protective vaccination against tuberculosis with special reference to BCG vaccination. *Am Rev Tuberc*. 1948; 58:255-81.
- Aronson NE, Santosham M, Comstock GW. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60 year follow up study. *JAMA*. 2004; 291: 2086-91.
- Barreto, MB, Cunha SS, Pereira SM, Genser B, Hijjar MA, Ichihara MY, et al. Neonatal protects children and young adults against all forms of tuberculosis in Brazil. *Int J Tuberc Lung Dis*. 2005; 10: 1171-3.
- Bhat GJ, Diwan VK, Chintu C, Kabika M, Masona J, et al. HIV, BCG and Tb in children: a case study in Lusaka, Zambia. *J Trop Pediatr*. 1993; 39: 219-23.
- Brennan M. The tuberculosis vaccine challenge. *Tuberculosis*. 2005; 85: 7-12.
- Camargos, PAM, Guimarães MDC, Antunes CMF. Risk assessment for acquiring meningitis tuberculosis among children not vaccinated with BCG: a case-control study. *Int J Epidemiol*. 1988; 17: 193-97.
- Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA*. 1994;271: 98-702.
- Colditz GA, Berkey CS, Mosteller F, Brewer TF, Wilson ME, Burdick E, et al. The efficacy of Bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: meta-analysis of the published literature. *Pediatrics*. 1995; 96: 29-35.
- Collins DM, Lisle GWD. BCG identification by DNA restriction fragment patterns. *J Gen Microbiol*. 1987; 133: 1431-34.
- Comstock GW, Edwards PQ. An American view of BCG vaccination, illustrated by results of a controlled trial in Puerto Rico. *Scand J Resp Dis*. 1972;53:207-17.
- Costa MCN, Mota ELA, Pinto LLS. Efeito protetor do BCG intradérmico na Meningite Tuberculosa. *Bol Of Sanit Panam*. 1991; 110: 26-32.
- Dantas O, Ximenes RA, de Albuquerque M de F, da Silva NL, Montarroyos UR, de Souza WV, et al. A case-control study of protection against tuberculosis by BCG revaccination in Recife, Brazil. *Int J Tuberc Lung Dis*. 2006; 10: 536-41.
- Deeks SL, Clark M, S cheifele DW, Law BJ, Dawar M, Ahmadipour N, et al. Serious adverse events associated with bacille Calmette-Guérin vaccine in Canada. *Pediatr Infect Dis J*. 2005; 24: 538-41.
- Dourado I, Rios MH, Pereira SM, Cunha SS, Ichihara MY, Goes JC, et al. Rates of adverse reactions to first and second doses of BCG vaccination: results of a large community trial in Brazil schoolchildren. *Int J Tuberc Lung Dis*. 2003; 7: 399-402.
- Fine PE, Vynnycky E. The effect of heterologous immunity upon the apparent efficacy of (e.g. BCG) vaccines. *Vaccine*. 1998; 16:1923-8.
- Grange JM, Gibson J, Osborn TW, Collins CH, Yates MD. What is BCG? *Tubercle*. 1983;64:129-39.
- Grant AD, De Cock KM. The growing challenge of HIV/AIDS in developing countries. *Br Med Bull*. 1998;54:369-381.
- Hart PDA, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *Br Med J*. 1977;2:293-95.
- Hesseling A, Rabie H, Marais BJ, Manders M, Lips M, Schaaf HS, et al. Bacille Calmette-Guérin Vaccine-Induced disease in HIV-infected and HIV-uninfected children. *CID*. 2006;42:548-58.
- Hewinson RG. TB vaccines for the world. *Tuberculosis* 2005;85:1-6.
- Ibanga HB, Brooks RH, Hill PC, Owiafe PK, Fletcher HA, Lienhardt C, et al. Early clinical trials with a new tuberculosis vaccine, MVA85A, in tuberculosis-endemic countries: issues in study design. *Lancet Infect Dis*. 2006;6:522-28.
- Infuso A, Falzon D. European survey on BCG vaccination policies and surveillance in children, 2005. *Euro Surveill*. 2006;11:6-11.
- Karonga Prevention Trial Group, Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. [see comments]. *Lancet*. 1996;348:17-24.
- Lotte A, Wasz-Hockert W, Poisson N, Engbaek H, Landmann H, Quast U, et al. Second IUATLD study on complications induced by intradermal vaccination. *Bull Int Union Lung Dis*. 1988;63:47-59.
