

References for BCG Vaccines: WHO Position Paper, February 2018

Abubakar I, Pimpin L, Ariti C, Beynon R, Mangtani P, Sterne JAC, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus calmette-guerin vaccination against tuberculosis. Health Technology Assessment. 2013;17(37):1.

Background: Recent evidence suggests that the duration of protection by bacillus Calmette-Guerin (BCG) may exceed previous estimates with potential implications for estimating clinical and cost-efficacy. **Objectives:** To estimate the protection and duration of protection provided by BCG vaccination against tuberculosis, explore how this protection changes with time since vaccination, and examine the reasons behind the variation in protection and the rate of waning of protection. Data sources: Electronic databases including MEDLINE, Excerpta Medica Database (EMBASE), Cochrane Databases, NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE), Web of Knowledge, Biosciences Information Service (BIOSIS), Latin American and Caribbean Health Sciences Literature (LILACs), MEDCARIB Database, Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched from inception to May 2009. Index to Theses, System for Information on Grey Literature in Europe (SIGLE), Centre for Agricultural Bioscience International (CABI) Abstracts, Scopus, Article First, Academic Complete, Africa-Wide Information, Google Scholar, Global Health, British National Bibliography for Report Literature, and clinical trial registration websites were searched from inception to October 2009. Review **Methods:** Electronic databases searches, screening of identified studies, data extraction and analysis were undertaken. Meta-analysis was used to present numerical and graphical summaries of clinical efficacy and efficacy by time since vaccination. Evidence of heterogeneity was assessed using the tau-squared statistic. Meta-regression allowed the investigation of observed heterogeneity. Factors investigated included BCG strain, latitude, stringency of pre-BCG vaccination tuberculin testing, age at vaccination, site of disease, study design and vulnerability to biases. Rate of waning of protection was estimated using the ratio of the measure of efficacy after 10 years compared with the efficacy in the first 10 years of a study. **Results:** Study selection A total of 21,030 references were identified, providing data on 132 studies after abstract and full-text review. Efficacy Protection against pulmonary tuberculosis in adults is variable, ranging from substantial protection in the UK MRC trial {rate ratio 0.22 [95% confidence interval (CI) 0.16 to 0.31]}, to absence of clinically important benefit, as in the large Chingleput trial [rate ratio 1.05 (95% CI 0.88 to 1.25)] and greater in latitudes further away from the equator. BCG vaccination efficacy was usually high, and varied little by form of disease (with higher protection against meningeal and miliary tuberculosis) or study design when BCG vaccination was given only to infants or to children after strict screening for tuberculin sensitivity. High levels of protection against death were observed from both trials and observational studies. The observed protective effect of BCG vaccination did not differ by the strain of BCG vaccine used in trials. Duration: Reviewed studies showed that BCG vaccination protects against pulmonary and extrapulmonary tuberculosis for up to 10 years. Most studies either did not follow up participants for long enough or had very few cases after 15 years. This should not be taken to indicate an absence of effect: five studies (one trial and four observational studies) provided evidence of measurable protection at least 15 years after vaccination. Efficacy declined with time. The rate of decline was variable, with faster decline in latitudes further from the equator and in situations where BCG vaccination was given to tuberculin-sensitive participants after stringent tuberculin testing. Limitations: The main limitation of this review relates to quality of included trials, most of which were conducted before current standards for reporting were formulated. In addition, data were lacking in some areas and the review had to rely on evidence from observational studies. **Conclusions:** BCG vaccination protection against tuberculosis varies between populations, to an extent that cannot be attributed to chance alone. Failure to exclude those already sensitised to mycobacteria and

study latitude closer to the equator were associated with lower efficacy. These factors explained most of the observed variation. There is good evidence that BCG vaccination protection declines with time and that protection can last for up to 10 years. Data on protection beyond 15 years are limited; however, a small number of trials and observational studies suggest that BCG vaccination may protect for longer. Further studies are required to investigate the duration of protection by BCG vaccination.

Alrabiaah AA, Alsubaie SS, Bukhari EI, Gad A, Alzamel FA. Outbreak of bacille calmette-guerin-related lymphadenitis in saudi children at a university hospital after a change in the strain of vaccine. Annals Of Saudi Medicine. 2012;32(1):4-8.

Background And Objectives: Bacille Calmette-Guerin (BCG) vaccination is part of the expanded program of vaccination in Saudi Arabia. Lymphadenitis is the most common complication of the BCG vaccine. We observed an increase in the rate of BCG lymphadenitis that coincided with the introduction of a new strain of BCG vaccine. The aim of this study was to determine the incidence and the possible causes of BCG lymphadenitis at a university hospital in Riyadh, Saudi Arabia. **DESIGN AND SETTING:** Retrospective chart review and prospective follow up of infants who received BCG vaccine. **Methods:** We studied all infants presenting with suppurative or nonsuppurative adenopathy with nodes ≥ 2 cm seen at the infectious diseases clinic at KKHU. The study duration was divided into two periods. The first period reviewed infants who received different BCG vaccine strains between January 2002 and December 2007. The second study period was conducted after close evaluation of the BCG administration technique of the vaccinating staff and reviewed infants who received the BCG SSI Danish strain 1331 between January 2008 and December 2010. **Results:** During the study period from January 2002 to December 2007, 19402 infants received four different BCG vaccine strains. Eight infants developed BCG lymphadenitis, and all were associated with the BCG SSI vaccine. The incidence rate in 2007 was 1.96 per 1000. In the second period, 66 of 9921 infants who received the BCG SSI vaccine developed BCG lymphadenitis between January 2008 and December 2010. The incidence rate was 10.14 per 1000 in 2010. **Conclusion:** We conclude that receipt of the BCG SSI vaccine might have contributed to the increased incidence of lymphadenitis in these children. Hence, caution should be exercised in switching from one vaccine to another, as is often done in developing countries.

Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in hiv-infected persons. A prospective cohort study. The gruppo italiano di studio tubercolosi e aids (gista). JAMA. 1995;274(2):143-8.

To analyze how demographic, clinical, and laboratory characteristics influence the risk of tuberculosis in human immunodeficiency virus (HIV)-infected individuals; to examine the incidence of tuberculosis associated with change in skin test responsiveness in HIV-infected, tuberculin-negative, nonanergic individuals. Multicenter cohort study. Twenty-three infectious disease units in public hospitals in Italy. A consecutive sample of 3397 HIV-infected subjects were considered for entry in the study. Of these, 2695 who were followed up for at least 4 weeks were enrolled in the study; 739 subjects (27.4%) were unavailable for follow-up. The median duration of follow-up was 91 weeks. Culture-proven tuberculosis. Eighty-three episodes of tuberculosis were observed. Incidence rates of tuberculosis were 5.42 per 100 person-years among tuberculin-positive subjects, 3.00 per 100 person-years among anergic subjects, and 0.45 per 100 person-years among tuberculin-negative non-anergic subjects. In multivariate analysis, being tuberculin-positive (hazard ratio [HR], 9.94; 95% confidence interval [CI], 3.84 to 25.72) or anergic (HR, 3.35; 95% CI, 1.40 to 8.00), or having a CD4⁺ lymphocyte count less than $0.20 \times 10^9/L$ (HR, 4.87; 95% CI, 2.35 to 10.11) or between 0.20 and $0.35 \times 10^9/L$ (HR, 2.35; 95% CI, 1.09 to 5.05) were statistically significantly associated with the risk of tuberculosis. Incidence of tuberculosis increased with decreasing levels of CD4⁺ lymphocytes in the three

groups of subjects with different skin test responsiveness. Skin tests were repeated 1 year after enrollment in 604 tuberculin-negative non-anergic subjects; three cases of tuberculosis were observed among the 13 subjects who converted to tuberculin reactivity. Risk of tuberculosis in HIV-infected persons can be more precisely quantified by jointly considering skin test reactivity and CD4+ lymphocyte count. Periodic skin tests in tuberculin-negative non-anergic individuals can be useful in identifying individuals at high risk of active tuberculosis.

Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, et al. Long-term efficacy of BCG vaccine in american indians and alaska natives: A 60-year follow-up study. JAMA. 2004;291(17):2086-91.

Context: The duration of protection from tuberculosis of BCG vaccines is not known. **Objective:** To determine the long-term duration of protection of a BCG vaccine that was previously found to be efficacious. **Design:** Retrospective record review using Indian Health Service records, tuberculosis registries, death certificates, and supplemental interviews with trial participants. **Setting And Participants:** Follow-up for the period 1948-1998 among American Indians and Alaska Natives who participated in a placebo-controlled BCG vaccine trial during 1935-1938 and who were still at risk of developing tuberculosis. Data from 1483 participants in the BCG vaccine group and 1309 in the placebo group were analyzed. **Main Outcome Measures:** Efficacy of BCG vaccine, calculated for each 10-year interval using a Cox regression model with time-dependent variables based on tuberculosis events occurring after December 31, 1947 (end of prospective case finding). **Results** The overall incidence of tuberculosis was 66 and 138 cases per 100 000 person-years in the BCG vaccine and placebo groups, respectively, for an estimate of vaccine efficacy of 52% (95% confidence interval, 27%-69%). Adjustments for age at vaccination, tribe, subsequent BCG vaccination, chronic medical illness, isoniazid use, and bacille Calmette-Guérin strain did not substantially affect vaccine efficacy. There was slight but not statistically significant waning of the efficacy of BCG vaccination over time, greater among men than women. **Conclusion** In this trial, BCG vaccine efficacy persisted for 50 to 60 years, suggesting that a single dose of an effective BCG vaccine can have a long duration of protection.

Azzopardi P, Bennett CM, Graham SM, Duke T. Bacille calmette-guerin vaccine-related disease in hiv-infected children: A systematic review [review article]. The International Journal of Tuberculosis and Lung Disease. 2009;13(11):1331-44.

Objective: To describe the characteristics and risk of bacille Calmette-Guérin (BCG) vaccine related disease in human immunodeficiency virus (HIV) infected infants. **Methods:** Systematic literature review of articles published from 1950 to April 2009 in the English language. We identified all microbiologically confirmed cases of disseminated BCG disease in vertically HIV-infected children reported in the literature. **Results:** Sixteen observational studies and 11 case reports/series were included. Observational studies suffered from high rates of loss to follow-up and death. Loco-regional BCG disease was reported in both HIV-infected and non-infected children. Disseminated BCG disease was reported only in children with immunodeficiency and only in studies employing sophisticated laboratory techniques. Sixty-nine cases of disseminated BCG were identified in the literature: 47 cases were reported in six observational studies, the majority (41/47) from the Western Cape of South Africa. A Brazilian cohort study reported no cases of disseminated BCG amongst 66 HIV-infected children observed over a 7-year period. A recent South African surveillance study reported 32 cases of disseminated BCG over a 3-year period, estimating the risk of disseminated BCG to be 992 per 100 000 vaccinations in HIV-infected children. Few cases of severe disseminated TB were reported in the cohort studies among HIV-infected children vaccinated with BCG. **Conclusion:** Data on the risk of BCG vaccination in HIV-infected children are limited. Targeted surveillance for BCG complications employing sophisticated diagnostic techniques is required to inform vaccination policy.

Bagshawe A, Scott GC, Russell DA, Wigley SC, Merianos A, Berry G. BCG vaccination in leprosy - final results of the trial in karimui, papua-new-guinea, 1963-79. Bulletin Of The World Health Organization. 1989;67(4):389-99.

The efficacy of BCG vaccine in preventing the clinical manifestations of leprosy in a tuberculosis-free area of Papua New Guinea is reported. Between 1963 and 1966 a total of 5356 subjects, randomized to receive BCG or saline inoculations, were examined for leprosy before the vaccination and surveillance was continued until 1979. BCG afforded 48% protection against clinical leprosy, being most effective against borderline tuberculoid leprosy and in children vaccinated when under 15 years old. Protection was evident within 12 months in those vaccinated between the ages of 10 and 15 years but was delayed in other age groups. There was evidence for accelerated manifestations of tuberculoid leprosy in children vaccinated when under 5 years of age. Tuberculin sensitivity was more likely to be sustained following multiple BCG inoculations; vaccinees with sustained tuberculin sensitivity had the lowest incidence of leprosy, but protection was also evident in tuberculin-negative vaccinees. These results may have implications for ongoing trials of leprosy vaccine incorporating BCG.; The Bacille Calmette-Guerin (BCG) vaccine protects individuals from tuberculosis, and its effectiveness in preventing leprosy was evaluated. The infectious agent *Mycobacterium tuberculosis*, which causes tuberculosis, is of the same species as *Mycobacterium leprae*, which causes leprosy. The two bacteria have a number of antigens in common, and it was considered possible that protection against one might provide protection against the other. There are no preclinical symptoms or available tests which would indicate infection with *Mycobacterium leprae* before the clinical symptoms are manifested, so the effectiveness of the vaccination with BCG can be measured only by the number of cases of leprosy which develop. Controlled trials were initiated in 1963 in Karimui, Papua New Guinea, as well as in Uganda and Burma. Tuberculosis has not been seen in Karimui. The trial consisted of 5,356 subjects, either vaccinated with BCG or given saline, as a control, between the years of 1963 and 1966. Results show that the incidence of leprosy was 3.3 per 1,000 person-years in the vaccinated subjects, compared with 6.3 in the controls. Therefore, vaccination with BCG protected 48 percent of the subjects against leprosy. There was no difference in rate of protection between the sexes. The vaccine was most effective against leprosy which was borderline tuberculoid, and in children between the ages of 5 and 15 years of age. Children vaccinated under five showed accelerated manifestations of tuberculoid leprosy. Protection occurred within 12 months in children who were vaccinated between the ages of 10 and 15 years old. Protection took longer in other age groups. Although BCG is not effective enough to be used as the only component of a vaccine against leprosy, it may be used as a part of a multiple component vaccine. Additional trials are needed.

Barreto ML, Pereira SM, Pilger D, Cruz AA, Cunha SS, Sant'Anna C, et al. Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in brazil: Second report of the BCG-revac cluster-randomised trial. Vaccine. 2011;29(31):4875-7.

BCG revaccination is still used in some tuberculosis endemic countries. Until now, the little evidence available suggested that BCG revaccination confers very limited additional protection, although there was no information on whether protection depends on the setting and age of revaccination, or if protection increases with time since vaccination. Here we report on an extended follow up of the BCG-REVAC trial, a cluster randomised trial conducted in the Brazilian cities Salvador and Manaus including over 200,000 children aged 7-14 years aimed to evaluate the efficacy of BCG revaccination in children who had received neonatal BCG vaccination. With the extended follow-up (9 years) and the additional cases accrued we now have enough power to report vaccine efficacy separately for the two cities (with different distances from Equator and presumably different prevalence of non-tuberculosis mycobacteria), and by age at vaccination and clinical form. The overall vaccine efficacy was 12% (-2 to 24%) as compared to 9% (-16 to

29%) for the 5-year follow up. Vaccine efficacy was higher in Salvador (19%, 3 to 33%) than in Manaus (1%, -27 to 27%) with the highest vaccine efficacy in children from Salvador aged <11 years at revaccination (33%, 3 to 54%). The findings are in line with the hypothesis that BCG vaccination offers higher efficacy in low NTM prevalence, and show that revaccination with BCG can offer weak protection in selected subgroups.

Biering-Sorensen S, Aaby P, Lund N, Monteiro I, Jensen KJ, Eriksen HB, et al. Early BCG-denmark and neonatal mortality among infants weighing < 2500 g: A randomized controlled trial. Clinical Infectious Diseases. 2017;65(7):1183-90.

Background. BCG vaccine may reduce overall mortality by increasing resistance to nontuberculosis infections. In 2 randomized trials in Guinea-Bissau of early BCG-Denmark (Statens Serum Institut) given to low-weight (LW) neonates (<2500 g at inclusion) to reduce infant mortality rates, we observed a very beneficial effect in the neonatal period. We therefore conducted the present trial to test whether early BCG-Denmark reduces neonatal mortality by 45%. We also conducted a meta-analysis of the 3 BCG-Denmark trials. **Methods.** In 2008-2013, we randomized LW neonates to "early BCG-Denmark" (intervention group; n = 2083) or "control" (local policy for LW and no BCG-Denmark; n = 2089) at discharge from the maternity ward or at first contact with the health center. The infants were randomized (1: 1) without blinding in blocks of 24. Data was analyzed in Cox hazards models providing mortality rate ratios (MRRs). We had pre-specified an analysis censoring follow-up at oral poliovirus vaccine campaigns. **Results.** Early administration of BCG-Denmark was associated with a nonsignificant reduction in neonatal mortality rate (MRR, 0.70; 95% confidence interval [CI],.47-1.04) and a 34% reduction (0.66;.44-1.00) when censoring for oral poliovirus vaccine campaigns. There was no reduction in mortality rate for noninfectious diseases, but a 43% reduction in infectious disease mortality rate (MRR, 0.57; 95% CI,.35-.93). A meta-analysis of 3 BCG trials showed that early BCG-Denmark reduced mortality by 38% (MRR, 0.62; 95% CI,.46-.83) within the neonatal period and 16% (0.84;.71-1.00) by age 12 months. **Conclusion.** Early administration of BCG-Denmark in LW infants is associated with major reductions in mortality rate. It is important that all LW infants receive early BCG in areas with high neonatal mortality rates.

