

Report on BCG vaccine use for protection against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections

Prepared by the SAGE Working Group on BCG Vaccines and WHO Secretariat

22. September 2017

List of abbreviations

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| AFR. <i>african region</i> | MDR-TB. <i>multidrug-resistant TB</i> |
| AMR. <i>antimicrobial resistances</i> | MDT. <i>multi-drug therapy, multidrug therapy</i> |
| BCG. <i>bacillus calmette-guérin</i> | MICs. <i>middle income countries</i> |
| BUD. <i>buruli ulcera disease</i> | MICS. <i>multiple indicator cluster surveys</i> |
| CFU. <i>colony forming units</i> | MOTT. <i>mycobacteria other than tuberculosis</i> |
| DHS. <i>demographic health surveys</i> | NRA. <i>national regulatory authority</i> |
| DRDR. <i>drug resistance determining regions</i> | NS. <i>needle and syringe</i> |
| DSJI. <i>disposable-syringe jet injectors</i> | NTM. <i>non-tuberculous mycobacterial</i> |
| DST. <i>drug susceptibility testing</i> | OPV. <i>oral polio vaccine</i> |
| EID. <i>early infant HIV diagnosis</i> | PB. <i>pauci-bacillary</i> |
| EMR. <i>eastern mediterranean region</i> | PEP. <i>post-exposure prophylaxis</i> |
| EUR. <i>european region</i> | PMTCT. <i>prevention of mother to child transmission</i> |
| G2D. <i>grade-2 disabilities</i> | POC. <i>point-of-care</i> |
| GLP. <i>global leprosy programm</i> | PQ'd. <i>prequalified</i> |
| GTB. <i>global TB programme</i> | PTB. <i>pulmonary tuberculosis</i> |
| HBsAg. <i>hepatitis B surface antigen</i> | R&D. <i>research and development</i> |
| HCWs. <i>health care workers</i> | SAGE. <i>strategic advisory group of experts on immunization</i> |
| HICs. <i>high income countries</i> | SDGs. <i>sustainable development goals</i> |
| IRIS. <i>immune reconstitution inflammatory syndrome</i> | SEAR. <i>south east asian region</i> |
| IUATLD. <i>international union against TB and lung disease</i> | TB. <i>tuberculosis</i> |
| JRF. <i>WHO/UNICEF Joint Reporting</i> | UHC. <i>universal health coverage</i> |
| LBW. <i>low birth weight</i> | VENICE. <i>vaccine european new integrated collaboration effort</i> |
| LICs. <i>low income countries</i> | WPR. <i>western pacific region</i> |
| LMICs. <i>lower-middle income countries</i> | WUENIC. <i>WHO/UNICEF estimates of national immunization Coverage</i> |
| MB. <i>multi-bacillary</i> | XDR-TB. <i>extensively drug-resistant TB</i> |
| MDGs. <i>millennium development goals</i> | |

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1. Executive summary

Background: Bacillus Calmette-Guérin (BCG) vaccines continue to be the only vaccines in use for prevention of tuberculosis (TB). BCG vaccines were first used in 1921, subsequently rolled out in developed countries and since 1974, have been included in the WHO Expanded Programme on Immunization (EPI). The use of BCG in routine infant vaccination programmes (estimated coverage at 90%) is estimated to globally prevent 117,132 TB deaths per birth cohort in the first 15 years of life. Although BCG vaccines until now are not specifically indicated for prevention of leprosy, there is evidence that BCG vaccination has also contributed to the significant decline in leprosy incidence. Further, BCG has been found to be effective against other mycobacterial infections such as Buruli ulcer disease. Finally, BCG vaccination has also been reported to have beneficial non-specific effects (NSE), in particular reducing all-cause infant mortality in certain settings.

Disease burden: In spite of high vaccination coverage with BCG in 2015, there were an estimated 10.4 million new TB cases (142 per 100,000 population) reported worldwide. Of those, an estimated 1.8 million people died, including 210,000 children. About 1.2 million people (11%) developed HIV-associated TB and 480,000 multi-drug resistant TB. In addition, a quarter of the world's population has latent tuberculosis infections. Prevention of TB-related deaths relies mainly on two strategies: firstly, BCG vaccination of infants preferably at birth, and secondly, treatment of latent TB infection, mainly in HIV-infected persons and young childhood contacts of TB patients. Although the fight against leprosy has gained considerable success, more than 200,000 cases were notified in 2016 and the annual case detection rate is only slowly declining. The South-East Asia region (SEAR) accounts for 75% of the global leprosy burden and reported 161,263 new leprosy cases in 2016 but cases are reported in all regions.

Current WHO recommendations: WHO published the last BCG position paper in 2004 and recommended that, in settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of a BCG vaccine should be given to all infants at birth. A systematic review at the time showed little evidence that revaccination with BCG afforded additional protection, and revaccination was therefore not recommended. In low TB burden settings, many countries were advised to consider moving to limiting BCG vaccination to selective risk groups based on guidelines from the International Union against TB and Lung Disease (IUATLD). In an additional guidance note published in 2007, WHO provided specific guidance for children who are HIV infected or HIV exposed. It was recommended that BCG vaccine should not be given to children who were known to be HIV-infected. There are currently no formal WHO recommendations on the use of BCG vaccine to prevent *M. leprae* (leprosy) or other mycobacterial infections such as *M. ulcerans* (Buruli ulcer being the third most common mycobacterial disease in the world).

Implementation: Most countries have opted to recommend universal BCG vaccination at birth. Only a few countries recommend BCG later during childhood. In some countries with low TB endemicity (mainly western European countries, North America and Australia), only specific subpopulations at high risk for TB are vaccinated with BCG. Changes in available evidence, TB incidence, HIV prevalence, vaccine shortages, and perceptions of risks and benefits of BCG can all alter vaccine policy within a country and across regions. In 2016, the global BCG vaccine coverage estimate was 90% reported from 169 countries, and all WHO regions have an average BCG vaccine coverage greater than 86%. Timeliness analyses, however, reveal that BCG vaccination is often not administered at birth but rather is frequently delayed to later in the first weeks of life and in some countries is administered together with the first diphtheria-tetanus-pertussis (DTP) containing vaccine at six weeks of age or even later.

Demand and supply: BCG vaccines are produced worldwide and several large countries are self-sufficient producing BCG vaccine for their own needs (e.g. China, India and Indonesia); nevertheless, over recent years a serious shortage of BCG vaccine supply has emerged, forcing WHO and UNICEF to prioritize supplies of prequalified BCG vaccines to the populations most in need. BCG vaccine supply for 2017 is estimated to be 1.5 times greater than the forecasted demand.