- Lugosi, L. Analysis of efficacy of mass BCG vaccination from 1959 to 1983 in TB control in Hungary. *Bull IUATLD*. 1987; 62: 15-34.
- Medical Research Council. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *Bull World Health Organ*. 1972;4:371-385.
- Miceli I, de Kantor IN, Colaiovo D, Peluffo G, Cutillo I, Gorra R, et al. Evaluation of the effectiveness of BCG vaccination using the case-control method in Buenos Aires, Argentina. *Int J Epidemiol*. 1988;17:629-34.
- 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;68:93-108.
- Moss WJ, Clements J, Halsey N. Immunization of children at risk of infection with human immunodeficiency virus. *Bull World Health Organ*. 2003;81:61-70.
- Orme IM. Safety issues regarding new vaccines for tuberculosis, with an emphasis on post-exposure vaccination. *Tuberculosis*. 2006; 86: 68-73.

32. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *Int J Epidemiol*. 1993; 22: 1154-168.
33. Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, de Brito SC, et al. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet*. 2005; 366:1290-5.
34. Rosenthal SR, Loewensohn E, Graham ML, Liveright D, Thorne G, Johnson V. BCG vaccination against tuberculosis in Chicago. A twenty-year study statistically analyzed. *Pediatrics*. 1961;28:622-41.
35. Romanus V. Selective BCG vaccination in a country with low incidence of tuberculosis. *Euro Surveill*. 2006; 11:14-7.
36. Sepulveda RL, Parcha C, Sorensen RU. Case-control study of the efficacy of BCG immunization against pulmonary tuberculosis in young adults in Santiago, Chile. *Tuber Lung Dis*. 1993; 73: 372-77.
37. Soysal A, Millington K, Bakir M, Dosanjh D, Aslan Y, Deeks JJ, et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community. *Lancet*. 2005; 366: 1433-51.
38. Springett VH, Sutherland I. A re-examination of the variations in the efficacy of BCG vaccination against tuberculosis in clinical trials. *Tuber Lung Dis*. 1994; 75: 227-33.
39. Starke JR, Connelly KK. Bacille Calmette-Guerin vaccine. In: Plotkin MEA, editor. *Vaccines*. Philadelphia: WB Saunders;2004. p. 456-89.
40. Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? *Int J Tuber Lung Dis*. 1998;2:200-7.
41. Tala-Heikkilä MM, Tuominen J.E, Tala EOJ. Bacillus Calmette-Guérin revaccination questionable with low tuberculosis incidence. *Am J Respir Care Med*. 1998; 157: 1324-27.
42. ten Dam H, Pio A. Pathogenesis of tuberculosis and effectiveness of BCG vaccination. *Tubercle*. 1982; 63: 225-33.
43. Tocque K, Doherty MJ, Bellis MA, Spence DP, Williams CS, Davies PD. Tuberculosis notifications in England: the relative effects of deprivation and immigration. *Int J Tuberc Lung Dis*. 1998; 2: 213-18.
44. Trunz BB, Fine PEM, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and military tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006; 367: 1173-1180.
45. Tuberculosis Prevention Trial. Trial of BCG vaccines in south India for tuberculosis prevention. *Indian J Med Res*. 1980;72(Suppl):1-74.
46. Wilson ME, Fineberg HV, Colditz G. Geographic latitude and the efficacy of Bacillus Calmette-Guerin Vaccine. *Clin Infect Dis*. 1995; 20: 982-91.
47. World Health Organization. Global tuberculosis programme and global programme on vaccines. Statement on BCG revaccination for the prevention of tuberculosis. *Wkly Epidemiol Rec*. 1995;70: 229-31.
48. World Health Organization. Global tuberculosis control: surveillance, planning, financing. [WHO report 2006]. Geneva; 2006.
49. World Health Organization. Global Advisory Committee on Vaccine Safety. *Wkly Epidemiol Rec*. 2003;78:277-284.
50. World Health Organization. WHO vaccine-preventable diseases: monitoring system 2006 Global summary. Geneva; 2006.
51. Wunsch Filho V, de Castilho EA, Rodrigues LC, Huttly S R. Effectiveness of BCG vaccination against tuberculous meningitis: a case-control study in São Paulo, Brazil. *Bull World Health Organ*. 1990; 68: 69-74.