Biering-Sørensen S, Jensen KJ, Monterio I, Ravn H, Aaby P, Benn CS. Rapid protective effects of early BCG on neonatal mortality among low birth weight boys: Observations from randomized trials. The Journal of Infectious Diseases. 2017;jix612-jix.

Background Three randomized trials (RCTs) in low-weight (<2.5 kg) infants have shown that Bacille Calmette-Guérin (BCG) vaccine nonspecifically reduces all-cause mortality in the neonatal period. **Methods** Using data from 3 RCTs of early BCG (n = 6583) we examined potential sex differences in the timing of the mortality reduction in the neonatal period, presenting metaestimates of the main outcome mortality rate ratios (MRR) for BCG-vaccinated and controls. **Results** Among controls, boys had a particularly high mortality during the first week after randomization: male–female MRR 2.71 (95% CI, 1.70–4.50). During the first week, BCG had a marked beneficial effect for boys, reducing mortality 3-fold (MRR [BCG/no BCG] = 0.36 [0.20–0.67]). In weeks 2–4 the effect waned for boys (MRR = 0.91 [0.51–1.69]). In girls, the pattern was opposite with a limited effect in the first week (MRR = 0.85 [0.46–1.54]), but a significant reduction in weeks 2–4 (MRR = 0.56 [0.31–1.00]). This was consistent in all 3 trials. Verbal autopsies linked early benefit to fewer sepsis-related deaths among BCG-vaccinated boys. **Discussion** The marked reduction in mortality in the days after BCG vaccination in boys emphasizes the importance of providing BCG soon after birth. Trial registration numbers ClinicalTrials.gov (NCT00146302) and ClinicalTrials.gov (NCT00625482).

Camargos P, Ribeiro Y, Teixeira A, Menezes L. Tuberculin skin reactivity after neonatal BCG vaccination in preterm infants in minas gerais, brazil, 2001-2002. Revista Panamericana De Salud Publica-Pan American Journal Of Public Health. 2006;19(6):403-7.

Objectives. The efficacy of BCG vaccination in preterm babies is unknown, and available data on conversion rates to tuberculin in this age group are scarce and controversial. This study assessed the tuberculin response in preterm infants after BCG vaccination. **Methods.** This randomized cohort study was carried out at the Neonatal Department, University Hospital, Federal University of Minas Gerais in Brazil during 2001 and 2002. The BCG vaccine was administered at birth to 65 full-term (control) and 40 preterm newborns. All of them were tested with 5 tuberculin units of purified protein derivative-S approximately 3 months after vaccination. **Results.** A typical BCG scar was verified in 96.9% of the control group and in 90.0% of the preterm infants ($P = 0.19$). Indurations ≥ 5 mm in diameter were recorded in 87.7% of the full-term and 67.5% of the preterm infants ($P = 0.02$). Indurations ≥ 10 mm were recorded in 70.8% of the full-term and 42.5% of the preterm infants ($P = 0.007$). For indurations ≥ 5 mm the upper and the lower limits of the 95% confidence interval for the difference between proportions were 8.5% to 31.8%, and for indurations 10 mm these limits were 18.0% to 38.4%. No adverse reactions were observed in the study population. **Conclusion.** BCG vaccination could be recommended for preterm infants upon discharge from the neonatal unit to reduce morbidity and mortality in infants at risk for tuberculous infection, and to increase BCG vaccination coverage rates, especially in countries with high prevalence rates of tuberculosis.

Cambeau E et al. Results of the global antimicrobial resistance surveillance network for leprosy 2009–2015: a call for vigilance for all communicable diseases, 2018. [In press]
No abstract available.

Cobelens FGJ, van Deutekom H, Draayer-Jansen IWE, Schepp-Beelen ACHM, van Gerven PJHJ, van Kessel RPM, et al. Risk of infection with mycobacterium tuberculosis in travellers to areas of high tuberculosis endemicity. The Lancet. 2000;356(9228):461-5.

Background: No data exist on risks of infection with Mycobacterium tuberculosis in travellers. We studied incidences of and risk factors for tuberculin skin-test conversion among Dutch long-term travellers to countries of high tuberculosis endemicity. **Methods:** In a multicentre, prospective cohort study based in travel and tuberculosis clinics in the Netherlands, 1072 BCG-naïve immunocompetent travellers to countries with an estimated annual risk of M. tuberculosis infection of at least 1% were skin tested before departure with 1 tuberculin unit purified protein derivative (PPD) of M. tuberculosis in Tween-80. Those with Results less than 2 mm were retested 2-4 months after their return with simultaneous testing for cross-sensitivity to environmental mycobacteria (1 tuberculin unit PPD of M. scrofulaceum in Tween-80). M. tuberculosis infection was defined as a post-travel M. tuberculosis tuberculin skin-test result of at least 10 mm that was 3 mm or more larger than the M. scrofulaceum result. **Findings:** Post-travel skin-test results were available for 656 (66%) of 988 individuals who were eligible for follow-up. Among these, 12 M. tuberculosis infections were identified (1.8%). The overall incidence rate was 3.5 per 1000 person-months of travel (95% CI 2.0-6.2), and 2.8 per 1000 person-months of travel (1.2-5.5) after exclusion of health-care workers. Two had active tuberculosis at the time of testing (incidence rate 0.6 per 1000 person-months of travel [0.3-2.3]). Work in patient care abroad was an independent risk factor (adjusted rate ratio 5.34, $p=0.015$). **Interpretation:** The risk of M. tuberculosis infection in long-term travellers to high-endemicity countries, even if not engaged in health-care work, is substantial and of similar magnitude to the average risk for the local population. BCG vaccination or post-travel tuberculin skin-testing of high-risk travellers should be considered.

Cunha SS, Alexander N, Barreto ML, Pereira ES, Dourado I, Maroja MD, et al. BCG revaccination does not protect against leprosy in the Brazilian Amazon: A cluster randomised trial. Plos Neglected Tropical Diseases. 2008;2(2):e167.

Background Although BCG has been found to impart protection against leprosy in many populations, the utility of repeat or booster BCG vaccinations is still unclear. When a policy of giving a second BCG dose to school children in Brazil was introduced, a trial was conducted to assess its impact against tuberculosis, and a leprosy component was then undertaken in parallel.

Objective: to estimate the protection against leprosy imparted by a second dose of BCG given to schoolchildren. **Methods and Findings** This is a cluster randomised community trial, with 6 years and 8 months of follow-up. Study site: City of Manaus, Amazon region, a leprosy-endemic area in Brazil. Participants: 99,770 school children with neonatal BCG (aged 7-14 years at baseline), of whom 42,662 were in the intervention arm (revaccination). Intervention: BCG given by intradermal injection. Main outcome: Leprosy (all clinical forms). **Results:** The incidence rate ratio of leprosy in the intervention over the control arm within the follow-up, in schoolchildren with neonatal BCG, controlled for potential confounders and adjusted for clustering, was 0.99 (95% confidence interval: 0.68 to 1.45). **Conclusions/Significance** There was no evidence of protection conferred by the second dose of BCG vaccination in school children against leprosy during the trial follow-up. These results point to a need to consider the effectiveness of the current policy of BCG vaccination of contacts of leprosy cases in Brazilian Amazon region.

Dawodu AH. Tuberculin conversion following BCG vaccination in preterm infants. Acta paediatrica Scandinavica. 1985;74(4):564.

Tuberculin conversion following BCG vaccination was evaluated in 3 groups of infants. Group I consisted of 12 preterm appropriate-for-gestational-age (AGA) infants given BCG vaccination at birth; Group II was made up of 15 term AGA infants similarly immunized while 8 preterm AGA infants (Group III) received BCG about the time estimated to be their normal birth-date. The tuberculin conversion rates of 83%, 93% and 88% in groups I, II and III respectively were not significantly different (p greater than 0.5). The results suggest that the preterm AGA infants born at 32-36 weeks of gestation can be effectively immunized with BCG at birth.

Debacker M, Portaels F, Aguiar J, Steunou C, Zinsou C, Meyers W, et al. Risk factors for Buruli ulcer, Benin. Emerging Infectious Diseases. 2006;12(9):1325-31.

We identified risk factors for Buruli ulcer (BU) in Benin in an unmatched case-control study at the Centre Sanitaire et Nutritionnel Gbemoten in southern Benin. A total of 2,399 persons admitted from 1997 through 2003 and 1,444 unmatched patients with other conditions in 2002 were recruited. Adjusted odds ratios were determined for age, sex, place of residence, Mycobacterium bovis BCG vaccination at birth, type of water for domestic use, and occupation. Children < 15 years of age and adults > 49 years of age had a higher risk for BU. Use of unprotected water from swamps was associated with increased risk for BU; this association was strongest in adults > 49 years of age. Sex was not a risk factor for BU. Our data showed that BU was mainly associated with age, place of residence, and water sources in all age groups. Risk for BU was higher in BCG vaccinated patients \geq 5 years of age. We identified risk factors for Buruli ulcer (BU) in Benin in an unmatched case-control study at the Centre Sanitaire et Nutritionnel Gbemoten in southern Benin. A total of 2,399 persons admitted from 1997 through 2003 and 1,444 unmatched patients with other conditions in 2002 were recruited. Adjusted odds ratios were determined for age, sex, place of residence, Mycobacterium bovis BCG vaccination at birth, type of water for domestic use, and occupation. Children <15 years of age and adults >49 years of age had a higher risk for BU. Use of unprotected water from swamps was associated with increased risk for BU; this association was strongest in adults >49 years of age. Sex was not a risk factor for BU. Our data showed that BU was mainly associated with age, place of residence,

and water sources in all age groups. Risk for BU was higher in BCG-vaccinated patients ≥ 5 years of age.

Dhanawade SS, Kumbhar SG, Gore AD, Patil VN. Scar formation and tuberculin conversion following BCG vaccination in infants: A prospective cohort study. Journal of family medicine and primary care. 2015;4(3):384-7.

Background: There is considerable variation in BCG scar failure rate on available data and correlation between BCG scar and tuberculin conversion remains controversial. Through this study we aimed to determine the scar failure rate and tuberculin conversion in term infants vaccinated with BCG within the first month. **Materials and Methods:** A prospective cohort study was conducted among 85 consecutive infants weighing >2 kg attending the immunization clinic of a medical college hospital. Fifteen subjects who could not complete the follow up were excluded. Total of 70 cases were analyzed. All babies were administered 0.1 ml of BCG and examined at 3 months (+1 week) for scar. Tuberculin test was done with 5TU PPD. An induration of >5 mm was considered positive. Statistical analysis was done using Microsoft Excel and SPSS-22. **Results:** Out of the 70 infants, 41 (58.6%) were males. Although majority (72.9%) of infants were vaccinated within 7 days, only 18 (25.7%) received BCG within 48 hours of birth. Sixty-four (91.4%) had a visible scar at 12 weeks post vaccination representing a scar failure rate of 8.6%. Tuberculin test was positive in 50 (71.4%). The mean \pm s.d. for scar and tuberculin skin test (TST) reaction size was 4.93 ± 2.01 mm and 6.01 ± 3.22 mm, respectively. The association between scar formation and tuberculin positivity was highly significant ($P < 0.001$). There was significant correlation between scar size and TST size ($r = 0.401$, $P = 0.001$). **Conclusions:** Less than 10% of infants fail to develop a scar following BCG vaccination. There is good correlation between scar positivity and tuberculin conversion.

Engelis A, Kakar M, Meiksans R, Petersons A. BCG-ssi (r) vaccine-associated lymphadenitis: Incidence and management. Medicina-Lithuania. 2016;52(3):187-91.

Background and Objective: There is a high incidence of childhood tuberculosis in Latvia, including children aged less than 1 year, while BCG-associated lymphadenitis is one of the most frequent adverse events requiring surgical treatment. The aim of this study was to analyze the incidence of purulent BCG adenitis through-out the population of Latvia after the introduction of BCG-SSI® vaccine and to evaluate the treatment results. **Material and Methods:** The study included 194 patients. All patients had received the BCG-SSI® vaccine during the first week of life routinely or at a later time according to the indications. The indications for surgical treatment were lymph node destruction also affecting the skin. All patients in this study received surgical treatment – the affected lymph node extirpation. **Results:** The mean age of the patients was 5.12 ± 0.96 months. A total of 172 patients had purulent axillar lymphadenitis, 14 had purulent supraclavicular lymphadenitis, 8 patients had lymphadenitis at both localizations. During the whole study period the incidence of BCG adenitis varied from 0.02% to 0.36%, while the mean rate was $0.11\% \pm 0.08\%$ from 184,068 vaccinated children during the study period. We observed an increasing trend in the incidence of BCG lymphadenitis during the study period. The primary and complete healing rate at the end of period was 99.5% ($n = 193$) following an affected lymph node extirpation. The mean hospitalization time after the operation was 3.71 ± 0.18 days. **Conclusions:** The incidence of BCG-SSI® vaccine associated purulent lymphadenitis varied widely with an increasing trend, followed by the return to the product characteristic limits. Indications for the surgical treatment should not be changed. Extirpation of the purulent BCG adenitis is a safe treatment method and leads to the primary wound healing in the majority of cases.

Fine PEM, Ponnighaus JM, Warndorff DK, Gruer PJK, Oxborrow S, Pharoah PDP, et al. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in malawi. The Lancet. 1996;348(9019):17-24.

Background Repeat BCG vaccination is standard practice in many countries for prevention of tuberculosis and leprosy, but its effectiveness has not been evaluated. The addition of Mycobacterium leprae antigens to BCG might improve its effectiveness against leprosy. A double-blind, randomised, controlled trial to evaluate both these procedures was carried out in Karonga District, northern Malawi, where a single BCG vaccine administered by routine health services had previously been found to afford greater than 50% protection against leprosy, but no protection against tuberculosis. **Methods** Between 1986 and 1989, individuals lacking a BCG scar were randomly assigned BCG alone (27 904) or BCG plus killed M leprae (38 251). Individuals with a BCG scar were randomly allocated placebo (23 307), a second BCG (23 456), or BCG plus killed M leprae (8102). Incident cases of leprosy and tuberculosis were ascertained over the subsequent 5-9 years. **Findings** 139 cases of leprosy were identified by May, 1995; 93 of these were diagnostically certain, definitely postvaccination cases. Among scar-positive individuals, a second BCG vaccination gave further protection against leprosy (about 50%) over a first BCG vaccination. The rate ratio for all diagnostically certain, definitely postvaccination cases, all ages, was 0.51 (95% CI 0.25-1.03, $p=0.05$) for BCG versus placebo. This benefit was apparent in all subgroups, although the greatest effect was among individuals vaccinated below 15 years of age (RR=0.40 [95% CI 0.15-1.01], $p=0.05$). The addition of killed M leprae did not improve the protection afforded by a primary BCG vaccination. The rate ratio for BCG plus killed M leprae versus BCG alone among scar-negative individuals was 1.06 (0.62-1.82, $p=0.82$) for all ages, though 0.37 (0.11-1.24, $p=0.09$) for individuals vaccinated below 15 years of age. 376 cases of postvaccination pulmonary tuberculosis and 31 of glandular tuberculosis were ascertained by May, 1995. The rate of diagnostically certain tuberculosis was higher among scar-positive individuals who had received a second BCG (1.43 [0.88-2.35], $p=0.15$) than among those who had received placebo and there was no evidence that any of the trial vaccines contributed to protection against pulmonary tuberculosis. **Interpretation** In a population in which a single BCG vaccination affords 50% or more protection against leprosy, but none against tuberculosis, a second vaccination can add appreciably to the protection against leprosy, without providing any protection against tuberculosis.

Godal T, Negassi K. Subclinical infection in leprosy. The British Medical Journal. 1973;3(5880):557-9.