However, there is limited flexibility in the supply due to national product registration constraints and supply is still concentrated to a few large manufacturers with prequalified products serving most countries.

Different BCG vaccine seed strains have evolved over time due to mutations and deletions during replication at different manufacturing sites. As a result, BCG products differ substantially in their genetic and phenotypic properties. Worldwide, the most commonly used vaccine strains are: Russian BCG-I/Bulgaria (approx. 100 countries), Danish 1331, and Tokyo 172-1.

Impact: Neonatal BCG vaccination provides protection against the more severe types of disseminated TB, such as miliary TB and tuberculous meningitis, to which infants and young children are particularly susceptible. However more recent evidence suggest consistent protection against pulmonary TB for up to 10 years and more recently some evidence of moderate protection for 20 years in settings that include Brazil, Saudi Arabia and Europe. A systematic review of published trials did not find an association with vaccine strains. However, there is a report of a large trial and one observational study which suggest an association between BCG strain and protective efficacy which suggests that further studies are warranted. Unpublished modelling data comparing BCG administration at birth and 6 weeks of age estimates that delaying BCG vaccination to age 6 weeks may lead to a 1.8% increase in TB deaths. Evidence indicates that BCG given at birth is also effective for preventing leprosy, conferring higher protection than against TB. Several studies suggest it might prevent other mycobacterial infections including Buruli ulcer.

The evidence for benefits of BCG revaccination against TB and leprosy is still limited and does not support this practice. BCG vaccination is safe in immunocompetent children. However, vaccination of immunocompromised, including vaccination of HIV infected infants is not recommended. However delays in ascertaining HIV status of newborns continue to occur thus BCG is often administered to HIV infected infants whose status is still unknown at the time of vaccination. While robust evidence is missing, reduction in HIV mother to child transmission rates, earlier diagnosis of neonatal HIV infection and earlier antiretroviral treatment initiation are expected to reduce the risk of BCG adverse events in HIV infected children.

Review of economic analyses in the literature show that universal BCG vaccination remains cost-effective in countries where TB incidence is high. However in countries where the TB incidence is low, selective BCG vaccination of high-risk populations can be considered, when an efficient surveillance system is in place. There are no cost-effectiveness studies for BCG vaccination against leprosy and other mycobacterial infections. BCG revaccination is not considered cost-effective since no increased effectiveness has been observed. In 2014, SAGE concluded that the available data suggest the current WHO recommended schedule for BCG vaccination at birth has a beneficial effect on all-cause infant mortality.

New vaccine pipeline: Many activities have taken place with respect to the development of new TB vaccine candidates, with three vaccine candidates currently in phase IIb or III clinical trials. Most approaches focus on adolescent and adult vaccination after BCG “priming” of newborns. It is therefore important to understand if available BCG vaccines vary in their priming and protective efficacy. A new sub-unit vaccine for leprosy is currently in phase Ib clinical testing.

Working group conclusions: The working group concludes, that due to paucity of evidence to assess differences in the vaccine efficacy / effectiveness and safety of vaccination at different ages (birth versus age 6 weeks, 6 months or one year), no policy change regarding the age is justified. BCG vaccination at birth together with hepatitis B vaccination is strongly recommended. The group recommends continuing universal BCG vaccination in high incidence TB settings and to expand this recommendation of universal BCG vaccination to high incidence leprosy settings regardless of the TB incidence. Recommendations for selective vaccination of individuals or groups at risk in low endemic countries, switching from universal to selective vaccination, vaccination of HIV-exposed children, immunocompetent HIV-infected individuals on anti-retroviral therapy (ART) and other special risk groups including adolescents and adults are proposed. The group highlighted the urgent need for further research in the development of new vaccines, which should be tested for effectiveness against different pathogenic mycobacterial infections (TB, leprosy and other mycobacterial infections such as Buruli ulcer), and all-cause infant mortality. The group also recommended further detailed molecular characterization of currently available BCG vaccines in terms of strain and product specific aspects, as well as conduct of comparative effectiveness studies to inform vaccination policy makers.

2. BCG Working Group Recommendations

Universal vaccination at birth

In countries or settings with a high incidence of TB and/or leprosy, a single dose of BCG vaccine should be given to neonates at birth, or as soon as possible thereafter, for prevention of TB and leprosy disease. If it cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed. Any delay in vaccination may lead to opportunities for known or unknown exposure to TB or leprosy infected contacts.

As newborns are also recommended to receive their first dose of hepatitis B vaccine as soon as possible after birth, ideally within 24 hours, co-administration of BCG with the hepatitis B birth dose is strongly recommended as it is safe to do so.

If the birth dose was missed, catch-up vaccination of unvaccinated older infants and children is recommended since evidence shows it is beneficial. Catch-up vaccination should be done at the earliest convenient encounter with the health-care system to minimize known or unknown exposure to TB or leprosy infected contacts.

Selective risk group vaccination at birth

Countries with a low incidence of TB or leprosy may choose to selectively vaccinate neonates in recognized risk groups for developing disease.¹

High-risk groups to be considered for vaccination include the following:

- Neonates to parents (or other close contacts/relatives) with previous TB or leprosy
- Neonates in immigrant populations from countries with high incidence of TB² and/or leprosy.
- Neonates in any other locally identified risk group for TB and/or leprosy.

In a few countries with low TB incidence, BCG vaccination is largely replaced by intensified case detection, contact tracing and supervised early treatment.

Switching from universal to selective risk group vaccination at birth

Countries with declining rates of TB are encouraged to periodically evaluate the epidemiology of TB and consider if a switch from universal vaccination to selective risk group vaccination would be appropriate.

¹ Countries with a low-incidence of TB are those with a TB notification rate of <100 TB cases (all forms) per 1 million population per year.

² >40 per 100,000 population

Before switching to selective BCG vaccination, countries should consider the impact of a switch on prevention of leprosy. Consideration may be given also to other mycobacterial infections, as well as any potential NSE of BCG vaccination on all-cause infant mortality.

When considering switching from universal to selective risk group vaccination, an efficient disease surveillance system capable of showing the current average annual rate of smear-positive pulmonary TB cases is a pre-requisite. Additional data shall be taken into consideration, in particular the average annual rate of tuberculous meningitis in children aged under five years and/or the average annual risk of tuberculous infection in children and should be monitored. Finally the epidemiological situation for leprosy should be assessed through both routine notification data and especially active screening activities. The burden of other mycobacterial infections such as Buruli ulcer disease in the country could be also reviewed.