Lymphocyte transformation has been used to study the immune response to Mycobacterium leprae among contacts and non-contacts of leprosy patients. Of 26 subjects living in a leprosy endemic area for less than two months none responded to M. leprae; 24% of subjects who had lived in an endemic area for more than a year gave a positive response to M. leprae; more than 50% of individuals with occupational contact of leprosy for more than a year responded; and about 50% of contacts of tuberculoid and treated lepromatous patients responded to M. leprae, while only 22% (4/18) of contacts of lepromatous patients treated for less than six months responded. It seems that leprosy is more highly infectious than is indicated by the prevalence of the disease and that a subclinical infection commonly follows exposure to M. leprae. The relatively low response found in contacts of active lepromatous patients suggests that in these contacts "superexposure" to M. leprae can bring about a decrease in host resistance.

Guirado E, Schlesinger LS. Modeling the mycobacterium tuberculosis granuloma - the critical battlefield in host immunity and disease. Frontiers In Immunology. 2013;4:98. Granulomas are the hallmark of Mycobacterium tuberculosis (M.tb) infection and thus sit at the

center of tuberculosis (TB) immunopathogenesis. TB can result from either early progression of a primary granuloma during the infection process or reactivation of an established granuloma in a latently infected person. Granulomas are compact, organized aggregates of immune cells consisting of blood-derived infected and uninfected macrophages, foamy macrophages, epithelioid cells (uniquely differentiated macrophages) and multinucleated giant cells (Langerhans cells) surrounded by a ring of lymphocytes. The granuloma's main function is to localize and contain M.tb while concentrating the immune response to a limited area. However, complete eradication does not occur since M.tb has its own strategies to persist within the granuloma and to reactivate and escape under certain conditions. Thus M.tb-containing granulomas represent a unique battlefield for dictating both the host immune and bacterial response. The architecture, composition, function and maintenance of granulomas are key aspects to study since they are expected to have a profound influence on M.tb physiology in this niche. Granulomas are not only present in mycobacterial infections; they can be found in many other infectious and non-infectious diseases and play a crucial role in immunity and disease. Here we review the models currently available to study the granulomatous response to M.tb.

Gupte MD, Vallishayee RS, Anantharaman DS, Nagaraju B, Sreevatsa, Balasubramanyam S, et al. Comparative leprosy vaccine trial in south india. Indian journal of leprosy. 1998;70(4):369.

This report provides results from a controlled, double blind, randomized, prophylactic leprosy vaccine trial conducted in South India. Four vaccines, viz BCG, BCG+ killed M. leprae, M.w and ICRC were studied in this trial in comparison with normal saline placebo. From about 3,00,000 people, 2,16,000 were found eligible for vaccination and among them, 1,71,400 volunteered to participate in the study. Intake for the study was completed in two and a half years from January 1991. There was no instance of serious toxicity or side effects subsequent to vaccination for which premature decoding was required. All the vaccine candidates were safe for human use. Decoding was done after the completion of the second resurvey in December 1998. Results for vaccine efficacy are based on examination of more than 70% of the original "vaccinated" cohort population, in both the first and the second resurveys. It was possible to assess the overall protective efficacy of the candidate vaccines against leprosy as such. Observed incidence rates were not sufficiently high to ascertain the protective efficacy of the candidate vaccines against progressive and serious forms of leprosy. BCG+ killed M. leprae provided 64% protection (CI 50.4-73.9), ICRC provided 65.5% protection (CI 48.0-77.0), M.w gave 25.7% protection (CI 1.9-43.8) and BCG gave 34.1% protection (CI 13.5-49.8). Protection observed with the ICRC vaccine and the combination vaccine (BCG+ killed M. leprae) meets the requirement of public health utility and these vaccines deserve further consideration for their ultimate applicability in leprosy prevention.

Hanekom W et al. Tuberculosis (and Leprosy), In: Vaccines, 7th edition. Edited by Plotkin SA, Orenstein WA, Offit PA, Philadelphia,PA: WB Saunders Company, 2017.

No abstract available.

Hesseling AC, Johnson LF, Jaspan, Cotton MF, Whitelaw, Schaaf HS, et al. Disseminated bacille calmette-guérin disease in hiv-infected south african infants. Bulletin of the World Health Organization. 2009;87(7):505-11.

Objective: To determine the population-based incidence of disseminated bacille Calmette-Guérin (BCG) disease in HIV-infected infants (aged < 1 year) in a setting with a high burden of tuberculosis and HIV infection coupled with a well-functioning programme for the prevention of HIV infection in infants. **Methods:** The numerator, or number of new cases of disseminated BCG disease, was derived from multicentre surveillance data collected prospectively on infants with a confirmed HIV infection during 2004-2006. The denominator, or

total number of HIV-infected infants who were BCG-vaccinated, was derived from population-based estimates of the number of live infants and from reported maternal HIV infection prevalence, vertical HIV transmission rates and BCG vaccination rates. **FINDINGS:** The estimated incidences of disseminated BCG disease per 100 000 BCG-vaccinated, HIV-infected infants were as follows: 778 (95% confidence interval, CI: 361-1319) in 2004 (vertical HIV transmission rate: 10.4%); 1300 (95% CI: 587-2290) in 2005 (transmission rate: 6.1%); and 1013 (95% CI: 377-1895) in 2006 (transmission rate: 5.4%). The pooled incidence over the study period was 992 (95% CI: 567-1495) per 100 000. **Conclusion:** Multicentre surveillance data showed that the risk of disseminated BCG disease in HIV-infected infants is considerably higher than previously estimated, although likely to be under-estimated. There is an urgent need for data on the risk-benefit ratio of BCG vaccination in HIV-infected infants to inform decision-making in settings where HIV infection and tuberculosis burdens are high. Safe and effective tuberculosis prevention strategies are needed for HIV-infected infants.

Higgins JPT, Soares-Weiser K, Lopez-Lopez JA, Kakourou A, Chaplin K, Christensen H, et al. Association of BCG, dtp, and measles containing vaccines with childhood mortality: Systematic review. BMJ. 2016;355:i5170.

Objectives To evaluate the effects on non-specific and all cause mortality, in children under 5, of Bacillus Calmette-Guerin (BCG), diphtheria-tetanus-pertussis (DTP), and standard titre measles containing vaccines (MCV); to examine internal validity of the studies; and to examine any modifying effects of sex, age, vaccine sequence, and co-administration of vitamin A. **DESIGN** Systematic review, including assessment of risk of bias, and meta-analyses of similar studies. **STUDY ELIGIBILITY CRITERIA** Clinical trials, cohort studies, and case-control studies of the effects on mortality of BCG, whole cell DTP, and standard titre MCV in children under 5. **DATA SOURCES** Searches of Medline, Embase, Global Index Medicus, and the WHO International Clinical Trials Registry Platform, supplemented by contact with experts in the field. To avoid overlap in children studied across the included articles, findings from non-overlapping birth cohorts were identified. **Results** Results from 34 birth cohorts were identified. Most evidence was from observational studies, with some from short term clinical trials. Most studies reported on all cause (rather than non-specific) mortality. Receipt of BCG vaccine was associated with a reduction in all cause mortality: the average relative risks were 0.70 (95% confidence interval 0.49 to 1.01) from five clinical trials and 0.47 (0.32 to 0.69) from nine observational studies at high risk of bias. Receipt of DTP (almost always with oral polio vaccine) was associated with a possible increase in all cause mortality on average (relative risk 1.38, 0.92 to 2.08) from 10 studies at high risk of bias; this effect seemed stronger in girls than in boys. Receipt of standard titre MCV was associated with a reduction in all cause mortality (relative risks 0.74 (0.51 to 1.07) from four clinical trials and 0.51 (0.42 to 0.63) from 18 observational studies at high risk of bias); this effect seemed stronger in girls than in boys. Seven observational studies, assessed as being at high risk of bias, have compared sequences of vaccines; Results of a subset of these suggest that administering DTP with or after MCV may be associated with higher mortality than administering it before MCV. **Conclusions** Evidence suggests that receipt of BCG and MCV reduce overall mortality by more than would be expected through their effects on the diseases they prevent, and receipt of DTP may be associated with an increase in all cause mortality. Although efforts should be made to ensure that all children are immunised on schedule with BCG, DTP, and MCV, randomised trials are needed to compare the effects of different sequences.

Houben R, Dodd PJ. The global burden of latent tuberculosis infection: A re-estimation using mathematical modelling. PLoS Medicine. 2016;13(10):e1002152.

Background The existing estimate of the global burden of latent TB infection (LTBI) as "one-third" of the world population is nearly 20 y old. Given the importance of controlling LTBI as part of the End TB Strategy for eliminating TB by 2050, changes in demography and scientific

understanding, and progress in TB control, it is important to re-assess the global burden of LTBI. **Methods** and Findings We constructed trends in annual risk in infection (ARI) for countries between 1934 and 2014 using a combination of direct estimates of ARI from LTBI surveys (131 surveys from 1950 to 2011) and indirect estimates of ARI calculated from World Health Organisation (WHO) estimates of smear positive TB prevalence from 1990 to 2014. Gaussian process regression was used to generate ARIs for country-years without data and to represent uncertainty. Estimated ARI time-series were applied to the demography in each country to calculate the number and proportions of individuals infected, recently infected (infected within 2 y), and recently infected with isoniazid (INH)-resistant strains. Resulting estimates were aggregated by WHO region. We estimated the contribution of existing infections to TB incidence in 2035 and 2050. In 2014, the global burden of LTBI was 23.0% (95% uncertainty interval [UI]: 20.4%-26.4%), amounting to approximately 1.7 billion people. WHO South-East Asia, Western Pacific, and Africa regions had the highest prevalence and accounted for around 80% of those with LTBI. Prevalence of recent infection was 0.8% (95% UI: 0.7%-0.9%) of the global population, amounting to 55.5 (95% UI: 48.2-63.8) million individuals currently at high risk of TB disease, of which 10.9% (95% UI: 10.2%-11.8%) was isoniazid-resistant. Current LTBI alone, assuming no additional infections from 2015 onwards, would be expected to generate TB incidences in the region of 16.5 per 100,000 per year in 2035 and 8.3 per 100,000 per year in 2050. Limitations included the quantity and methodological heterogeneity of direct ARI data, and limited evidence to inform on potential clearance of LTBI. **Conclusions** We estimate that approximately 1.7 billion individuals were latently infected with *Mycobacterium tuberculosis* (M.tb) globally in 2014, just under a quarter of the global population. Investment in new tools to improve diagnosis and treatment of those with LTBI at risk of progressing to disease is urgently needed to address this latent reservoir if the 2050 target of eliminating TB is to be reached.

Jenkins HE, Yuen CM, Rodriguez CA, Nathavitharana RR, McLaughlin MM, Donald P, et al. Mortality in children diagnosed with tuberculosis: A systematic review and meta-analysis. Lancet Infectious Diseases. 2017;17(3):285-95.

Background Case fatality ratios in children with tuberculosis are poorly understood particularly those among children with HIV and children not receiving tuberculosis treatment. We did a systematic review of published work to identify studies of population-representative samples of paediatric (ie, <15 years) tuberculosis cases. **Methods** We searched PubMed and Embase for reports published in English, French, Portuguese, or Spanish before Aug 12, 2016, that included terms related to tuberculosis, children, mortality, and population representativeness. We also reviewed our own files and reference lists of articles identified by this search. We screened titles and abstracts for inclusion, excluding studies in which outcomes were unknown for 10% or more of the children and publications detailing non-representative samples. We used random-effects meta-analysis to produce pooled estimates of case fatality ratios from the included studies, which we divided into three eras: the pre-treatment era (ie, studies before 1946), the middle era (1946-80), and the recent era (after 1980). We stratified our analyses by whether or not children received tuberculosis treatment, age (0-4 years, 5-14 years), and HIV status. **Findings** We identified 31 papers comprising 35 datasets representing 82 436 children with tuberculosis disease, of whom 9274 died. Among children with tuberculosis included in studies in the pre-treatment era, the pooled case fatality ratio was 21.9% (95% CI 18.1-26.4) overall. The pooled case fatality ratio was significantly higher in children aged 0-4 years (43.6%, 95% CI 36.8-50.6) than in those aged 5-14 years (14.9%, 11.5-19.1). In studies in the recent era, when most children had tuberculosis treatment, the pooled case fatality ratio was 0.9% (95 CI 0.5-1.6). US surveillance data suggest that the case fatality ratio is substantially higher in children with HIV receiving treatment for tuberculosis (especially without antiretroviral therapy) than in those without HIV. **Interpretation** Without adequate treatment, children with tuberculosis, especially those younger than 5 years, are at high risk of death. Children with HIV have an increased

mortality risk, even when receiving tuberculosis treatment.

Johnson MM, Odell JA. Nontuberculous mycobacterial pulmonary infections. Journal Of Thoracic Disease. 2014;6(3):210-20.

Pulmonary infections due to nontuberculous mycobacteria (NTM) are increasingly recognized worldwide. Although over 150 different species of NTM have been described, pulmonary infections are most commonly due to *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus*. The identification of these organisms in pulmonary specimens does not always equate with active infection; supportive radiographic and clinical findings are needed to establish the diagnosis. It is difficult to eradicate NTM infections. A prolonged course of therapy with a combination of drugs is required. Unfortunately, recurrent infection with new strains of mycobacteria or a relapse of infection caused by the original organism is not uncommon. Surgical resection is appropriate in selected cases of localized disease or in cases in which the infecting organism is resistant to medical therapy. Additionally, surgery may be required for infections complicated by hemoptysis or abscess formation. This review will summarize the practical aspects of the diagnosis and management of NTM thoracic infections, with emphasis on the indications for surgery and the results of surgical intervention. The management of NTM disease in patients with human immunodeficiency virus (HIV) infections is beyond the scope of this article and, unless otherwise noted, comments apply to hosts without HIV infection;

Kandasamy R, Voysey M, McQuaid F, de Nie K, Ryan R, Orr O, et al. Non-specific immunological effects of selected routine childhood immunisations: Systematic review. BMJ. 2016;355:i5225.

Objective To identify and characterise non-specific immunological effects after routine childhood vaccines against BCG, measles, diphtheria, pertussis, and tetanus. Design Systematic review of randomised controlled trials, cohort studies, and case-control studies. Data sources Embase, PubMed, Cochrane library, and Trip searched between 1947 and January 2014. Publications submitted by a panel of experts in the specialty were also included. Eligibility criteria for selecting studies All human studies reporting non-specific immunological effects after vaccination with standard childhood immunisations. Studies using recombinant vaccines, no vaccine at all, or reporting only vaccine specific outcomes were excluded. The primary aim was to systematically identify, assemble, and review all available studies and data on the possible non-specific or heterologous immunological effects of BCG; measles; mumps, measles, and rubella (MMR); diphtheria; tetanus; and pertussis vaccines. **Results** The initial search yielded 11 168 references; 77 manuscripts met the inclusion criteria for data analysis. In most included studies (48%) BCG was the vaccine intervention. The final time point of outcome measurement was primarily performed (70%) between one and 12 months after vaccination. There was a high risk of bias in the included studies, with no single study rated low risk across all assessment criteria. A total of 143 different immunological variables were reported, which, in conjunction with differences in measurement units and summary statistics, created a high number of combinations thus precluding any meta-analysis. Studies that compared BCG vaccinated with unvaccinated groups showed a trend towards increased IFN-[GAMMA] production in vitro in the vaccinated groups. Increases were also observed for IFN-[GAMMA] measured after BCG vaccination in response to in vitro stimulation with microbial antigens from *Candida albicans*, tetanus toxoid, *Staphylococcus aureus*, lipopolysaccharide, and hepatitis B. Cohort studies of measles vaccination showed an increase in lymphoproliferation to microbial antigens from tetanus toxoid and *C. albicans*. Increases in immunogenicity to heterologous antigens were noted after diphtheria-tetanus (herpes simplex virus and polio antibody titres) and diphtheria-tetanus-pertussis (pneumococcus serotype 14 and polio neutralising responses) vaccination. **Conclusions** The papers reporting non-specific immunological effects had

heterogeneous study designs and could not be conventionally meta-analysed, providing a low level of evidence quality. Some studies, such as BCG vaccine studies examining in vitro IFN-[GAMMA] responses and measles vaccine studies examining lymphoproliferation to microbial antigen stimulation, showed a consistent direction of effect suggestive of non-specific immunological effects. The quality of the evidence, however, does not provide confidence in the nature, magnitude, or timing of non-specific immunological effects after vaccination with BCG, diphtheria, pertussis, tetanus, or measles containing vaccines nor the clinical importance of the findings.

Kendall BA, Winthrop KL. Update on the epidemiology of pulmonary nontuberculous mycobacterial infections preface. Seminars In Respiratory And Critical Care Medicine. 2013;34(1):87-94.

For decades, the incidence of pulmonary nontuberculous mycobacteria (NTM) has been reported to be increasing, yet formal epidemiological evaluation of this notion has been lacking until recently. Defining the epidemiology of NTM has been more challenging than with *Mycobacterium tuberculosis* (MTB). Unlike MTB, NTM are soil and water organisms, and infection is thought to be acquired from the environment rather than transmitted from person-to-person, with very rare exceptions. Due to their nearly ubiquitous presence in municipal water supplies, exposure to NTM is common. Further, NTM can colonize the respiratory tract without causing disease. NTM disease is not reportable to public health authorities; therefore, epidemiological and surveillance data are not readily available. Nonetheless, the prevalence of pulmonary NTM disease has increased dramatically in the United States and globally over the past 3 decades. *Mycobacterium avium* complex (MAC) accounts for the majority of NTM infections worldwide, but there is significant regional variability of various species. Additionally, novel species have been implicated in several countries in NTM pulmonary disease.

Kroger AT, Sumaya CV, Pickering LK, Atkinson WL, National Center for I, Respiratory D. General recommendations on immunization: Recommendations of the advisory committee on immunization practices (acip). Morbidity and Mortality Weekly Report: Recommendations and Reports. 2011;60(2):1-60.

This report is a revision of the General Recommendations on Immunization and updates the 2006 statement by the Advisory Committee on Immunization Practices (ACIP) (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2006;55[No. RR-15]). The report also includes revised content from previous ACIP recommendations on the following topics: adult vaccination (CDC. Update on adult immunization recommendations of the immunization practices Advisory Committee [ACIP]. MMWR 1991;40[No. RR-12]); the assessment and feedback strategy to increase vaccination rates (CDC. Recommendations of the Advisory Committee on Immunization Practices: programmatic strategies to increase vaccination rates-assessment and feedback of provider-based vaccination coverage information. MMWR 1996;45:219-20); linkage of vaccination services and those of the Supplemental Nutrition Program for Women, Infants, and Children (WIC program) (CDC. Recommendations of the Advisory Committee on Immunization Practices: programmatic strategies to increase vaccination coverage by age 2 years-linkage of vaccination and WIC services. MMWR 1996;45:217-8); adolescent immunization (CDC. Immunization of adolescents: recommendations of the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Medical Association. MMWR 1996;45[No. RR-13]); and combination vaccines (CDC. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], the American Academy of Pediatrics [AAP], and the American Academy of Family Physicians [AAFP]. MMWR 1999;48[No. RR-5]). Notable revisions to the 2006 recommendations include 1) revisions to the

tables of contraindications and precautions to vaccination, as well as a separate table of conditions that are commonly misperceived as contraindications and precautions; 2) reordering of the report content, with vaccine risk-benefit screening, managing adverse reactions, reporting of adverse events, and the vaccine injury compensation program presented immediately after the discussion of contraindications and precautions; 3) stricter criteria for selecting an appropriate storage unit for vaccines; 4) additional guidance for maintaining the cold chain in the event of unavoidable temperature deviations; and 5) updated revisions for vaccination of patients who have received a hematopoietic cell transplant. The most recent ACIP recommendations for each specific vaccine should be consulted for comprehensive details. This report, ACIP recommendations for each vaccine, and additional information about vaccinations are available from CDC at <http://www.cdc.gov/vaccines>.

Leung CC, Yew WW, Au KF, Tam CM, Chang KC, Mak KY, et al. A strong tuberculin reaction in primary school children predicts tuberculosis in adolescence. *Pediatric Infectious Disease Journal*. 2012;31(2):150-3.

Background: In Hong Kong, neonatal bacillus Calmette-Guerin vaccination coverage has been around 99% since 1970. Children younger than 14 years of age appear to have a relatively low risk of tuberculosis (TB), but the risk of TB increases rapidly after 15 years of age to a secondary peak in young adulthood. **Methods:** We followed prospectively 19,383 students who were 6 to 10 years of age participating in the 1999/2000 bacillus Calmette-Guerin revaccination program by cross-matching with the territory-wide TB registry until December 31, 2010, using the identity card number as a unique identifier. **Results:** After 214,753 person-years of follow-up, 44 active TB cases (22 culture-confirmed) were detected for an overall incidence of 20.5/100,000 person-years. The incidence differed significantly by baseline tuberculin reaction sizes (13.0, 18.8, 22.5, 280.4 per 100,000 person-years for reaction size of 0-4, 5-9, 10-14, and ≥ 15 mm, respectively, $P < 0.001$). Consistent results were observed for culture-confirmed cases and after adjustment for gender and baseline age. For those with tuberculin reaction size ≥ 15 mm, the incidence of TB was significantly higher beyond the age of 15 years than for those less than 15 years (608.1 vs. 37.5 per 100,000 person-years, $P < 0.001$). Although older baseline age was associated with larger tuberculin reaction sizes, it did not independently predict subsequent development of disease. **Conclusion:** Strong tuberculin reactions in primary school children predicted TB in adolescents after an initial quiescent period. Endogenous reactivation, possibly related to changes in host immunity, might account for the upsurge of TB in adolescence.

Lotte A, Wasz-Höckert O, Poisson N, Dumitrescu N, Verron M, Couvet E. A bibliography of the complications of BCG vaccination. A comprehensive list of the world literature since the introduction of BCG up to July 1982, supplemented by over 100 personal communications. *Advances in tuberculosis research Fortschritte der Tuberkuloseforschung Progrès de l'exploration de la tuberculose*. 1984;21:194.

No abstract available.

Lotte A, Wasz-Höckert O, Poisson N, Engbaek H, Landmann H, Quast U, et al. Second international study on complications induced by intradermal BCG-vaccination. *Bulletin of the International Union against Tuberculosis and Lung Disease*. 1988;63(2):47.

No abstract available.

Luca S, Mihaescu T. History of BCG vaccine. *Mædica*. 2013;8(1):53.

Tuberculosis (TB) is still responsible for 2 million deaths every year despite being a treatable airborne infectious disease. "Consumption" and "Phthisis" were terms historically used to describe TB, which was responsible for one in four deaths in the 19th century. Due to its infectious nature, chronic progression and long treatment, TB is a great burden for society.

Moreover the emergence of multi-drug resistant TB and the current TB-HIV epidemic has raised even greater concern. Treating and preventing TB has become a permanent challenge since the ancient times. Bacille Calmette-Guérin (BCG) is the only vaccine available today and has been used for more than 90 years with astonishing safety records. However, its efficacy remains controversial. No universal BCG vaccination policy exists, with some countries merely recommending its use and others that have implemented immunization programs. In this article we review several important milestones of BCG vaccine development from the discovery till today.

Lwin K, Sundaresan T, Gyi MM, Bechelli LM, Tamondong C, Garbajosa PG, et al. BCG vaccination of children against leprosy: Fourteen-year findings of the trial in burma. Bulletin of the World Health Organization. 1985;63(6):1069.

The value of BCG vaccination in preventing leprosy among children was studied in an area of high leprosy endemicity in Burma through a controlled trial; one group of 13 066 children received BCG and another group of 13 176 served as controls. The overall protective effect of BCG, which was only about 20% over the 14-year period, was found to vary with the batch of vaccine, as well as age, sex, and contact status of the children. BCG protection was found to be independent of the initial tuberculin status of the children. The protective effect of BCG against the lepromatous type of leprosy could not be measured because of the low incidence. Protection was observed throughout the fourteen years of the study except for the first year. The results are compared with those of three other major BCG trials in leprosy. The trial has shown that BCG provides only a very modest level of protection and that BCG vaccination is not likely to be an important solution for leprosy control.

Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: A systematic review of randomized controlled trials. Clinical Infectious Diseases. 2014;58(4):470-80.

Background. Randomized trials assessing BCG vaccine protection against tuberculosis have widely varying **Results**, for reasons that are not well understood. **Methods.** We examined associations of trial setting and design with BCG efficacy against pulmonary and miliary or meningeal tuberculosis by conducting a systematic review, meta-analyses, and meta-regression. **Results.** We identified 18 trials reporting pulmonary tuberculosis and 6 reporting miliary or meningeal tuberculosis. Univariable meta-regression indicated efficacy against pulmonary tuberculosis varied according to 3 characteristics. Protection appeared greatest in children stringently tuberculin tested, to try to exclude prior infection with *Mycobacterium tuberculosis* or sensitization to environmental mycobacteria (rate ratio [RR], 0.26; 95% confidence interval [CI], .18-.37), or infants (RR, 0.41; 95% CI, .29-.58). Protection was weaker in children not stringently tested (RR, 0.59; 95% CI, .35-1.01) and older individuals stringently or not stringently tested (RR, 0.88; 95% CI, .59-1.31 and RR, 0.81; 95% CI, .55-1.22, respectively). Protection was higher in trials further from the equator where environmental mycobacteria are less and with lower risk of diagnostic detection bias. These associations were attenuated in a multivariable model, but each had an independent effect. There was no evidence that efficacy was associated with BCG strain. Protection against meningeal and miliary tuberculosis was also high in infants (RR, 0.1; 95% CI, .01-.77) and children stringently tuberculin tested (RR, 0.08; 95% CI, .03-.25). **Conclusions.** Absence of prior *M. tuberculosis* infection or sensitization with environmental mycobacteria is associated with higher efficacy of BCG against pulmonary tuberculosis and possibly against miliary and meningeal tuberculosis. Evaluations of new tuberculosis vaccines should account for the possibility that prior infection may mask or block their effects.

Mangtani P, Nguipdop-Djomo P, Keogh RH, Sterne JAC, Abubakar I, Smith PG, et al. The duration of protection of school-aged BCG vaccination in England: A population-based case-control study. *International Journal of Epidemiology*. 2017;dyx141-dyx.

Background: Evidence of protection from childhood Bacillus Calmette-Guerin (BCG) against tuberculosis (TB) in adulthood, when most transmission occurs, is important for TB control and resource allocation. **Methods:** We conducted a population-based case-control study of protection by BCG given to children aged 12–13 years against tuberculosis occurring 10–29 years later. We recruited UK-born White subjects with tuberculosis and randomly sampled White community controls. Hazard ratios and 95% confidence intervals (CIs) were estimated using case-cohort Cox regression, adjusting for potential confounding factors, including socio-economic status, smoking, drug use, prison and homelessness. Vaccine effectiveness ($VE = 1 - \text{hazard ratio}$) was assessed at successive intervals more than 10 years following vaccination. **Results:** We obtained 677 cases and 1170 controls after a 65% response rate in both groups. Confounding by deprivation, education and lifestyle factors was slight 10–20 years after vaccination, and more evident after 20 years. VE 10–15 years after vaccination was 51% (95% CI 21, 69%) and 57% (CI 33, 72%) at 15–20 years. Subsequently, BCG protection appeared to wane; 20–25 years $VE = 25\%$ (CI –14%, 51%) and 25–29 years $VE = 1\%$ (CI –84%, 47%). Based on multiple imputation of missing data (in 17% subjects), VE estimated in the same intervals after vaccination were similar [56% (CI 33, 72%), 57% (CI 36, 71%), 25% (–10, 48%), 21% (–39, 55%)]. **Conclusions:** School-aged BCG vaccination offered moderate protection against tuberculosis for at least 20 years, which is longer than previously thought. This has implications for assessing the cost-effectiveness of BCG vaccination and when evaluating new TB vaccines.

Marais BJ, Gie RP, Schaaf HS, Hesselning AC, Obihara CC, Nelson LJ, et al. The clinical epidemiology of childhood pulmonary tuberculosis: A critical review of literature from the pre-chemotherapy era. *International Journal Of Tuberculosis And Lung Disease*. 2004;8(3):278-85.

The pre-chemotherapy literature represents an impressive body of evidence that clarifies important epidemiological concepts in childhood tuberculosis. Reports describe the major transitions in tuberculosis, from exposure to infection and from infection to disease (morbidity and mortality), without the influence of chemotherapy. Children with household exposure to a sputum smear-positive source case experienced the greatest risk of becoming infected and of developing subsequent disease. Household exposure to a sputum smear-negative source case or non-household exposure still posed an appreciable, although greatly reduced, risk. Infection in children less than 2 years of age indicated a probable household source case. The majority of older children who were infected did not have a household source identified, and presumably became infected in the community. The annual risk of infection (ARI) was not constant across all ages, but seemed to increase during periods of widening social contact. Infants and adolescents were the groups at highest risk for disease development and death following primary infection.

Merle CSC, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: Review of current evidence and status of BCG in leprosy control. *Expert Review Of Vaccines*. 2010;9(2):209-22.

The bacillus Calmette-Guerin (BCG) vaccine, initially developed to provide protection against TB, also protects against leprosy; and the magnitude of this effect varies. Previous meta-analyses did not provide a summary estimate of the efficacy due to the heterogeneity of the results. We conducted a meta-analysis of published data including recently published studies (up to June 2009) to determine the efficacy of BCG protection on leprosy and to investigate whether age at vaccination, clinical form, number of doses, type of study, the latitude of study area and year of

publication influence the degree of efficacy and explain the variation. In the light of the results, we argue for more emphasis on the role of BCG vaccination in leprosy control and research.;The bacillus Calmette-Guérin (BCG) vaccine, initially developed to provide protection against TB, also protects against leprosy; and the magnitude of this effect varies. Previous meta-analyses did not provide a summary estimate of the efficacy due to the heterogeneity of the results. We conducted a meta-analysis of published data including recently published studies (up to June 2009) to determine the efficacy of BCG protection on leprosy and to investigate whether age at vaccination, clinical form, number of doses, type of study, the latitude of study area and year of publication influence the degree of efficacy and explain the variation. In the light of the results, we argue for more emphasis on the role of BCG vaccination in leprosy control and research.

Nguipdop-Djomo P, Haldal E, Rodrigues LC, Abubakar I, Mangtani P. Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in norway: A retrospective population-based cohort study. Lancet Infectious Diseases. 2016;16(2):219-26.

Background Little is known about how long the BCG vaccine protects against tuberculosis. We assessed the long-term vaccine effectiveness (VE) in Norwegian-born individuals. **Methods** In this retrospective population-based cohort study, we studied Norwegian-born individuals aged 12-50 years who were tuberculin skin test (TST) negative and eligible for BCG vaccination as part of the last round of Norway's mandatory mass tuberculosis screening and BCG vaccination programme between 1962 and 1975. We excluded individuals who had tuberculosis before or in the year of screening and those with unknown TST and BCG status. We obtained TST and BCG information and linked it to the National Tuberculosis Register, population and housing censuses, and the population register for emigrations and deaths. We followed individuals up to their first tuberculosis episode, emigration, death, or Dec 31, 2011. We used Cox regressions to estimate VE against all tuberculosis and just pulmonary tuberculosis by time since vaccination, adjusted for age, time, county-level tuberculosis rates, and demographic and socioeconomic indicators.

Findings Median follow-up was 41 years (IQR 32-49) for 83 421 BCG-unvaccinated and 44 years (41-46) for 297 905 vaccinated individuals, with 260 tuberculosis episodes. Tuberculosis rates were 3.3 per 100 000 person-years in unvaccinated and 1.3 per 100 000 person-years in vaccinated individuals. The adjusted average VE during 40 year follow-up was 49% (95% CI 26-65), although after 20 years, the VE was not significant (up to 9 years VE [excluding tuberculosis episodes in the first 2 years] 61% [95% CI 24-80]; 10-19 years 58% [27-76]; 20-29 years 38% [-32 to 71]; 30-40 years 42% [-24 to 73]). VE against pulmonary tuberculosis up to 9 years (excluding tuberculosis episodes in the first 2 years) was 67% (95% CI 27-85), 10-19 years was 63% (32-80), 20-29 years was 50% (-19 to 79), and 30-40 years was 40% (-46 to 76).

Interpretation Findings are consistent with long-lasting BCG protection, but waning of VE with time. The vaccine could be more cost effective than has been previously estimated.

Nissen TN, Birk NM, Kjærgaard J, Thøstesen LM, Pihl GT, Hoffmann T, et al. Adverse reactions to the bacillus calmette-guérin (BCG) vaccine in new-born infants—an evaluation of the danish strain 1331 ssi in a randomized clinical trial. Vaccine. 2016;34(22):2477-82.