Vaccination of older age groups

BCG vaccination of unvaccinated/tuberculin skin test (TST)-or interferon gamma release assay (IGRA) negative school-children provides long-term effectiveness (up to 20 years or more). BCG vaccination of older age groups should be considered in:

- Unvaccinated older children, adolescents and adults living in high incidence settings of TB and/or leprosy.
- Unvaccinated older children, adolescents and adults moving from low incidence to high incidence TB/leprosy settings.
- Unvaccinated/TST- or interferon gamma release assay (IGRA) negative persons at risk of occupational exposure in low and high TB incidence areas (e.g. health care workers, laboratory workers, medical students, prison workers)

Need for re-vaccination

There is little additional benefit of repeat BCG vaccination against TB or leprosy. Therefore, revaccination is not recommended even if the TST reaction or result of an IGRA is negative. The absence of a BCG scar after vaccination is not indicative of a lack of protection and is not an indication for revaccination.

HIV exposed and other immunocompromised

BCG vaccination is contraindicated for persons with impaired congenital or acquired immunity (e.g. acquired immune deficiency syndrome (AIDS), known or suspected congenital immunodeficiencies, leukaemia, lymphoma or other malignant disease) and for patients under immunosuppressive treatment (e.g. corticosteroids, alkylating agents, biologic response modifiers, antimetabolites, radiation).

BCG vaccination is contraindicated for HIV infected persons due to their immunosuppression. However, if HIV infected individuals are started on anti-retroviral therapy (ART), are clinically well and immunologically stable

(CD4% > 25% for children under 5 years or CD4 count ≥ 200 if age > 5 years), BCG administration can be considered, especially for those living in high incidence TB settings.

In general, populations with a high prevalence of HIV infection also have the greatest incidence of TB. The following guidance is provided to facilitate national and local decisions on the use of BCG vaccine in infants at risk for HIV infection:

- **Benefits outweigh risks for BCG vaccination.** Neonates born to women of unknown HIV status should be vaccinated.
- **Benefits usually outweigh risks for BCG vaccination.** Neonates born to known HIV-infected women and whose HIV infection status is unknown but who demonstrate no signs or reported symptoms suggestive of HIV infection should be vaccinated particularly if the mother is already on ART.
- **Risks usually outweigh benefits for BCG vaccination.** Neonates who are born to HIV-infected mothers and whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection should not be vaccinated. However, this recommendation will only be applicable to infants who have not yet received BCG in the first few weeks of life, since clinical manifestations typically occur after the neonatal period. Although evidence is limited, if HIV infection status can be established with early HIV testing, BCG may then be administered once HIV infection has been ruled out *or* the HIV-infected child has become immunologically stable on ART.
- **Risks outweigh benefits for BCG vaccination.** For newborns who are confirmed HIV infected through early virologic testing, although evidence is limited, BCG should not be administered until the infant has been started on ART and confirmed to be immunologically stable (CD4% > 25%).

Vaccination of special populations, contraindications and precautions

BCG vaccination is contraindicated for individuals known to be allergic to any component of the vaccine.

Low birth weight children, although evidence is limited, can receive BCG vaccination at birth. A normal infant dose should be used.

Preterm infants, although evidence is limited, can receive BCG vaccination from gestational age 34-36 weeks, and this should be administered at discharge from the neonatal ward.

Pregnant women— BCG is contraindicated during pregnancy.

Lactating women – There is no contraindication for BCG vaccination of lactating women.

Travelers – An individual risk-strategy based on age, duration of travel and the TB incidence in the country to be visited should be considered before vaccination of travelers from non TB endemic countries to TB endemic countries. For young children traveling to TB endemic countries, particularly those under 2 years of age and those likely to have repeated travel during childhood, should be vaccinated.

Asymptomatic neonates born to mothers with confirmed or suspected infectious drug-susceptible TB should receive preventive therapy once TB disease has been excluded and should be regularly followed up to ensure that TB disease does not develop. If an infant remains asymptomatic at the end of preventive therapy, and the baby is HIV-negative, usual practice is that BCG is given.

Programmatic considerations for BCG vaccination

Choice of vaccine – Among the many available BCG products there is no preferred product for use, in any age- or risk group.

Dose of vaccine – The standard dose of BCG vaccine is 0.05 mL of the reconstituted vaccine given intradermally for children age below one year, and 0.10 mL for recipients aged one year or more. Only one dose of vaccine should be administered.

Co-administration with other vaccines - Co-administration at birth with hepatitis B vaccine is recommended. BCG can be co-administered with any other infant routine childhood vaccines.

Route of administration - BCG vaccines should be administered strictly intradermally. Some licensed BCG products are available with multi-puncture devices for percutaneous administration. BCG vaccination should be given in a healthy and clean area of skin, and the skin should not be cleaned with antiseptic prior to administration of the vaccine. The vaccine should preferably be given in the lateral aspect of the upper arm. There are no published data on efficacy and safety for other anatomic sites of administration.

Recommendations for specific measures including surveillance

Currently, reporting of childhood TB cases by countries to WHO is broken into two age ranges: 0-4 years and 5-14 years. To better understand the effectiveness of BCG vaccination at various ages, it should be encouraged that national EPI programmes report TB cases by age in years, (and if possible by months for those less than 1 year) including status of BCG vaccination of cases (preferably with information with used product/batch).

Recommendations on research needs

Development of new vaccines against TB and leprosy is strongly recommended. New vaccines should be assessed for effectiveness against TB, leprosy and Buruli ulcer disease. Their effect on all-cause infant mortality should also be assessed.

More evidence is needed on the influence of BCG vaccine strain on efficacy, effectiveness, and adverse effects. Detailed molecular characterization of BCG products is encouraged. The lack of information on specific strains and their use in different products has significantly hampered interpretation of research studies. Therefore, it is recommended that the strain (including manufacturer and preparation) used for BCG vaccination is specified (i) when recording BCG vaccination in an individual infant's immunization record and (ii) when reporting studies relating to BCG vaccination.

The implementation of BCG vaccination of HIV infected children including those on ART should be monitored and research on effectiveness and safety should be considered

Research for strategies to improve timeliness of BCG vaccination, including limiting wastage of vaccine in multi-dose preparations, should be conducted.

Long-term studies could usefully be conducted to explore BCG vaccine effectiveness, duration of protection particularly in low latitudes. Studies on BCG vaccine efficacy and effectiveness should be carefully assessed when BCG is not given soon after birth or after stringent testing if given in childhood. Other studies could also include the effectiveness of revaccination in different subgroups of the population as well as research on BCG revaccination for TB- and leprosy prevention and on BCG revaccination to contacts of leprosy patients and vaccination after treatment of TB infection in contacts.