Objective: To evaluate adverse reactions of the Bacillus Calmette Guerin (BCG) Statens Serum Institut (SSI) (Danish strain 1331) used as intervention in a randomized clinical trial. **Design:** A randomized clinical multicenter trial, The Danish Calmette Study, randomizing newborns to BCG or no intervention. Follow-up until 13 months of age. **Setting:** Pediatric and maternity wards at three Danish university hospitals. **Participants:** All women planning to give birth at the three study sites (n = 16,521) during the recruitment period were invited to participate in the study. Four thousand one hundred and eighty four families consented to participate and 4262 children, gestational age 32 weeks and above, were randomized: 2129 to BCG vaccine and 2133 to no

vaccine. None of the participants withdrew because of adverse reactions. **Main outcome and measure:** Trial-registered adverse reactions after BCG vaccination at birth. Follow-up at 3 and 13 months by telephone interviews and clinical examinations. **Results:** Among the 2118 BCG-vaccinated children we registered no cases of severe unexpected adverse reaction related to BCG vaccination and no cases of disseminated BCG disease. Two cases of regional lymphadenitis were hospitalized and thus classified as serious adverse reactions related to BCG. The most severe adverse reactions were 10 cases of suppurative lymphadenitis. This was nearly a fivefold increase compared to what was expected based on the summary of product characteristics of the vaccine. All cases were treated conservatively and recovered. Six of 10 (60%) families of children experiencing suppurative lymphadenitis compared to 117/2071 (6%) of those with no lymphadenitis indicated that the vaccine had more adverse effects than expected (p -value <0.001). **Conclusions and relevance:** BCG vaccination was associated with only mild morbidity and no mortality. A higher incidence of suppurative lymphadenitis than expected was observed. All children were treated conservatively without sequelae or complications. Trial registration number NCT01694108 at www.clinicaltrials.gov.

Pereira SM, Barreto ML, Pilger D, Cruz AA, Sant'Anna C, Hijjar MA, et al. Effectiveness and cost-effectiveness of first BCG vaccination against tuberculosis in school-age children without previous tuberculin test (BCG-revac trial): A cluster-randomised trial. Lancet Infectious Diseases. 2012;12(4):300-6.

Background Neonatal BCG vaccination is part of routine vaccination schedules in many developing countries; vaccination at school age has not been assessed in trials in low-income and middle-income countries. Catch-up BCG vaccination of school-age children who missed neonatal BCG vaccination could be indicated if it confers protection and is cost-effective. We did a cluster-randomised trial (BCG REVAC) to estimate the effectiveness (efficacy given in routine settings) of school-age vaccination. **Methods** We assessed the effectiveness of BCG vaccination in school-age children (aged 7-14 years) with unknown tuberculin status who did not receive neonatal BCG vaccination (subpopulation of the BCG REVAC cluster-randomised trial), between July, 1997, and June, 2006, in Salvador, Brazil, and between January, 1999, and December, 2007, in Manaus, Brazil. 763 schools were randomly assigned into BCG vaccination group or a not-vaccinated control group. Neither allocation nor intervention was concealed. Incidence of tuberculosis was the primary outcome. Cases were identified via the Brazilian Tuberculosis Control Programme. Study staff were masked to vaccination status when identified cases were linked to the study population. We estimated cost-effectiveness in Salvador by comparison of the cost for vaccination to prevent one case of tuberculosis (censored at 9 years) with the average cost of treating one case of tuberculosis. Analysis of all included children was by intention to treat. For calculation of the incidence rate we used generalised estimating equations and correlated observations over time. **Findings** We randomly assigned 20 622 children from 385 schools to the BCG vaccination group and 18 507 children from 365 schools to the control group. The crude incidence of tuberculosis was 54.9 (95% CI 45.3-66.7) per 100 000 person-years in the BCG vaccination group and 72.7 (62.8-86.8) per 100 000 person-years in the control group. The overall vaccine effectiveness of a first BCG vaccination at school age was 25% (3-43%). In Salvador, where vaccine effectiveness was 34% (8-53%), vaccination of 381 children would prevent one case of tuberculosis and was cheaper than treatment. The frequency of adverse events was very low with only one axillary lymphadenitis and one ulcer greater than 1 cm in 11980 BCG vaccinations. **Interpretation** Vaccination of school-age children without previous tuberculin testing can reduce the incidence of tuberculosis and could reduce the costs of tuberculosis control. Restriction of BCG vaccination to the first year of life is not in the best interests of the public nor of programmes for tuberculosis control.

Pluschke G, Röltgen K. Epidemiology and disease burden of buruli ulcer: A review. Research and Reports in Tropical Medicine. 2015;2015:59-73.

Abstract: Buruli ulcer (BU) is a neglected tropical skin disease caused by *Mycobacterium ulcerans*. Infection foci occur mainly in remote, rural areas of Central and West Africa, but also in Australia and Papua New Guinea. In addition, infections caused by *M. ulcerans* strains of a different lineage are sporadically reported from scattered foci in Asia and the Americas. While in the past decade more than 42,000 BU cases have been reported worldwide, an assessment of the actual global disease burden is complicated by the remoteness of affected populations and a lack of data on the incidence of BU in a number of countries, from which cases have been historically reported. Moreover, as BU patients present with diverse clinical manifestations ranging from relatively unspecific nodules, plaques, or edema to necrotic, ulcerative lesions, differential diagnosis is manifold and thus clinical misclassification may occur. Since to date reservoirs and transmission pathways of *M. ulcerans* remain equivocal, early diagnosis and treatment of patients are key determinants to control the disease. Particularly in view of the apparent decline in BU incidence in regions of West Africa, awareness and knowledge of BU in endemic regions must be retained to ensure a continuous monitoring and control. An integrated approach for the control of tropical skin diseases should be considered to cope with this difficult task. This review article aims at providing an overview of the current global burden of BU and summarizes the state of knowledge on the various epidemiological aspects of this enigmatic disease.

Poobalan A et al. Systematic review on the effectiveness and efficacy of BCG against leprosy. 2017. published summary in the SAGE BCG working Group report. Available at: http://www.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf (Accessed November 2017).

No abstract available.

Rabie H, Violari A, Duong T, Madhi SA, Josipovic D, Innes S, et al. Early antiretroviral treatment reduces risk of bacille calmette-guerin immune reconstitution adenitis. International Journal Of Tuberculosis And Lung Disease. 2011;15(9):1194-200.

Setting: Two centres in Soweto and Cape Town, South Africa. **Objective:** To assess the effects of timing of initiation of antiretroviral treatment (ART) and other factors on the risk of bacille Calmette-Guerin (BCG) related regional adenitis due to immune reconstitution inflammatory syndrome (BCG-IRIS) in human immunodeficiency virus (HIV) infected infants. **Design:** HIV-infected infants aged 6-12 weeks with CD4 count $\geq 25\%$ enrolled in the Children with HIV Early Antiretroviral Therapy (CHER) Trial received early (before 12 weeks) or deferred (after immunological or clinical progression) ART; infants with CD4 count $<25\%$ all received early ART. All received BCG vaccination after birth. Reactogenicity to BCG was assessed prospectively during routine study follow-up. **Results:** Of 369 infants, 32 (8.7%) developed BCG-IRIS within 6 months of starting ART, 28 (88%) within 2 months after ART initiation. Of the 32 cases, 30 (93.8%) had HIV-1 RNA >750000 copies/ml at initiation. Incidence of BCG-IRIS was 10.9 and 54.3 per 100 person-years (py) among infants with CD4 count $\geq 25\%$ at enrolment receiving early (at median age 7.4 weeks) vs. deferred (23.2 weeks) ART, respectively (HR 0.24, 95% CI 0.11-0.53, $P < 0.001$). Infants with CD4 count $<25\%$ receiving early ART had intermediate incidence (41.7/100 py). Low CD4 counts and high HIV-1 RNA at initiation were the strongest independent risk factors for BCG-IRIS. **Conclusions:** Early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis.;

Rani SH, Vijayalakshmi V, Sunil K, Lakshmi KA, Suman LG, Murthy KJ. Cell mediated immunity in children with scar-failure following BCG vaccination. Indian pediatrics. 1998;35(2):123.

To find out the incidence of BCG-scar failure, in BCG vaccinated children and assess their in vitro cellular response. Four year prospective cohort observational study. Immunization centers at: (a) State Tuberculosis Center; (b) Tuberculosis Association of Andhra Pradesh; and (c) Niloufer Hospital for Women and Children in Hyderabad. Healthy children brought to the immunization centers for BCG vaccination and were followed up till 6 months of age for scar failure. These 655 BCG vaccinated children were classified into three groups based on the age at vaccination: (i) 0 day-1 day; (ii) 2 days-30 days; and (iii) 31 days-90 days. Of these children, in vitro leukocyte migration inhibition (LMI) levels against PHA/PPD were investigated in 228 of them. Of the 655 children, 591 (90.2%) showed presence of scar. Out of the three groups, number of children belonging to the first group in whom the scar was absent, was highest. Of 591 children with scar, LMI was performed in 34, 110 and 43 of them in the three different age groups, respectively out of whom 88.2%, 87.2% and 86% had positive response ($\geq 20\%$) to PPD. Of 64 children who failed to develop a scar, LMI was performed in 17, 19 and 5 in three different age groups out of whom 88.2%, 94.7% and 80% had positive ($\geq 20\%$) in vitro response to PPD. Scar failure may occur in 10% of BCG vaccinated and is more common with immunization within 48 hours of life. Failure of formation of BCG-scar at the site of BCG vaccination may not necessarily imply failure of immunization because majority of them do elicit positive in vitro LMI response.

Richardus R, Butlin CR, Alam K, Kundu K, Geluk A, Richardus JH. Clinical manifestations of leprosy after BCG vaccination: An observational study in bangladesh. Vaccine. 2015;33(13):1562-7.

Background Although BCG is used as a vaccine against tuberculosis, it also protects against leprosy. Previous evaluation over 18 years of an intervention of two doses BCG for 3536 household contacts of leprosy patients showed that 28 (23%) out of 122 contacts diagnosed with leprosy, developed symptoms 2-10 months after vaccination. This study describes contacts of leprosy patients in Bangladesh who developed leprosy within 12 weeks after receiving a single BCG dose. **Methods** A cluster RCT in Bangladesh aims to study the effectiveness of the BCG vaccine versus BCG in combination with single dose rifampicin (SDR) given 2 to 3 months after BCG, in the prevention of leprosy among contacts of newly diagnosed leprosy patients. During the first 1,5 years of this ongoing trial we identified contacts who developed leprosy within the first 12 weeks after receiving BCG vaccination, the timeframe before SDR is given. **Results** We identified 21 contacts who developed leprosy within 12 weeks after BCG vaccination among 5196 vaccinated contacts (0.40%). All 21 cases presented with paucibacillary (PB) leprosy, including children and adults. About half of these cases had previously received BCG vaccination as indicated by the presence of a BCG scar; 43% presented with signs of nerve function impairment and/or Type 1 (reversal) reaction, and 56% of the index patients had multibacillary (MB) leprosy. **Conclusion** An unexpectedly high proportion of healthy contacts of leprosy patients presented with PB leprosy within 12 weeks after receiving BCG vaccination, possibly as a result of boosted cell-mediated immunity by homologues of Mycobacterium leprae antigens in BCG. Various immunological mechanisms could underlie this phenomenon, including an immune reconstitution inflammatory syndrome (IRIS). Further studies are required to determine whether BCG vaccination merely altered the incubation period or actually changed the course of the infection from self-limiting, subclinical infection to manifest disease.

Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. International journal of leprosy and other mycobacterial diseases : official organ of the International Leprosy Association. 1966;34(3):255.

No abstract available.

Ritz N, Connell TG, Curtis N. To BCG or not to BCG? Preventing travel-associated tuberculosis in children. Vaccine. 2008;26(47):5905-10.

With the rise in travel to countries with a high prevalence of tuberculosis (TB), the risk of travel-associated TB is of increasing concern. However, the use of Bacille Calmette-Guérin (BCG) vaccine for the prevention of travel-associated TB is a neglected area. We review and discuss national and international recommendations and guidelines for the prevention of travel-associated TB in children. Three children who developed travel-associated TB disease are described to illustrate that current recommendations, and in particular the use of pre-travel BCG immunisation, are inconsistent and controversial. The wide variation in recommendations reflects the paucity of data on the effectiveness of BCG immunisation and other preventive strategies in this setting. Until evidence-based guidelines can be produced, we believe that a low threshold for recommending BCG immunisation for travelling children is the safest strategy. A practical approach to deciding which children should be immunised with BCG prior to travel is presented.

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. The Lancet. 2005;366(9493):1290-5.

Background Many countries offer a second BCG vaccination to prevent tuberculosis, although there is little evidence of whether this confers additional protection. BCG vaccination is routine in Brazil but BCG revaccination procedures vary by state. We studied revaccination efficacy in two Brazilian cities with tuberculosis prevalence representative of Brazil. **Methods** We did a cluster-randomised trial of the protection against tuberculosis from BCG revaccination in school-aged children who had had one BCG vaccination as infants. 767 schools in the cities of Salvador and Manaus, Brazil, participated; schools were the unit of randomisation. The study was open label with no placebo. Cases of tuberculosis were identified through record linkage to the Tuberculosis Control Programme. Revaccination status was masked during linkage and validation of cases. The incidence of tuberculosis was the primary outcome. Analysis was by intention to treat. **Findings** 386 schools (176 846 children) were assigned BCG revaccination and 365 (171 293 children) no revaccination. 42 053 children in the vaccine group and 47 006 in the control group were absent from school on the day of the visit and were excluded. 31 163 and 27 146, respectively were also excluded because they had no BCG scar, two or more scars, or a doubtful scar on assessment. The crude incidence of tuberculosis in the intervention group was 29.3 per 100 000 person years and in the control group 30.2 per 100 000 person-years (crude-rate ratio 0.97; 95% CI 0.76-1.28). The efficacy of BCG revaccination was 9% (-16 to 29%). **Interpretation** Revaccination given to children aged 7-14 years in this setting does not provide substantial additional protection and should not be recommended. Follow-up is ongoing and needed to assess the effect of other factors on revaccination efficacy: time since vaccination, age at vaccination, and high or low prevalence of environmental mycobacteria.

Romanus V. First experience with BCG discontinuation in europe. Experience in sweden 15 years after stopping general BCG vaccination at birth. Bulletin of the International Union against Tuberculosis and Lung Disease. 1990;65(2-3):32.

No abstract available.

Romanus V, Hallander HO, Wahlen P, Olindernielsen AM, Magnusson PHW, Juhlin I. Atypical mycobacteria in extrapulmonary disease among children - incidence in sweden from 1969 to 1990, related to changing BCG-vaccination coverage. Tubercle And Lung Disease. 1995;76(4):300-10.

Setting: In April 1975, the general BCG vaccination of newborns in Sweden was replaced by selective vaccination of groups at increased risk for tuberculosis. **Objective:** To relate the incidence of atypical mycobacterial disease in children to BCG vaccination. **Design:** A nationwide survey in Sweden during the period 1969-90 disclosed 390 children under 15 years of age with bacteriologically confirmed atypical mycobacteria from extrapulmonary lesions. **Results:** The average, annual incidence of atypical mycobacterial disease per 100 000 children under 5 years of age increased from 0.06 during the period 1969-74 to a maximum level of 5.7 during 1981-85. Among the cohorts born in Sweden in the period 1975-85, the cumulative incidence rate before 5 years of age was estimated at 26.8 per 100 000 non-BCG-vaccinated children and at 4.6 among those BCG-vaccinated, ratio 5.9 (95% confidence limits 1.6, 48.5). Mycobacterium avium-intracellulare was found in 83%. Disseminated, fatal disease developed in 3 children. The remaining ones suffered from local infections, most often lymphnode or soft-tissue lesions. The observed incidence of bacteriologically confirmed diagnosis was estimated to represent approximately 40% of the 'true' number, if patients with diagnosis based on histological, clinical and epidemiological findings only were included. **Conclusion:** The present study indicates that BCG vaccination plays a role in protection against localized disease caused by atypical mycobacteria in children.

Roth A, Jensen H, Garly ML, Djana Q, Martins CL, Sodemann M, et al. Low birth weight infants and calmette-guerin bacillus vaccination at birth community study from guinea-bissau. Pediatric Infectious Disease Journal. 2004;23(6):544-50.

Background: In developing countries, low birth weight (LBW) children are often not vaccinated with Calmette-Guerin bacillus (BCG) at birth. Recent studies have suggested that BCG may have a nonspecific beneficial effect on infant mortality. We evaluated the consequences of not vaccinating LBW children at birth in Guinea-Bissau. **Methods:** Between 1989 and 1999, 7138 children born at the central hospital had a birth weight registered. We assessed BCG coverage until 3 years of age. Data on tuberculin skin test (TST) for 297 children and BCG scar for 1319 children in the study population were reanalyzed for differences between normal birth weight (NBW) children and LBW children. We assessed the effect of early BCG vaccination on mortality to 12 months of age. **Results:** Among LBW children there were 1.5- to 3-fold more unvaccinated individuals than among NBW children up to 4 months of age. There was no overall difference between LBW and NBW children in TST or BCG scarring; LBW children vaccinated early may have had slightly reduced reactions to tuberculin. Among 845 LBW children, 182 had received BCG within the first week of life. Controlling for background factors and censoring at first diphtheria-tetanus-pertussis vaccination, measles vaccination or at 6 months of age (whichever came first), the mortality rate ratio for BCG-vaccinated versus -unvaccinated LBW children was 0.17 (95% confidence interval, 0.06-0.49), with an even stronger effect for LBW children vaccinated in the first week of life (mortality rate ratio, 0.07; 95% confidence interval, 0.01-0.62). **Conclusions:** The policy of not vaccinating with BCG at birth had a negative impact on vaccination coverage for LBW children. Early BCG vaccination had no large negative impact on TST and BCG scarring. Mortality was lower for BCG-vaccinated than for unvaccinated LBW children controlling for available background factors. BCG vaccination of LBW children may have a beneficial effect on survival that cannot be explained by protection against tuberculosis. Future studies should examine possible adverse effects from equalizing BCG policy for LBW and NBW children.

Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against mycobacterium tuberculosis infection in children: Systematic review and meta-analysis. BMJ : British Medical Journal. 2014;349(aug04 5):g4643-g.

Objectives To determine whether BCG vaccination protects against Mycobacterium tuberculosis infection as assessed by interferon. release assays (IGRA) in children. Design Systematic review and meta-analysis. Searches of electronic databases 1950 to November 2013, checking of reference lists, hand searching of journals, and contact with experts. **Setting** Community congregate settings and households. Inclusion criteria Vaccinated and unvaccinated children aged under 16 with known recent exposure to patients with pulmonary tuberculosis. Children were screened for infection with M tuberculosis with interferon. release assays. Data extraction Study results relating to diagnostic accuracy were extracted and risk estimates were combined with random effects meta-analysis. **Results** The primary analysis included 14 studies and 3855 participants. The estimated overall risk ratio was 0.81 (95% confidence interval 0.71 to 0.92), indicating a protective efficacy of 19% against infection among vaccinated children after exposure compared with unvaccinated children. The observed protection was similar when estimated with the two types of interferon. release assays (ELISpot or QuantiFERON). Restriction of the analysis to the six studies (n = 1745) with information on progression to active tuberculosis at the time of screening showed protection against infection of 27% (risk ratio 0.73, 0.61 to 0.87) compared with 71% (0.29, 0.15 to 0.58) against active tuberculosis. Among those infected, protection against progression to disease was 58% (0.42, 0.23 to 0.77). **Conclusions** BCG protects against M tuberculosis infection as well as progression from infection to disease.

Ryu YJ, Koh W-J, Daley CL. Diagnosis and treatment of nontuberculous mycobacterial lung disease: Clinicians' perspectives. Tuberculosis and Respiratory Diseases. 2016;79(2):74-84.

Nontuberculous mycobacteria (NTM) are emerging pathogens that affect both immunocompromised and immunocompetent patients. The incidence and prevalence of NTM lung disease are increasing worldwide and rapidly becoming a major public health problem. For the diagnosis of NTM lung disease, patients suspected to have NTM lung disease are required to meet all clinical and microbiologic criteria. The development of molecular methods allows the characterization of new species and NTM identification at a subspecies level. Even after the identification of NTM species from respiratory specimens, clinicians should consider the clinical significance of such findings. Besides the limited options, treatment is lengthy and varies by species, and therefore a challenge. Treatment may be complicated by potential toxicity with discouraging outcomes. The decision to start treatment for NTM lung disease is not easy and requires careful individualized analysis of risks and benefits. Clinicians should be alert to those unique aspects of NTM lung disease concerning diagnosis with advanced molecular methods and treatment with limited options. Current recommendations and recent advances for diagnosis and treatment of NTM lung disease are summarized in this article.

SAGE meeting of April 2014: Background documents. Session: Non-specific effects of vaccines on mortality in children under 5 years of age. Available at http://www.who.int/immunization/sage/meetings/2014/april/1_NSE_Backgroundpaper_final.pdf?ua=1 (Accessed January 2018).

No Abstract available.

Saroha M, Faridi MMA, Batra P, Kaur I, Dewan DK. Immunogenicity and safety of early vs delayed BCG vaccination in moderately preterm (31-33 weeks) infants. Human Vaccines & Immunotherapeutics. 2015;11(12):2864-71.

Minimum gestation at which infant can be given BCG (Bacillus Calmette-Guerin) vaccine safely

at birth is not clearly defined. Our objectives were the following: to compare Mantoux test after 6 months of BCG immunization in moderately preterm babies (31-33 weeks) vaccinated at birth and 34 weeks post conception age and to compare in above groups: (a) Interferon - gamma (IFN- γ) levels in BCG vaccinated infants who did not react to Mantoux test (b) Local BCG reaction at 6, 10, 14 weeks and 6 months (c) Complications of BCG vaccination. Interventional, randomized comparative trial. Moderately preterm infants (31-33 weeks), 90 in each group. At birth, 180 moderately preterm infants were recruited and randomly allocated into 2 groups. Two ml venous blood was drawn for estimation of IFN- γ levels. Infants were given BCG vaccine within 72 hours of birth and followed up after 2, 4, 6, 10, 14 weeks and 6 months (group 1). Infants were recruited at birth and held up till 34 weeks post conception age (group 2) and then given BCG vaccine and followed up similarly as group 1. At each visit, local BCG reaction, any local or unusual complication and anthropometric measurements were noted. At six months, Mantoux test was done and 2 ml venous blood sample was collected for IFN- γ levels post vaccination. Presence or absence of BCG local reaction, PPD conversion rates and complications were analyzed using Chi square or Fisher's exact test. IFN- γ levels were analyzed by ANOVA. In all 117 infants could be followed till 6 months after BCG immunization in 2 groups, and Mantoux test was positive in 38.4% of them. The rate of Mantoux test positivity was similar irrespective of the age of giving BCG immunization (group 1- 39.1% vs group 2- 37.5%; $p > 0.05$). IFN- γ levels were significantly raised at 6 months in 60% ($n = 21/41$) and 65% ($n = 15/27$) Mantoux negative infants in group 1 and group 2 respectively. The sequence and order of local BCG reaction at 2, 4, 6, 10, 14 weeks and 6 months was in the form of papule, pustule, ulcer, scab and scar. Scar was formed in 94.2% and 89.5% infants in group 1 and group 2 respectively. One infant in group 1 showed abortive reaction (0.85%). Only 3.4% of infants developed lymphadenopathy and was similar in both the groups. Moderately preterm infants (31-33 weeks) exhibited 98.3% immunogenicity after BCG immunization at birth and can be safely vaccinated without any risk of severe complications.

Schuring RP, Richardus JH, Pahan D, Oskam L. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. Vaccine. 2009;27(50):7125-8.

BCG vaccination and rifampicin chemoprophylaxis are both strategies for leprosy prevention. While the combined effect is unknown, the combination may give the desired push to halt leprosy transmission. Secondary analysis was done on results from a single centre, double blind, cluster randomized, and placebo-controlled trial. Individually, BCG (given at infancy) and rifampicin showed to protect against leprosy (57% [95% CI: 24-75%] and 58% [95% CI: 30-74%], respectively). The combined strategies showed a protective effect of 80% (95% CI: 50-92%). This is the first time that the additive effect of BCG and rifampicin are shown; the combined strategies can possibly lower leprosy incidence.

Sedaghatian MR, Kardouni K. Tuberculin response in preterm infants after BCG vaccination at birth. Archives Of Disease In Childhood. 1993;69(3):309-11.

A total of 101 preterm infants between 26 and 37 weeks' gestation who received BCG vaccination at birth were evaluated between two and four months after vaccination. Altogether 32% of these infants had no visible BCG scar. All infants were then tested with tuberculin purified protein derivative (PPD) but only 70 returned for the test to be read 48-72 hours later. The test was negative in 22 (31%) and there was an induration of ≤ 5 mm in another 26 (37%) of the infants. Of 22 infants with no BCG scar, 19 (86%) had an induration of ≤ 5 mm. In infants with a positive BCG scar a significantly higher number had an induration of PPD > 5 mm. There were no significant differences between the rate of scarring and tuberculin conversion in the infants born before or after 32 weeks' gestation. It is considered that routine BCG vaccination at birth on preterm infants is not indicated until a much larger study has been performed.

Sedaghatian MR et al. BCG vaccination and immune response in preterm infants: The role of gestational age. Emirates Med J 2009;27:25–28.

Aim: To evaluate and correlate the immune response of premature infants after BCG vaccination

Methods: Three groups of infants received BCG vaccination; preterm at birth, preterm when they reached chronological term, and term infants. All were evaluated for BCG scar, PPD induration and lymphocyte proliferation test (LTT) **Results:** Out of 254 vaccinated infants of different gestational ages, 113 returned for PPD and LTT, and of those, 98 returned for PPD reading.

Fifty-two preterm infants were vaccinated at birth, 29 were vaccinated when they reached at term, and 31 full-term vaccinated at birth: (a) There was a correlation between the BCG scar and both PPD>5mm indurations and LTT≥2 response. In contrast, no correlation was found between PPD indurations and LTT, (b) Birth weight and gestational age were significantly correlated with LTT response but neither correlated with BCG scar or PPD induration, (c) There was significant increase in response in (LTT) when preterms were vaccinated at ≥34 weeks gestational age (P=0.001) but this was not significantly correlated with PPD induration or positive BCG scar.

Conclusions: Our study indicates that delaying BCG vaccination in very low birth weight preterm infants until they reach 34 weeks gestational age may providesomewhat better protection. There was no correlation between PPD induration and LTT response. These two tests may measure two different dimensions of immune response. Additional longitudinal studies are needed to follow-up preterms after BCG vaccination to measure the duration of their immunity and indicate an age for revaccination.

Sepulveda RL, Parcha C, Sorensen RU. Case-control study of the efficacy of BCG immunization against pulmonary tuberculosis in young-adults in santiago, chile. Tubercle And Lung Disease. 1992;73(6):372-7.

We performed a case-control study of the efficacy of BCG immunization against pulmonary tuberculosis in 15- to 35-year-old Chilean patients born during a period when BCG coverage was incomplete. Our aims were to determine BCG efficacy against pulmonary tuberculosis in young adults, to determine if repeated BCG immunization increased its protective effect, and to determine factors that could explain the failure of BCG immunization in patients with tuberculosis. We studied 68 patients who had pulmonary tuberculosis based on positive AFB in at least 1 of 2 sputum smears, a positive confirmatory culture and compatible chest roentgenogram abnormalities. The control group were 188 individuals without pulmonary tuberculosis seeking medical care for other ailments. The percentage of non-immunized individuals was 13.2 among patients with tuberculosis and 12.2 among controls. The vaccine efficacy calculated from these data was 10%. There was no difference in the percentage of individuals with 1, 2 and 3 BCG scars between tuberculosis patients and controls. The number and percent of individuals exposed to tuberculosis among BCG-immunized and non-immunized tuberculosis patients and controls were similar. No significant differences between BCG-immunized and non-immunized individuals were detected in tuberculosis patients or in the control group. However, tuberculosis patients as a group had significantly lower weight, education level, employment rate and family income than controls. These observations suggest that the development of pulmonary tuberculosis in BCG-immunized young adults is favored by the presence of genetic and/or acquired predisposing factors capable of overriding protective immunity induced by BCG vaccination.

Soh SBL, Han PY, Tam KT, Yung CF, Liew WK, Tan NWH, et al. Investigations into an outbreak of suppurative lymphadenitis with BCG vaccine ssi (r) in singapore. VACCINE. 2014;32(44):5809-15.

Introduction From 2011 to 2012, we received an unexpectedly high number of reports of suppurative lymphadenitis following administration of a BCG vaccine used in our childhood

vaccination programme in Singapore. We sought to determine the local incidence rates of BCG-associated suppurative lymphadenitis across the 2009 to 2012 vaccinated cohorts, and to analyse the potential factors contributing to this outbreak. **Methods** Reports of lymphadenitis following BCG vaccination from an AEFI active surveillance system at the KK Women's and Children's Hospital (KKH) and passive surveillance data from other healthcare institutions were reviewed. All valid reports received from January 2009 to December 2013 involving neonates vaccinated with the BCG vaccine in 2009 to 2012 that met case definitions were included in our analysis. Details of the demographics and vaccination history of the child, and statistics from the local vaccination programme were also obtained. Potential contributory factors were selected for further investigation based on a literature review of similar outbreaks overseas. **Results** We identified 283 cases of lymphadenitis, of which 76% were suppurative. A spike in suppurative lymphadenitis cases was seen in the 2011 vaccinated cohort, with an incidence rate of 3.16 per 1000 vaccinees, as compared to 0.71 to 0.85 per 1000 in the 2009, 2010 and 2012 cohorts. Our investigations identified the likely cause of the outbreak to be batch-related, arising from manufacturing issues encountered by the manufacturer, after ruling out vaccine administration-related and host-related factors. **Conclusions** The three-fold spike in BCG-associated suppurative lymphadenitis cases observed in the 2011 vaccinated cohort, possibly due to batch-to-batch variation of the vaccine, highlights that manufacturing controls can continue to be a challenge. Development of a more sensitive assay to test the reactogenicity of the BCG vaccine may help reduce the occurrence of such outbreaks and improve public confidence in the nation's vaccination programme.

Stanley SJ, Howland C, Stone MM, Sutherland I. BCG vaccination of children against leprosy in Uganda: Final results. The Journal of Hygiene. 1981;87(2):233-48.

A total of 19 200 children, all contacts or relatives of known leprosy patients, and all free of visible leprosy lesions, were included in a controlled trial of BCG vaccination against leprosy in Uganda between 1960 and 1964. They were followed for an average of 8 years, during which time 261 developed early leprosy lesions. A less comprehensive follow-up was carried out for a further 5 years, when 8 more cases of leprosy were identified. In the main intake, between 1960 and 1962, 16 150 tuberculin-negative or weakly tuberculin-positive (Heaf Grades O-II) children were allocated by an effectively random process to either a BCG-vaccinated or an unvaccinated control group. Both groups were seen and examined in an identical fashion for leprosy at approximately 2-year intervals, and precautions were taken to ensure unbiased assessment of new cases of leprosy. After 8 years, 41 cases of leprosy had been identified in the BCG-vaccinated group, and 201 in the control group, a percentage reduction in the BCG-vaccinated group compared with the control group of 80%. The percentage reduction was similar for those initially tuberculin-negative, and for those initially weakly positive, and did not depend upon the age at vaccination. It was also similar for both sexes, for contacts of lepromatous and contacts of non-lepromatous leprosy, for children having contact with one or more than one patient, and for differing grades of physical contact and genetic relationship with a patient. The protective effect of BCG vaccination continued over the 8-year period, although it may have fallen off slightly at the end. In a group of 1074 strongly tuberculin-positive (Heaf Grades III-IV) children followed in parallel with the other two groups a total of 16 cases of leprosy were identified. When adjusted for age, this incidence is 58% lower than that in the unvaccinated control children who were initially tuberculin-negative, indicating a protective effect against leprosy of naturally-acquired strong tuberculin sensitivity. Between 1970 and 1975, one new case of leprosy was identified in a child who had initially been strongly tuberculin-positive and had therefore not been vaccinated, one in a BCG-vaccinated child, and 6 in control children. Although the follow-up in this period was less comprehensive than that in the main part of the trial, the ascertainment of cases was unlikely to have been biased towards either vaccinated or control children. These results indicate a continuing protective effect of BCG up to 12-13 years

after vaccination.

Tala-Heikkilä MM, Tuominen JE, Tala EOJ. Bacillus calmette-guerin revaccination questionable with low tuberculosis incidence. American Journal Of Respiratory And Critical Care Medicine. 1998;157(4):1324-7.

Bacillus Calmette-Guerin (BCG) revaccination was discontinued in Finland in 1990. The objective of this study was to assess the impact of BCG revaccination of tuberculin-negative school-children in prevention of tuberculosis. The tuberculosis cases in 1990-1995 were calculated among age cohorts born 1979-1984 and no longer covered by the BCG revaccination program. Corresponding data were collected for comparison from the period of revaccination in 1980-1985 among age cohorts born in 1969-1974. The National Tuberculosis Register was reviewed in order to observe the tuberculosis trend since 1980 in the age groups of 10-14 and 15-19 yr. Three cases of tuberculosis have been registered among non-BCG-revaccinated children during 6 yr after discontinuation of the program, i.e., 2.23 cases (95% CI 0.72 to 6.90) per million person yr. The control group revealed five cases, 3.78 (95% CI 1.57 to 9.07) per million person yr. The relative risk of tuberculosis in non-BCG-revaccinated children is 0.59 (95% CI 0.14 to 2.47) compared with the control group. The incidence of tuberculosis has continued to decline among adolescents since 1980. The follow-up data confirm that the cessation of BCG revaccination program had no effect on the continuing overall decline of tuberculosis in Finland. The efficacy of BCG revaccination seems to be low or nonexistent in countries with low tuberculosis incidence.