Additional studies on the effect of BCG vaccination on all-cause childhood mortality should be undertaken in a greater variety of settings.

Granted that such studies are difficult and expensive, further investigations rigorously designed and implemented may however help clarify outstanding questions.

Recommendations to pre-empt BCG vaccine shortages

Many self-procuring countries have only one registered BCG product and therefore their access to BCG supply is vulnerable. It is recommended that: (i) manufacturers be incentivised to register available BCG products in these countries; (ii) encourage these countries to follow the “WHO Collaborative Procedure for Registration of Prequalified Products³”. This pathway would facilitate the registration process in countries where there is a lack of regulatory capacity, and would facilitate the introduction of the vaccine in the country.

The supply base of prequalified BCG vaccine is highly concentrated to a few manufacturers. It is therefore recommended that donors invest to ensure that the current supply base of BCG production is sustained to avoid risk of shortages due to production failure.

There appears to be over-procurement of BCG vaccine in several countries. It is recommended that (i) WHO and UNICEF investigate reasons for possible over-procurement of BCG vaccines; and (ii) to reduce wastage, manufacturers should consider producing smaller number of doses per vial without affecting production capacity.

³ WHO Collaborative Procedure for Registration of Prequalified Products. Available at http://www.who.int/immunization_standards/vaccine_quality/expedited_review/en/, accessed September 2017.

3. Background

Bacillus Calmette-Guérin (BCG) is an attenuated strain of *Mycobacterium bovis* used as a live vaccine against tuberculosis (TB). Since its introduction in 1921, more than 3 billion people have been vaccinated with BCG. BCG is highly effective in preventing the severe forms of tuberculosis that affect infants and young children.

The WHO BCG vaccine position paper⁴ was published in 2004. In settings where TB is highly endemic or where there is high risk of exposure to TB, it recommends that a single dose of BCG vaccine should be given to all infants.⁵ There is little evidence that revaccination with BCG affords much additional protection⁶, and revaccination is therefore not recommended.

Additional revised BCG vaccination guidelines for infants at risk for HIV infection were published separately in 2007⁷. WHO recommends that, in children who are known to be HIV-infected, BCG vaccine should not be given. In infants with unknown HIV status and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors: coverage and success of the prevention of mother to child transmission of HIV (PMTCT) programme; possibility of deferring BCG vaccination in HIV-exposed infants until HIV infection status has been established; availability of early diagnosis of HIV infection in infants; and provision of early ART to HIV-positive infants.

For the use of BCG against leprosy there is no vaccine position paper available. To date the most official recommendation on the use of BCG for leprosy has been provided through the Technical Report Series from the WHO Expert Committee on Leprosy held in 2010 and recommends that ‘Maintaining high levels of BCG immunization in newborns is important in the prevention of leprosy’.

There was a need to perform an updated review of evidence and to determine the need for an updating the recommendations according to current evidence-based standards. Accordingly the WHO Secretariat and the Strategic Advisory Group of Experts (SAGE) on Immunization initiated the process through establishment of a SAGE BCG Working Group in September 2016. The working group reviewed the evidence and requested new modeling data and updated systematic reviews on safety and efficacy and effectiveness.

The Secretariat of the working group is jointly ensured by staff from the 5 following Departments/Programmes: Department of Immunizations, Vaccines and Biologicals (IVB), the Global TB Programme (GTB), the Global Leprosy Programme (GLP), HIV-department and the Department of Essential Medicines and Health Products (EMP).

⁴ WER, No. 4, 2004, 79, 25–40, available <http://www.who.int/wer/2004/en/wer7904.pdf?ua=1>, accessed June 2017.

⁵ WHO, Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2014, available at: http://apps.who.int/iris/bitstream/10665/112360/1/9789241548748_eng.pdf, accessed June 2017.

⁶ Pereira SM 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 Infect Dis.* 2012 Apr;12(4):300-6.

⁷ WER No. 3, 2007, 82, pp. 18–24. http://www.who.int/immunization/wer8221bcg_May07_position_paper.pdf?ua=1, accessed July 2017.

4. Tuberculosis

Tuberculosis in humans and animals can be caused by a group of mycobacteria species, the *Mycobacterium tuberculosis* complex (MTC). The closely related mycobacteria of this complex are: *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium canettii*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium mungi*, *Mycobacterium orygis*, *Mycobacterium pinnipedii*, and *Mycobacterium tuberculosis*.

Mycobacterium tuberculosis is the most common cause of TB in humans. *M. africanum* and *M. canettii* can also cause human TB. *M. bovis* can affect humans, domestic or wild bovines and goats. Other species of the MTC have been reported to cause TB only in animals.^{8,9}

4.2. Epidemiology of TB

Report by the Global TB Programme

An estimated 2–3 billion people are said to be infected with *M. tuberculosis* globally with about 5–15% ending up developing TB disease during their lifetime.¹⁰ However, the probability or risk of developing TB disease is known to be much higher among people infected with HIV even in the context of ART. With respect to children, the risk of developing active TB following primary infection is greatest in very young children. In the first year of life it is 40% - 60% and 12% - 15% in the second year¹¹. The risk declines to 0.5% to 5% in age 2-5 year; <0.5% to 2% in 5-10 year-old children and increases to 10-20% for pulmonary TB (PTB) in children >10 years.

In 2015, an estimated 10.4 million people fell ill with TB (142 per 100,000 population) including 1 million children (10%), 3.5 million women and 5.9 million men. About 1.2 million people (11%) developed HIV-associated TB.¹⁰

In 2015, an estimated 1.8 million people died from TB among which were 210,000 children, 500,000 women and 1,100,000 men. This includes about 400,000 HIV-associated TB deaths and 190,000 in people with MDR-TB. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015 exceeding HIV.

The South East Asian region accounts for 46% of the 10.4 million estimated TB cases (new cases (estimated incidence)) that occurred in 2015; 26% occurred in Africa, 15% in the Western Pacific region; 7% in the Eastern Mediterranean region while Europe and the Americas accounted for 3% each. Six countries accounted for 60% of the new cases namely: India, Indonesia, China, Nigeria, Pakistan and South Africa.

⁸ Forrellad et al. Virulence factors of the *Mycobacterium tuberculosis* complex. *Virulence*. 2013 Jan 1; 4(1): 3–66.

⁹ Alexander et al. Novel *Mycobacterium tuberculosis* Complex Pathogen, *M. mungi*. *Emerg Infect Dis*. 2010 Aug; 16(8): 1296–1299.

¹⁰ WHO Global TB Report 2016. Available at http://www.who.int/tb/publications/global_report/en/, accessed September 2017.

¹¹ Marais BJ et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis*. 2004 Mar;8(3):278-85.

Case notifications are increasing but a large incidence/notification gap remains. In 2015, an estimated 4.3 million cases were not notified to national health authorities. Ten countries represent 77% of that gap out of which the following three countries represent nearly 50% of the notification gap (gap between estimated and notified): India, Indonesia and Nigeria.

HIV is known to be a powerful risk factor for developing TB. Globally, the proportion of TB cases co-infected with HIV was 15% globally with the highest rates in African region at 36% (with co-infection rate in excess of 50% in southern parts of the region). In 2015, Africa accounted for about 71% of the TB/HIV co-infection. Other co-morbidities such as diabetes are emerging in other WHO regions.¹²

TB spreads in poor, crowded and poorly ventilated settings and is linked to HIV infection, malnutrition, alcohol, drug and tobacco use, and diabetes. The most vulnerable populations at risk of TB include, among others, migrants, prisoners, minorities, refugees, and, urban poor.

During the Millennium Development Goals (MDGs), TB treatment saved an estimated 49 million lives between 2000 and 2015. Globally, TB incidence witnessed a decline at a rate of 1.4% per year in 2000–2015, and 1.5% (between 2014 and 2015). Priority actions to end TB in 2017 include: reach missing TB cases; address the MDR-TB crisis; accelerate the response to the TB/HIV co-epidemic; eliminate catastrophic costs; intensify TB research and uptake; and, close financing gaps.

4.3. TB control in the era of the UN Sustainable Development Goals

The UN Sustainable Development Goals (SDGs) 2016-2030 include 17 development goals. Goal 3 is about “good health and well-being” and has 13 targets, of which target 3.3 is to “End the epidemic of AIDS, TB, malaria & neglected tropical diseases and combat hepatitis, water-borne and other communicable diseases. In this new era, the response to TB is moving from halting TB to ending TB by 2030. In May 2014, during the 67th World Health Assembly, the WHO Member States adopted the End TB Strategy 2016-2035.¹³

The vision of the End TB Strategy 2016-2035 is “A World Free of TB: zero TB deaths, zero TB disease, and, Zero TB suffering”. The goal is to end the global TB epidemic. The strategy contains milestones and targets. As of 2020, none of the TB affected families should face catastrophic cost due to TB. By 2035, there should be a 95% reduction in the number of TB deaths compared with 2015 and a 90% reduction in TB incidence rate.¹³

The End TB Strategy has three pillars: Pillar 1 “Integrated, patient-centred TB care and prevention”; Pillar 2 “Bold policies and supportive systems”, and, Pillar 3 “Intensified research and innovation”.¹³ The success of the Strategy in driving down TB deaths and illness will depend on countries respecting the following key principles as they implement the interventions outlined in each pillar: Government

¹² Collaborative framework for care and control of tuberculosis and diabetes, WHO 2011. Available at http://apps.who.int/iris/bitstream/10665/44698/1/9789241502252_eng.pdf, accessed August 2017.

¹³ WHO. The End TB Strategy. Global strategy and targets for tuberculosis prevention, care and control after 2015. WHO, 2015. Available at http://www.who.int/tb/strategy/End_TB_Strategy.pdf?ua=1, accessed September 2017.

stewardship and accountability, with monitoring and evaluation; building a strong collation with civil society and communities; protecting and promoting human rights, ethics and equity; and, adaptation of the strategy and targets at country level, with global collaboration.

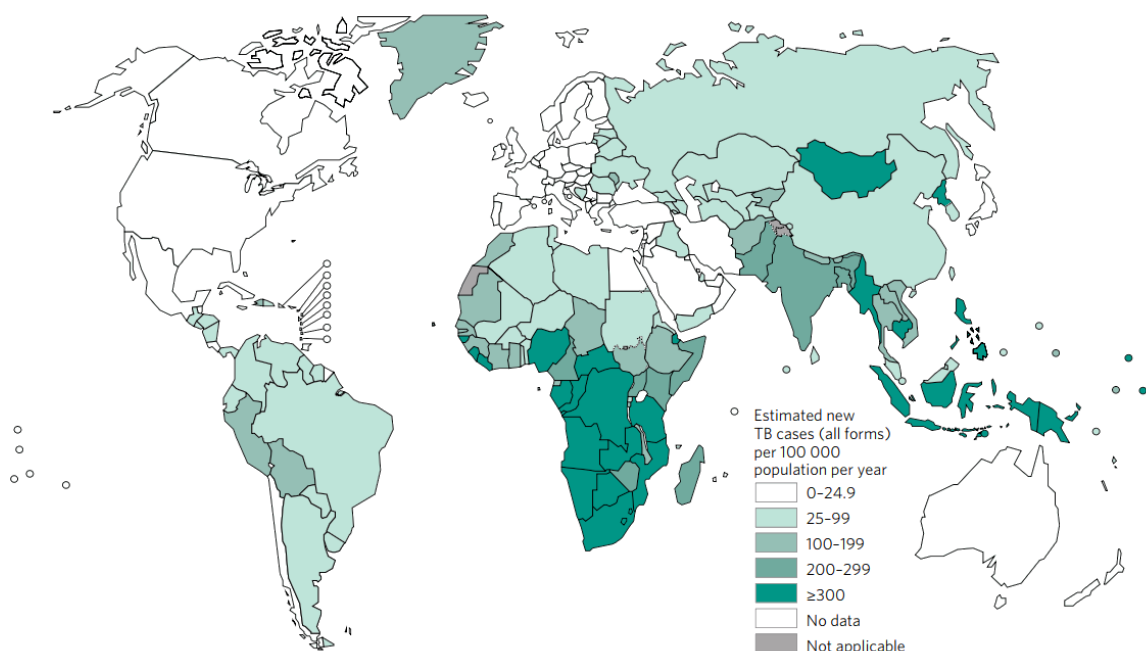


Figure 1: Estimated TB incidence rates, 2015. Source: Global TB Report 2016.¹⁰

Role of vaccines among other preventive measures- TB

Efforts to control the spread of TB will continue to rely on currently available tools, namely: early diagnosis of TB, including universal drug-susceptibility testing, and systematic screening of contacts and high risk groups; treatment of all people with TB including drug-resistant TB, and patient support; collaborative TB/HIV activities, and management of co-morbidities; and, preventive treatment of persons at high risk, and vaccination against TB.