Talbot EA, Perkins MD, Sandra Fagundes MS, Frothingham R. Disseminated bacille calmette-guérin disease after vaccination: Case report and review. Clinical Infectious Diseases. 1997;24(6):1139-46.

The attenuated bacille Calmette Guérin (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 coinfecting 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.

Thayyil-Sudhan S, Kumar A, Singh M, Paul VK, Deorari AK. Safety and effectiveness of BCG vaccination in preterm babies. Archives of disease in childhood Fetal and neonatal edition. 1999;81(1):F64-F6.

Aim To assess the cell mediated immune response to BCG vaccine in preterm babies. **Methods** Sixty two consecutive preterm babies born at < 35 weeks of gestation were randomly allocated into two groups. Babies in group A were vaccinated early at 34-35 weeks and group B were vaccinated late at 38-40 weeks of postconceptional age. The two groups were similar in terms of: gestational age (mean (SD) 33.1 (1.1) and 33 (1.2) weeks, respectively); birthweight 1583 (204) and 1546 (218) g; neonatal problems; socioeconomic status; and postnatal weight gain. The cell mediated immune response to BCG was assessed using the Mantoux test and the lymphocyte migration inhibition test (LMIT) 6-8 weeks after BCG vaccination. Induration of >5 mm after the

Mantoux test was taken as a positive response. **Results** There was no significant difference in the tuberculin conversion rates (80% and 80.7%, respectively), positive LMIT (86.6% and 90.3%, respectively), or BCG scar (90.0% and 87.1%, respectively) among the two groups.

Conclusions Prematurity seems to be an unlikely cause for poor vaccine uptake. Preterm babies can be effectively vaccinated with BCG at 34-35 weeks of postconceptional age, the normal time of discharge in a developing country.

Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural history of tuberculosis: Duration and fatality of untreated pulmonary tuberculosis in hiv negative patients: A systematic review. PLoS One. 2011;6(4):e17601.

Background: The prognosis, specifically the case fatality and duration, of untreated tuberculosis is important as many patients are not correctly diagnosed and therefore receive inadequate or no treatment. Furthermore, duration and case fatality of tuberculosis are key parameters in interpreting epidemiological data. **Methodology And Principal Findings:** To estimate the duration and case fatality of untreated pulmonary tuberculosis in HIV negative patients we reviewed studies from the pre-chemotherapy era. Untreated smear-positive tuberculosis among HIV negative individuals has a 10-year case fatality variously reported between 53% and 86%, with a weighted mean of 70%. Ten-year case fatality of culture-positive smear-negative tuberculosis was nowhere reported directly but can be indirectly estimated to be approximately 20%. The duration of tuberculosis from onset to cure or death is approximately 3 years and appears to be similar for smear-positive and smear-negative tuberculosis. **Conclusions:** Current models of untreated tuberculosis that assume a total duration of 2 years until self-cure or death underestimate the duration of disease by about one year, but their case fatality estimates of 70% for smear-positive and 20% for culture-positive smear-negative tuberculosis appear to be satisfactory.

Tripathy SP. The case for B.C.G. Annals of the National Academy of Medical Sciences (India). 1983;19(1):11.

A large BCG trial was undertaken by the Indian Council of Medical Research with the assistance of the World Health Organization and the US Public Health Service in Chingleput district in an effort to obtain reliable evidence of the efficacy of BCG in providing protection against tuberculosis and to investigate if there are differences between strains of BCG in their efficacy, if the vaccinating dose influenced the protective effect and whether nonspecific sensitivity interfered with the protective effect of BCG. A Leprosy Prevention Trial was superimposed on this study to determine if BCG provided protection against leprosy. The entire population of the Chingleput district -- about 360,000 persons -- was included in the trial. 2 BCG strains -- Danish and French -- were used to vaccinate randomly 2/3 of the population; the remaining 1/3 was administered a placebo injection. The vaccine was administered either in a normal dose of 0.1 mg or a lower dose of 0.01 mg, again by random allocation. The study design included an initial survey of prevalence of infection and disease and subsequent surveys at 2 1/2 year intervals to determine the incidence of tuberculosis in the vaccinated and control subjects. Approximately 270,000 subjects were vaccinated, of which about 1/3 were uninfected initially. These subjects formed the population for analysis of the protective effect of BCG. There were only 285 cases of tuberculosis within a 12-1/2 year period among 90,000 subjects, comprising about 1/5 of the expected incidence on the basis of a prevalence of 10.7 culture-positive cases/1000 subjects. There were at least as many cases of tuberculosis in each of the vaccinated groups -- 93 and 99 -- as in the placebo group -- 93, demonstrating that BCG vaccination either in a dose of 0.1 mg or 0.01 mg failed to protect against the development of bacteriologically positive pulmonary tuberculosis. Detailed analyses indicate that BCG most likely provided some protection. There was clear evidence of the presence of environmental mycobacteria, which caused sensitization and thus could detract from the possible beneficial effect from BCG by preempting BCG. Such

an effect, even if it had occurred, could not account for the total absence of the protective effect of BCG. There was a 3% incidence of infection as assessed by tuberculin conversions among those subjects initially tuberculin-negative. The BCG protection provided at least 30% protection against leprosy in the vaccinated subjects.

Trnka L, Danková D, Svandová E. Six years' experience with the discontinuation of BCG vaccination. 4. Protective effect of BCG vaccination against the mycobacterium avium intracellulare complex. Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1994;75(5):348.

In 1986, mass BCG vaccination of newborns was discontinued in an extensive territorial sample of neonates in the Czech Republic (30,000 infants annually). The non-vaccinated children have since been tuberculin tested at two-year intervals; those with continual or repeated intensive contact with animals in households or on farms were also tested with *Mycobacterium avium* intracellulare complex sensitin in addition to tuberculin. Within the frame work of the surveillance programme the incidence of infection and disease caused by *M. avium* intracellulare complex (*M. avium* complex) was evaluated and the protective effect of BCG vaccination analysed. In 1986-93, out of 190,874 non-vaccinated children, 36 were found to be infected by *M. avium* complex; 27 of them developed disease, i.e. mycobacteriosis other than tuberculosis (MOTT). The annual risk of infection with *M. avium* complex was 4.8/100,000 children per year, of whom 3.6/100,000 developed mycobacteriosis. 24 patients suffered from swelling of cervical lymph nodes, 2 of mediastinal lymph nodes and one child had the disease localized both in cervical and mediastinal lymph nodes. The disease was verified bacteriologically in 9 children. Most of the diseased children had impaired immunity; a marked skin reactivity of *M. avium* complex sensitin was present in all infected children. Animal sources infected by *M. avium* complex were detected in 5 cases. Another 14 children also had close contact with animals but without proven *M. avium* complex infection. In non-BCG vaccinated children the incidence of lymphadenitis caused by *M. avium* complex was considerably higher than in vaccinated children. BCG cells possess antigenic determinants which confer protective immunity probably both against *M. tuberculosis* and against *M. avium* complex infections. It may thus be assumed that BCG vaccination protects both against pathogenic tubercle bacilli and *M. avium* complex. This should be taken into consideration before recommending discontinuation of mass BCG vaccination of newborns in areas with a high prevalence of *M. avium* complex infection.

Trunz BB, Fine PEM, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: A meta-analysis and assessment of cost-effectiveness. The Lancet. 2006;367(9517):1173-80.

BCG vaccine has shown consistently high efficacy against childhood tuberculous meningitis and miliary tuberculosis, but variable efficacy against adult pulmonary tuberculosis and other mycobacterial diseases. We assess and compare the costs and effects of BCG as an intervention against severe childhood tuberculosis in different regions of the world. We calculated the number of tuberculous meningitis and miliary tuberculosis cases that have been and will be prevented in all children born in 2002, by combining estimates of the annual risk of tuberculosis infection, the proportion of infections that lead to either of these diseases in unvaccinated children, the number of children vaccinated, and BCG efficacy. We estimated that the 100.5 million BCG vaccinations given to infants in 2002 will have prevented 29,729 cases of tuberculous meningitis (5th-95th centiles, 24,063-36,192) in children during their first 5 years of life, or one case for every 3435 vaccinations (2771-4177), and 11,486 cases of miliary tuberculosis (7304-16,280), or one case for every 9314 vaccinations (6172-13,729). The numbers of cases prevented would be highest in South East Asia (46%), sub-Saharan Africa (27%), the western Pacific region (15%), and where the risk of tuberculosis infection and vaccine coverage are also highest. At US2-3 dollars per dose, BCG vaccination costs US206 dollars

(150-272) per year of healthy life gained. BCG vaccination is a highly cost-effective intervention against severe childhood tuberculosis; it should be retained in high-incidence countries as a strategy to supplement the chemotherapy of active tuberculosis.

Tu HA, Vu HD, Rozenbaum MH, Woerdenbag HJ, Postma MJ. A review of the literature on the economics of vaccination against tb. Expert review of vaccines. 2012;11(3):303-17.

The BCG vaccine was introduced in 1921 and remains the only licensed vaccine for the prevention of TB worldwide. Despite its extensive use, the BCG vaccine lacks the ability to fully control the TB-endemic and -pandemic situations. The BCG vaccine is most effective in preventing pediatric TB, in particular, miliary TB and tuberculous meningitis. However, it has a limited effect in preventing pulmonary TB, which occurs more frequently in adults. BCG vaccination has now been implemented in more than 157 countries worldwide. For various countries, the benefits of vaccination are only limited and potentially not cost effective. The International Union Against Tuberculosis and Lung Diseases had set the criteria for discontinuation of BCG vaccination in 1994. This decision, however, was not based on economic considerations. Many developed countries have met the criteria set by the International Union Against Tuberculosis and Lung Disease and stopped universal BCG vaccination. For developing countries, the BCG vaccine is still an effective intervention in protecting young children from TB infection. A lot of effort has been spent on R&D of new TB vaccines, the first of which are expected to be available within 5-7 years from now. Novel TB vaccines are expected to be better and more effective than the current BCG vaccine and should provide a viable strategy in controlling TB morbidity and mortality. In this review, the aim is to explore economic evaluations that have been carried out for vaccination against TB worldwide. In addition to epidemiological evidence, economic evidence can play a crucial role in supporting the governments of countries in making proper public health decisions on BCG vaccination policies, in particular, to implement, continue, or discontinue.

van Ingen J. Diagnosis of nontuberculous mycobacterial infections preface. Seminars In Respiratory And Critical Care Medicine. 2013;34(1):103-9.

The nontuberculous mycobacteria (NTM) are typically environmental organisms residing in soil and water. Although generally of low pathogenicity to humans, NTM can cause a wide array of clinical diseases; pulmonary disease is most frequent, followed by lymphadenitis in children, skin disease by *M. marinum* (particularly in fish tank fanciers), and other extrapulmonary or disseminated infections in severely immunocompromised patients. Of the > 140 NTM species reported in the literature, 25 species have been strongly associated with NTM diseases; the remainder are environmental organisms rarely encountered in clinical samples. Correct species identification is very important because NTM species differ in their clinical relevance. Further, NTM differ strongly in their growth rate, temperature tolerance, and drug susceptibility. The diagnosis of NTM disease is complex and requires good communication between clinicians, radiologists, and microbiologists. Isolation of *M. kansasii* and (in northwestern Europe) *M. malmoense* from pulmonary specimens usually indicates disease, whereas *Mycobacterium gordonae* and, to a lesser extent, *M. simiae* or *M. chelonae* are typically contaminants rather than causative agents of true disease. *Mycobacterium avium* complex (MAC), *M. xenopi*, and *M. abscessus* form an intermediate category between these two extremes. This review covers the clinical and laboratory diagnosis of NTM diseases and particularities for the different disease types and patient populations. Because of limited sensitivity and specificity of symptoms, radiology, and direct microscopy of clinical samples, culture remains the gold standard. Yet culture is time consuming and demands the use of multiple media types and incubation temperatures to optimize the yield. Outside of reference centers, such elaborate culture algorithms are scarce.

Walker SL, Lockwood DNJ. The clinical and immunological features of leprosy. British Medical Bulletin. 2006;77-78(1):103-21.

Leprosy is a granulomatous disease affecting the skin and nerves caused by *Mycobacterium leprae*. It continues to be a significant public health problem. Multidrug therapy (MDT) cures the infection, but immunological reactions may occur and neuropathy may lead to disability and deformity. It is important that the manifestations of the condition are recognized as early as possible so that early nerve damage can be identified and treated rapidly.

WER No. 4, 2004, pp. 27–38.

No abstract available.

WER No.21, 2007, pp. 181–196.

No abstract available.

WER 35, 2017, pp. 501–520.

No abstract available.

WER No.89, 2014, pp.221–236.

No abstract available.

WER No.92, 2017, pp.301–320.

No abstract available.

WHO. Buruli ulcer - Diagnosis of *Mycobacterium ulcerans* disease. Updated 2018. Available at <http://www.who.int/buruli/information/diagnosis/en/> (Accessed October 2017).

This manual is to assist health care providers and laboratory scientists to diagnose *Mycobacterium ulcerans* disease (Buruli ulcer). The manual aims to achieve a better understanding of the clinical presentation and its diagnosis. The methods described are tailored to various levels of care and available resources to improve the diagnosis and surveillance of the disease.

WHO. BCG Working Group Report, SAGE meeting October 2017. 2017. Available at http://www.who.int/entity/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf?ua=1 (Accessed October 2017).

No abstract available.

WHO. Compendium of WHO guidelines and associated standards: ensuring optimum delivery of the cascade of care for patients with tuberculosis. 2017. Available at <http://www.who.int/iris/handle/10665/259180> (Accessed November 2017).

Forward: Ending the tuberculosis (TB) epidemic requires speedy adoption and implementation of the World

Health Organization (WHO) End TB Strategy as the mean to reach the ambitious targets set within the Strategy and the Sustainable Development Goal framework. This requires full clarity about the best standards of prevention, diagnosis, treatment and significantly enhanced resources, both human and financial.

Beyond implementation of existing tools, an effective TB response must embrace innovation through the rapid uptake of new diagnostics, medicines, and digital platforms to modernize care provision. Working with communities, civil society and any partners, governments need to

assume full responsibility for ensuring access to person-centred, modern, high-quality TB services, regardless of whether care is sought from public, voluntary, private or corporate care providers. Securing comprehensive care along with essential support for each person with TB also calls for collaboration within and beyond the health sector.

After decades of stagnation, finally new diagnostics, drugs and regimens have become available through intensified research efforts and increased field experiences. This has engendered a growing need for expert guidance to the point that the production of guidelines and policy recommendations risks resulting in limited understanding if not seen in a comprehensive and coherent fashion. This document, therefore, has been conceived to provide a general overview of all recommendations made by WHO in the past few years. It incorporates all recent policy guidance from WHO's Global TB Programme; follows the care pathway of persons with signs or symptoms of TB in seeking diagnosis, treatment and care; and it includes those cross-cutting elements that are essential to a patient-centred approach to care delivery. The document, structured in 33 WHO TB standards, is designed to consolidate all WHO TB policy recommendations into a single resource, with internet links to all additional details contained in comprehensive guidelines.

By producing the Compendium, we hope to offer a clear concise instrument that will facilitate the understanding and planning of delivery of the standards for the care of everybody affected by tuberculosis. The document will be regularly updated, including in its digital format, to allow incorporation of all new evidence that will emerge out of the development pipeline in the years to come.

WHO. Definition of birth weight : Low birth weight: <2500 g ; Very low birth weight : <1500 g ; Extremely low birth weight : <1000 g. Available at <http://www.who.int/whosis/whostat2006NewbornsLowBirthWeight.pdf> (Accessed November 2017).

No abstract available.

WHO. Definition of preterm birth: Moderate to late preterm: 32 to <37 weeks; Very preterm: 28 to <32 weeks; Extremely preterm: <28 weeks. Updated November 2017. Available at <http://www.who.int/mediacentre/factsheets/fs363/en/> (Accessed November 2017).

No abstract available.

WHO. Evidence to recommendation table: BCG efficacy against leprosy. Available at http://www.who.int/entity/immunization/policy/position_papers/bcg_efficacy_leprosy.pdf (Accessed January 2018).

No abstract available.

WHO. Evidence to recommendation table: BCG efficacy against TB. Available at http://www.who.int/entity/immunization/policy/position_papers/bcg_efficacy_tb.pdf (Accessed January 2018).

No abstract available.

WHO. Evidence to recommendation table: BCG vaccination in HIV-infected. Available at http://www.who.int/entity/immunization/policy/position_papers/bcg_evidence_recommendation_table_hiv.pdf (Accessed January 2018).