BCG vaccine is highly effective in preventing the severe forms of TB that affect infants and young children. BCG vaccination also may reduce infant mortality by protecting against infections other than TB through beneficial non-specific effects (NSE) on the immune system (see section on NSE).

Ending the TB epidemic by 2030 requires an 80% drop in new TB cases; a 90% drop in people dying from TB; and, 100% of TB-affected families protected from catastrophic cost through better care and prevention; bolder policies and systems; and bigger investments in research and innovation. It is about saving lives, tackling poverty and inequity. Innovations and research are critical to break the trajectory of the TB epidemic. Improved TB vaccines (pre- and post-exposure) are a key element for successful TB control, along with better diagnostics, including new point-of-care tests; as well as safer, easier and shorter treatment regimens for disease and latent TB infection.

4.4. Trends in antibiotic resistance of TB

Multidrug-resistant TB (MDR-TB) has been recognized by WHO as a public health crisis requiring an accelerated response. In 2015, there were an estimated 480,000 new cases of MDR-TB plus an additional 100,000 new cases of rifampicin-resistant TB (580,000 MDR/RR-TB cases).

In 2015, a global average of 3.9% of incident (newly detected) TB cases were estimated to have MDR/RR-TB and 21% among previously treated cases. This pattern has been consistent with the levels reported in previous years. There is however a marked variation in the estimated rates of drug resistance between countries and regions, with the WHO Eastern European region currently having the highest rates of MDR-TB.

WHO has identified 30 countries that contribute about 90% of the global burden of MDR/RR-TB. Furthermore, 45% of the global MDR/RR-TB caseload (absolute numbers) are said to be in three countries namely India; China and the Russian Federation.

By October 2016, extensively drug-resistant TB (XDR-TB) had been reported by 118 WHO Member States. About 51% have resistance to a fluoroquinolone or a second-line injectable agent or both. Overall, 9.5% (95% CI: 7.0–12.1%) of MDR-TB cases have XDR-TB. In some countries the proportion of cases with strains resistant to second-line drugs is much higher than the global average.

Drug susceptibility testing (DST) coverage in 2015 was 24% of new cases; 53% of previously treated cases, 30% overall. In 2015, 132,000 MDR/RR-TB cases among notified TB patients were detected and 125,000 were enrolled on treatment highlighting a large gap between estimated incidence, case detection and treatment enrollment.

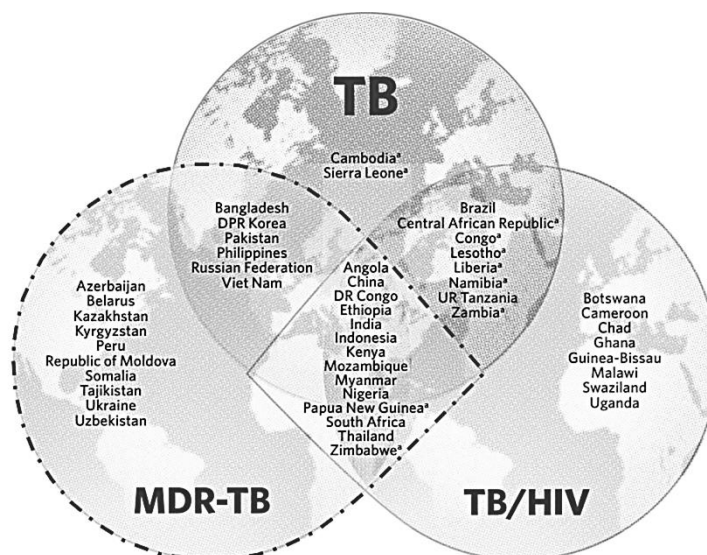


Figure 2: 30 High MDT-TB burden countries. Source: Global TB Report 2016.¹⁰

Treatment success rate for MDR/RR-TB cases has remained low with only 52% successfully treated among the most recent patient cohort of 2013. Treatment success is even lower among patients with XDR-TB with only 28%

of the 4,086 XDR-TB patients reported by 47 countries in 2015 successfully treated. The biggest numbers reported were in Europe (Russian Federation and Kazakhstan); while South Africa accounted for more than 80% of cases from the African region.

In May 2016, WHO issued updated guidelines for the treatment of drug-resistant TB. WHO now recommends a standardized 9-12 month (shorter) treatment regimen (instead of 24 months-long previously recommended) as the option of first choice in patients with RR or MDR-TB who do not have additional resistance or other factors making them ineligible for that shorter treatment regimen. The recommendation applies to adults, children and people living with HIV. This regimen is being implemented in over 20 countries in Africa and Asia.

WHO recommends rational introduction of new drugs for use in the treatment of MDR-TB. By the end of 2015, at least 70 countries were known to have introduced bedaquiline and 39 countries delamanid (two new drugs for treatment of MDR-TB). However, enrolment of eligible patients remains low, and in big countries namely China, India and Indonesia remains negligible.

In order to effectively address RR- and MDR-TB, five priority actions need to be implemented: (i) prevent the development of drug resistance through high quality treatment of drug-susceptible TB; (ii) expand rapid testing and detection of drug-resistant TB cases; (iii) provide immediate access to effective treatment and proper care; (iv) prevent transmission through infection control; and, (v) increase political commitment with financing.

In summary, although only 3.9% of new and 21% of previously treated TB cases have MDR/RR-TB, globally they amount to 580,000 incident cases each year, posing a serious challenge to goal of ending TB by 2035. Coverage of DST for first and second-line TB medicines is improving but only a fraction of MDR/RR-TB and XDR-TB patients are being detected and placed on adequate treatment. Scaling up the WHO-recommended shorter MDR-TB regimen as well as the use of new drugs is needed to impact on success rates for drug-resistant TB patients globally, but most especially in high burden countries. Surveillance and monitoring continue to improve as digital technologies offer an opportunity to help address some of the weaknesses in data management as well as for patient care (e.g. adherence support). Nevertheless there remains a crisis in the MDR-TB treatment gap that is not only attributable to drug access, but the overall health system capacity to detect and treat these patients. Effective pharmacovigilance for newly introduced drugs, use of trained health care workers and laboratory system capacities must all be considered when addressing MDR-TB.

5. Leprosy

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M. leprae*) primarily affecting skin, peripheral nerves, mucosal surfaces of upper respiratory tract and eyes. It is otherwise known as Hansen's disease.