No abstract available.

WHO. Evidence to recommendation table: Need for revaccination. Available at http://www.who.int/entity/immunization/policy/position_papers/bcg_evidence_recommendation_table_revaccination.pdf (Accessed January 2018).

No abstract available.

WHO. Evidence to recommendation table: Selective vaccination. Available at http://www.who.int/entity/immunization/policy/position_papers/bcg_evidence_recommendation_table_selective_vaccination.pdf (Accessed January 2018).

No abstract available.

WHO. Fact Sheet Buruli ulcer. Updated 2018. Available at <http://www.who.int/buruli/en/> (Accessed October 2017).

No abstract available.

World Health Organization (WHO). Global Leprosy Strategy 2016-2020-Accelerating towards a leprosy free world. 2016. Available at http://apps.who.int/iris/bitstream/10665/208824/1/9789290225096_Eng.pdf?ua=1 (Accessed October 2017).

The “Global Leprosy Strategy 2016–2020, Accelerating towards a leprosy-free world”, was officially launched on 20 April 2016. Its overall goal is to further reduce the burden of leprosy while providing more comprehensive and timely care following the principles of equity and social justice. The purpose of this Operational Manual is to provide guidance for managers of national leprosy programmes (or equivalent entities) to adapt and implement the Global Leprosy Strategy in their own countries. It follows the structure of the global strategy, providing a list of suggested actions under each of the three strategic pillars: i) strengthen government ownership and partnerships; ii) stop leprosy and its complications; and iii) stop discrimination and promote inclusion. Adapting the suggested actions to national contexts will help countries to reach the global targets set for the year 2020. The Operational Manual has been developed by the World Health Organization with inputs from various core stakeholders such as national programme managers, technical agencies, funding agencies and nongovernmental organizations.

WHO. Global TB Report 2017. 2017. Available at http://www.who.int/tb/publications/global_report/en/ (Accessed November 2017).

The purpose of WHO’s Global Tuberculosis Report is to provide a comprehensive and up-to-date assessment of the TB epidemic and of progress in care and prevention at global, regional and country levels. This is done in the context of recommended global TB strategies and associated targets, and broader development goals. For the period 2016–2035, these are WHO’s End TB Strategy and the United Nations’ (UN) Sustainable Development Goals (SDGs), which share a common aim: to end the global TB epidemic.

Specific targets set in the End TB Strategy include a 90% reduction in TB deaths and an 80% reduction in TB incidence (new cases per year) by 2030, compared with 2015. Achieving these targets requires provision of TB care and prevention within the broader context of universal health coverage, multisectoral action to address the social and economic determinants and consequences of TB, and technological breakthroughs by 2025 so that incidence can fall faster than rates achieved historically. Overall, the latest picture is one of a still high burden of disease, and progress that is not fast enough to reach targets or to make major headway in closing persistent gaps.

TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among

HIV-negative people (down from 1.7 million in 2000) and an additional 374 000 deaths among HIV-positive people. An estimated 10.4 million people fell ill with TB in 2016: 90% were adults, 65% were male, 10% were people living with HIV (74% in Africa) and 56% were in five countries: India, Indonesia, China, the Philippines and Pakistan.

Drug-resistant TB is a continuing threat. In 2016, there were 600 000 new cases with resistance to rifampicin (RRTB), the most effective first-line drug, of which 490 000 had multidrug-resistant TB (MDR-TB).⁴ Almost half (47%) of these cases were in India, China and the Russian Federation.

Globally, the TB mortality rate is falling at about 3% per year. TB incidence is falling at about 2% per year and 16% of TB cases die from the disease; by 2020, these figures need to improve to 4–5% per year and 10%, respectively, to reach the first (2020) milestones of the End TB Strategy.

Most deaths from TB could be prevented with early diagnosis and appropriate treatment. Millions of people are diagnosed and successfully treated for TB each year, averting millions of deaths (53 million 2000–2016), but there are still large gaps in detection and treatment.

In 2016, 6.3 million new cases of TB were reported (up from 6.1 million in 2015), equivalent to 61% of the estimated incidence of 10.4 million; the latest treatment outcome data show a global treatment success rate of 83%, similar to recent years. There were 476 774 reported cases of HIV-positive TB (46% of the estimated incidence), of whom 85% were on antiretroviral therapy (ART). A total of 129 689 people were started on treatment for drug-resistant TB, a small increase from 125 629 in 2015 but only 22% of the estimated incidence; treatment success remains low, at 54% globally.

Making large inroads into these gaps requires progress in a particular subset of high TB burden countries. Ten countries accounted for 76% of the total gap between TB incidence and reported cases; the top three were India (25%), Indonesia (16%) and Nigeria (8%). Ten countries accounted for 75% of the incidence-treatment enrolment gap for drug-resistant TB; India and China accounted for 39% of the global gap. Most of the gaps related to HIV-associated TB were in the WHO African Region.

TB preventive treatment is expanding, especially in the two priority risk groups of people living with HIV and children under 5. However, most people eligible for TB preventive treatment are not accessing it.

Financing for TB care and prevention has been increasing for more than 10 years, but funding gaps still exist (US\$ 2.3 billion in 2017). Total health spending also falls short of the resources needed to achieve universal health coverage. Closing these gaps requires more resources from both domestic sources (especially in middle-income countries) and international donors (especially in low-income countries).

Broader influences on the TB epidemic include levels of poverty, HIV infection, undernutrition and smoking. Most high TB burden countries have major challenges ahead to reach SDG targets related to these and other determinants. The pipelines for new diagnostics, drugs, treatment regimens and vaccines are progressing, but slowly. Increased investment in research and development is needed for there to be any chance of achieving the technological breakthroughs needed by 2025. The WHO Global Ministerial Conference on ending TB in the SDG era in November 2017 and the first UN General Assembly high-level meeting on TB in 2018 provide a historic opportunity to galvanize the political commitment needed to step up the battle against TB and put the world and individual countries on the path to ending the TB epidemic.

World Health Organization. Guidance for national TB programmes on the management of tuberculosis in children: second edition. 2014. Available at <http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf> (Accessed December 2017).

Executive Summary: Important recent changes or additions to guidelines for the management of tuberculosis (TB) in children have made it necessary to revise the first edition of Guidance for national tuberculosis programmes on the management of tuberculosis in children, published by WHO in 2006. Like the 2006 guidance, this document is targeted at national TB programmes, paediatricians and other health workers in low- and middle-income countries; it does not aim to outline recommendations for high-income countries with low TB prevalence. This distinction is especially important in the diagnostic approach and in contact investigation. Current and consistent guidance is important in the development and implementation of policy and practice for improving the management of children with TB and of children living in families with TB. Children are increasingly recognized as important in the widening global Stop TB Strategy, launched in 2006, revised in 2012 and now being revised for beyond 2015. This summary lists the recommendations of the second edition of the guidance and highlights the key changes since the 2006 (first) edition (labelled as “new” in the summary of recommendations below). The chapters that follow the summary provide comprehensive details on the WHO-recommended approaches to prevention, diagnosis and treatment. Updated literature searches were performed and new data were integrated with the existing evidence for all recommendations. During the development of this guidance, the Panel made strong recommendations, based on low or very low quality of evidence given that children are rarely included in TB clinical trials and experience disproportionate suffering as a result of limited detection and treatment. Despite the limited evidence showing a direct benefit to children, the Panel felt confident that existing clinical data from adults could be safely extrapolated to children, and that the individual and public health benefit of treating children with TB far outweigh any potential negative consequences. Panel considerations and decisions for each individual recommendation are included in Annex 1.

WHO. Guidelines for Leprosy treatment, 2018. (Under publication).
No abstract available.

WHO. Guidelines for treatment of drug-susceptible tuberculosis and patient care . Updated 2017. Available at http://www.who.int/tb/publications/2017/dstb_guidance_2017/en/ (Accessed October 2017).

The WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update) contains policy recommendations on priority areas in the treatment of drug-susceptible TB and patient care. The main highlights of the guidelines are:

The category II regimen is no longer recommended for patients who require TB retreatment and drug-susceptibility testing should be conducted to inform the choice of treatment regimen;

The use of adjuvant steroids is recommended in the treatment of tuberculous meningitis and pericarditis;

Recommendations on the provision of individual or a package of interventions on patient care and support, including patient or staff education, material support, psychological support, and tracers;

Recommendations on the use of digital health interventions such as SM or phone call as an tracer option), medication monitor, and video observed treatment (VOT – as a replacement for in-person directly observed treatment - DOT) when conditions of technology and operation allow;

Recommendations on the effective treatment administration options: community or home-based DOT, and DOT administered by trained lay providers or health-care workers; and

Decentralized model of care is recommended over centralized model for patients on MDR-TB treatment.

WHO. Policy statement: Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries. 2011. Available at:

http://apps.who.int/iris/bitstream/10665/44759/1/9789241502672_eng.pdf?ua=1&ua=1
(Accessed October 2017).

Research over the past decade has resulted in the development of two commercial interferon-gamma release assays (IGRAs), based on the principle that the T-cells of individuals who have acquired TB infection respond to re-stimulation with Mycobacterium tuberculosis-specific antigens by secreting interferon gamma (IFN- γ). The QuantiFERON-TB Gold (QFT-G, Cellestis, Australia) and the newer generation QuantiFERON-TB Gold In-Tube (QFT-GIT, Cellestis, Australia) are whole-blood based enzyme-linked immunosorbent assays (ELISAs) measuring the amount of IFN- γ produced in response to three M. tuberculosis antigens (QFT-G:ESAT-6 and CFP-10; QFT-GIT: ESAT-6, CFP-10 and TB7.7). In contrast, the enzyme-linked immunospot (ELISPOT)-based T-SPOT.TB (Oxford Immunotec, UK) measures the number of peripheral mononuclear cells that produce INF- γ after stimulation with ESAT-6 and CFP-10. Commercial IGRAs are FDA-approved as indirect and adjunct tests for TB infection, in conjunction with risk assessment, radiography and other medical and diagnostic evaluations. In recent years, IGRAs have become widely endorsed in high-income countries for diagnosis of latent TB infection (LTBI) and several guidelines (albeit equivocal) on their use have been issued. Currently, there are no guidelines for IGRA use in low- and middle-income countries - typically with high TB- and/or HIVburden - yet IGRAs are being marketed and promoted, especially in the private sector.

The majority of IGRA studies have been performed in high-income countries and mere extrapolation to low- and middle-income settings with high background TB infection rates is not appropriate. Systematic reviews have suggested that IGRA performance differs in high- versus low TB and HIV incidence settings, with relatively lower sensitivity in high-burden settings. The WHO Stop TB Department (WHO-STB) therefore commissioned systematic reviews on the use of IGRAs in low- and middle-income countries, in pre-defined target groups, with funding support from the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and TREAT-TB/The Union. The target groups and major findings of the GRADE evidence synthesis process are summarised below.

This Policy Statement applies to the use of commercial IGRAs in low- and middle-income countries only. Several international guidelines on IGRA use in high-income countries are available. This Policy Statement is not intended to apply to high-income countries or to supersede their national guidelines.

WHO. Prequalified Vaccines. Updated 2017. Available at:

https://extranet.who.int/gavi/PQ_Web/ (Accessed October 2017).

No abstract available.

WHO. Recommendations to assure the quality, safety and efficacy of BCG vaccines. 2013.

Available at: http://who.int/biologicals/areas/vaccines/TRS_979_Annex_3.pdf?ua=1
(Accessed October 2017).

Introduction: The last revision of the Requirements for dried bacille Calmette–Guérin (BCG) vaccine for human use was in 1985, and an amendment which updated the section on the expiry date was published in 1988 (1, 2). Recent WHO consultation meetings (3–6) have addressed issues concerning the improvement of vaccine characterization and quality control assays of BCG vaccine to reflect current state-of-the-art technology. In addition, a recommendation to replace the International Reference Preparation for BCG vaccine by substrain-specific

Reference Reagents evaluated by collaborative studies has been proposed. This document provides: recommendations for the production and control of BCG vaccines (Part A); guidelines for nonclinical evaluation (Part B); guidelines for the content of the clinical development programme applicable to BCG vaccines (Part C); and recommendations for NRAs (Part D). The guidelines for nonclinical evaluation apply to classic BCG vaccine products that are still in need of such evaluation, including newly manufactured products requiring clinical trial studies or those produced following changes in the manufacturing process. The clinical part of this document aims to provide a basis for assessment of efficacy and safety of BCG vaccines in pre-licensing clinical trials as well as in post-marketing surveillance, monitoring consistency of production and clinical testing of new classic BCG vaccine products. If important changes have been introduced to an authorized production process, the need for preclinical and clinical testing should be considered on a case-by-case basis in consultation with the NRA(s) concerned.

WHO. Role of specific antibiotics in *Mycobacterium ulcerans* (Buruli ulcer) management. Updated 2018. Available at <http://www.who.int/buruli/information/antibiotics/en/> (Accessed October 2017).

Background: Buruli ulcer, a disease caused by *Mycobacterium ulcerans*, is largely a problem of the poor in remote rural areas and, since 1980 has emerged as an important cause of human suffering. After tuberculosis (TB) and leprosy, Buruli ulcer is the third most common mycobacterial disease. In May 2004, the Fiftyseventh World Health Assembly adopted a resolution on Buruli ulcer which called for intensified research to develop tools to diagnose, treat and prevent the disease (1).

MacCallum et al. were the first to describe *M. ulcerans* in Australia in 1948 (2). The term Buruli ulcer came from Buruli county in Uganda where large numbers of cases were described in the 1960s (3). The condition has been reported or suspected in more than 30 countries worldwide, mainly in tropical and subtropical regions, and the numbers of reported cases are growing. Africa is the worst affected region (4). Other important foci are in Australia (5, 6), French Guiana (7) and Papua New Guinea (8, 9).

More than 50% of those affected are children under the age of 15 years who live in remote rural areas and have little or no access to health services (10, 11). About 90% of patients in Africa present too late, with extensive lesions that cause severe disabilities (12). Mortality is low but disability is high: a recent study estimated that 66% of those with healed lesions have disabilities (13). The median age of this group was 12 years.

Until recently, surgery often involving extensive excision, with or without skin grafting, was the only available treatment. However, because of inadequate surgical capacities in most affected areas of endemic developing countries, access to surgery has been very limited; moreover, where such capacities are available, the cost of surgery is far beyond the means of most of those severely affected (10). In addition, because of the need for prolonged hospitalization – averaging at least three months – limited bed capacity in hospitals where surgical treatment is possible further reduces the number of patients who can be admitted and treated. Recurrence rates after surgical treatment are variable and depend upon the experience of the doctor and the severity of the disease. In a one-year follow-up after excision of small early lesions in the Amansie West district of Ghana, Amofah et al. (14) estimated a 16% recurrence rate. Others have reported recurrence rates of 28%, mainly among late severe cases (11, 15).

Recurrences cause additional human suffering, inflate treatment costs and often frustrate successful management of the disease (16). In view of these difficulties, the need to develop drug treatment has been one of the major research priorities of the World Health Organization (WHO) since the establishment of the Buruli Ulcer Initiative in 1998 (17, 18).

WHO. The End TB Strategy. 2015. Available at: <http://www.who.int/tb/strategy/end-tb/en/> (Accessed October 2017).

No abstract available.

WHO. Treatment of drug-resistant TB: Resources. 2016. Available at <http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/> (Accessed October 2017).

The WHO treatment guidelines for drug-resistant tuberculosis (2016 update) contains policy recommendations on priority areas in the treatment of drug-resistant tuberculosis. The revision is in accordance with the WHO requirements for the formulation of evidence-informed policy.

The main novelties of the 2016 WHO guidelines are:

- a shorter MDR-TB treatment regimen is recommended under specific conditions;
- medicines used in the design of conventional MDR-TB treatment regimens are now reclassified to reflect updates in the evidence on their effectiveness and safety;
- specific recommendations are made on the treatment of children with rifampicin-resistant or MDR-TB based on a first-ever individual patient data meta-analysis;
- recommendations on the role of surgery in MDR-TB case management are included.

WHO. Updated and Consolidated Guidelines on the Programmatic Management of Latent Tuberculosis Infection, 2018. [In press]

No abstract available.

WHO. V3P database (Data 2017). Available at http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/en/ (Accessed November 2017).

No abstract available.

Zimmermann P et al. Does BCG vaccination protect against non-tuberculous mycobacterial infection? A systematic review and meta-analysis. 2017, personal communication (Department of Paediatrics, The University of Melbourne, Parkville, Australia).

No abstract available.

Yung CF. Non-specific effects of childhood vaccines. BMJ. 2016;355:i5434.

No Abstract Available.