Although the fight against leprosy has gained considerable success with the achievement of elimination of leprosy as public health problem (prevalence <1 per 10 000 at the global level) in 2000 and in most countries at national level in 2005, still more than 200 000 cases were reported in 2016 and the detection rate of the disease (a proxy of incidence rate) is only slightly declining at a rate of about 4% per year.¹⁴ Early diagnosis and complete treatment with multidrug therapy (MDT) remain the key strategies for reducing disease burden in leprosy control. To date guidance in relation to leprosy clinical management including its detection and treatment has been issued through the WHO Technical Report Series 968 and the WHO Expert committee on Leprosy reports, latest being the eighth report on the 2010 executive committee meeting. The previous meeting was held in 1997 (WHO Technical Report Series 874, WHO Expert Committee Meeting Seventh Report 1998). Advances in research in various fields including diagnostics, treatment and more importantly prevention of the disease, have led to countries to issue new policies in the area of prevention of leprosy. Such policies didn't provide guidelines using current WHO methods with defined recommendations in relation to specified level of scientific evidence. Thus, the GLP, planned to develop comprehensive guidelines in regard to all aspects of care including diagnosis, treatment and prophylaxis with the development process to take place within the year 2017. To date the most official recommendation on the use of BCG for leprosy has been provided through the 8th Technical Report Series from the WHO Expert Committee on Leprosy recommending 'Maintaining high levels of BCG immunization in newborns is important in for further reducing the burden of leprosy.'¹⁵

5.2. Epidemiology of Leprosy

Though disease usually starts with a skin lesion with loss of sensation, presence of one of the three cardinal signs is considered essential for diagnosis:

- skin lesion with definite loss of sensations
- thickened peripheral nerve trunk
- positive skin smears for acid fast bacilli¹⁶

Leprosy case definitions have been revised in 2017: paucibacillary (PB) cases have less than five skin lesions whereas, multibacillary (MB) cases have more than five skin lesions and/or involvement of at least one nerve trunk. A proportion of leprosy patients are positive for acid fast bacilli on skin slit smear examination however in leprosy control programmes most of the cases are diagnosed on clinical basis. If a skin slit smear is positive cases are automatically classified as MB. Tertiary care centers do perform histopathological examinations and Polymerase-chain reaction (PCR) as tools to confirm a clinical suspicion. WHO recommended multi-drug therapy

¹⁴WHO. Global leprosy update, 2016: accelerating reduction of disease burden. Weekly Epidemiological Record No 35, 2017, 92, 501–520.

¹⁵ WHO Expert Committee on Leprosy 8th report. Available at http://www.searo.who.int/entity/global_leprosy_programme/publications/8th_expert_comm_2012.pdf, accessed July 2017.

¹⁶ WHO Technical Report Series 968, Expert committee on Leprosy, eighth report 2010.

(MDT) for treatment of leprosy, six months with two drugs (Rifampicin and dapsone) for PB cases and 12 months with three drugs (Rifampicin, dapsone and clofazimine) for MB cases.

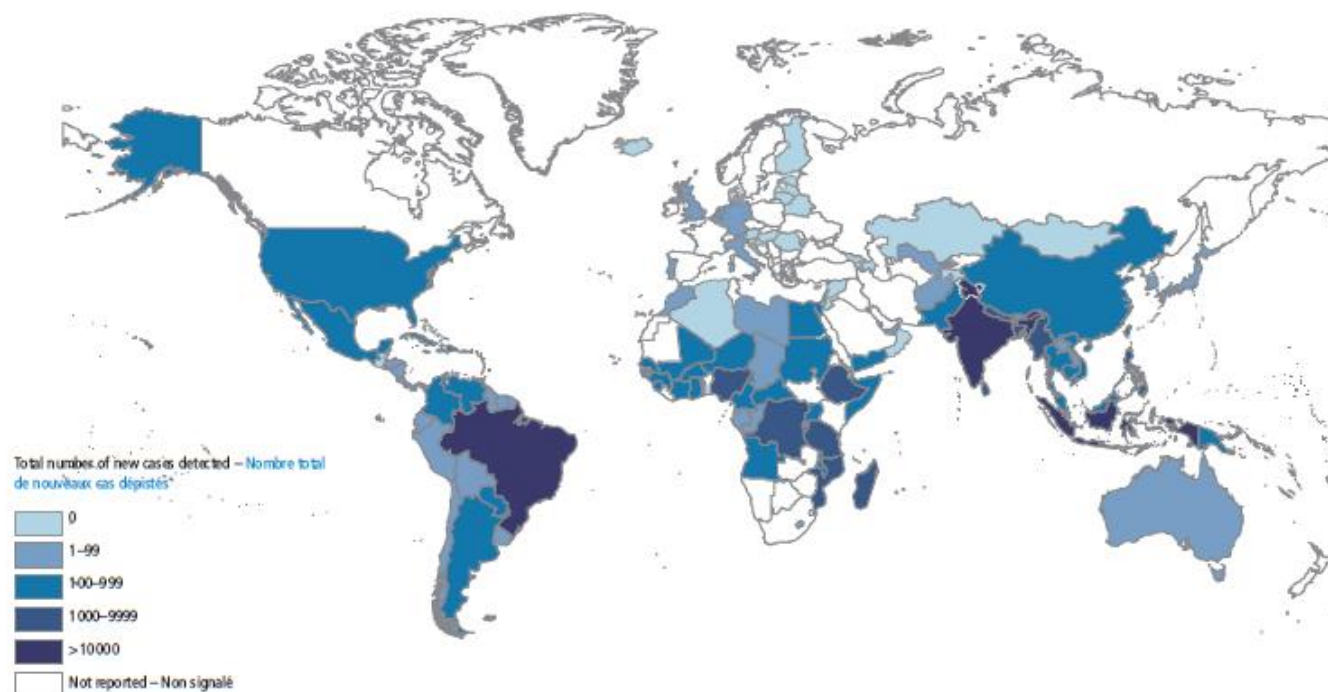


Figure 3: Geographic distribution of new leprosy cases in 2016.¹⁷

In 2016, out of 224 countries globally enlisted by GLP, 143 countries and territories sent their reports on the occurrence of leprosy cases. At the end of the year 2016, 171 948 cases were on MDT with a registered point prevalence rate of 0.23 per 10 000 people globally. The global new case detection rate is at 2.9 per 100 000 people. Trends of new detection of new cases by WHO region from 2006 to 2016 are presented in table 1.

New case detection is not uniform across the world. Out of 143 countries, thirty four reported zero cases; 61 countries reported between one and 99 cases; 36 countries reported between 100 and 999 cases and 12 countries reported more than 1 000 new cases during 2015. These 12 countries accounted for 95% of global new cases in 2015. India alone contributed to 60% of global new case load.

¹⁷ WHO, Global leprosy update, 2016: accelerating reduction of disease burden. Weekly epidemiological record. No 35, 2017, 92, 501–520.

Table 1: Trends in the detection of new cases of leprosy, by WHO Region, 2006–2016

| WHO REGION | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|--------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------|---------------|
| AFR | 34 468 | 29 814 | 28 935 | 25 345 | 20 213 | 20 599 | 20 911 | 18 597 | 20004 | 19384 |
| AMR | 42 135 | 41 891 | 40 474 | 37 740 | 36 832 | 36 178 | 33 084 | 33 789 | 28806 | 27356 |
| EMR | 4 091 | 3 938 | 4 029 | 4 080 | 4 357 | 4 235 | 1 680 | 2 342 | 2167 | 2834 |
| SEAR | 171 576 | 167 505 | 166 115 | 156 254 | 160 132 | 166 445 | 155 385 | 154 834 | 156118 | 161263 |
| WPR | 5 863 | 5 859 | 5 243 | 5 055 | 5 092 | 5 400 | 4 596 | 4 337 | 3645 | 3914 |
| EUR | NA | NA | NA | NA | NA | NA | NA | NA | 18 | 32 |
| Total | 258 133 | 249 007 | 244 796 | 228 474 | 226 626 | 232 857 | 215 656 | 213 899 | 210740 | 214783 |

The number of women detected with leprosy is collected routinely from all countries. Global data shows that 39% of new cases (84,202) reported in 2016 were women. The exact mechanism of transmission remains obscure, with transmission via the respiratory tract suggested by some studies. Proportion of child case or, better, leprosy child rate in a country area indirectly indicates continued transmission of the disease. In 2016, 18,230 new child cases (9%) have been reported. The age at which leprosy among children is seen is usually after five years of age. There are reports available that describe younger children between 2-5 years also have active skin signs of leprosy. The proportion of new cases among children and women is presented in the table. The SEAR has higher proportion of new child cases which is in line with the highest burden of the region compared to the rest of the world. The exact reason why more cases are reported in males is not known with certainty, but it is most likely due to increased exposure to leprosy and/or to sex-related predisposition.

Table 2: Percentage of Females and children among new cases by WHO Region in 2016

| WHO Region | Percentage of Female | Percentage of Children |
|--------------|----------------------|------------------------|
| AFR | 37.3 | 8.7 |
| AMR | 43.7 | 6.4 |
| EMR | 38.2 | 7.2 |
| EUR | 21.9 | 3.1 |
| SEAR | 38.8 | 8.8 |
| WPR | 34.6 | 9.5 |
| World | 39.2 | 8.5 |

Proportion of females with leprosy is similar in all regions ranging from 34.6% in WPR to 43.7% in AMR. Globally in 2016 12,819 new grade-2 disabilities (G2D) cases were reported. The numbers of new cases with G2D have reduced noticeably from 14,059 in 2015 to 12,819 in 2016. The lack of a more decisive reduction of the annual new case detection rate is mainly attributed to two reasons: 1. lack of awareness in the community and on early signs of leprosy and 2. A lower level of expertise among health staff as the disease is rarer compared to several decades ago and there has been lack of investments in national leprosy services after the year 2000.

5.3. Global Leprosy Strategy 2016-2020

The Global Leprosy Strategy 2016 – 2020 “Accelerating towards a leprosy-free world” was launched in April 2016 with the aim to identify current and potential tools to reduce the leprosy burden at an accelerated rate globally. For addressing leprosy control, the Global Leprosy Strategy 2016–2020 was developed. It aims at accelerating action towards a leprosy-free world. The strategy is structured around three pillars:

- (1) Strengthen government ownership, coordination and partnership
- (2) Stop leprosy and its complications
- (3) Stop discrimination and promote inclusion.

Its targets are:

Number of children diagnosed with leprosy and visible deformities: 0

Rate of newly diagnosed leprosy patients with visible deformities: <1 per million

Number of countries with legislation allowing discrimination on basis of leprosy: 0

Broad core areas of interventions are included under each pillar:

| PILLAR I | PILLAR II | PILLAR III |
|--|--|---|
| <p>Ensuring political commitment and adequate resources for leprosy programmes.</p> <ul style="list-style-type: none"> • Contributing to universal health coverage with a special focus on children, women and underserved populations including migrants and displaced people. • Promoting partnerships with state and non-state actors and promote intersectoral collaboration and partnerships at the international level and within countries. • Facilitating and conducting basic and operational research in all aspects of leprosy and maximize the evidence base to inform policies, strategies and activities. • Strengthening surveillance and health information systems for programme monitoring and evaluation (including geographical information systems) | <p>Strengthening patient and community awareness on leprosy.</p> <ul style="list-style-type: none"> • Promoting early case detection through active case-finding (e.g. campaigns) in areas of higher endemicity and contact management. • Ensuring prompt start and adherence to treatment, including working towards improved treatment regimens. • Improving prevention and management of disabilities. • Strengthening surveillance for antimicrobial resistance including laboratory network. • Promoting innovative approaches for training, referrals and sustaining expertise in leprosy such as eHealth. • Promoting interventions for the prevention of infection and disease | <p>Promoting societal inclusion through addressing all forms of discrimination and stigma.</p> <ul style="list-style-type: none"> • Empowering persons affected by leprosy and strengthen their capacity to participate actively in leprosy services. • Involving communities in actions for improvement of leprosy services. • Promoting coalition-building among persons affected by leprosy and encourage the integration of these coalitions and or their members with other community-based organizations. • Promoting access to social and financial support services, e.g. to facilitate income generation, for persons affected by leprosy and their families. • Supporting community-based rehabilitation for people with leprosy-related disabilities. • Working towards abolishing discriminatory laws and promote policies facilitating inclusion of persons affected by leprosy. |

Given the advances in research in various fields including diagnostics, treatment and more importantly prevention of the disease, this has led to countries issuing new policies especially in the area of prevention of

leprosy. Such policies were not based on current WHO methods for developing guidelines with defined recommendations in relation to specified levels of scientific evidence. Thus, GLP is currently in the process to develop guidelines in regard to all aspects of care, including diagnosis, treatment and prophylaxis with the process to take place within the year 2017. As part of that process the GLP commissioned a literature review on efficacy of BCG and other vaccines to prevent leprosy in the general population and among contacts in the months of March-May 2017 as part of a general review on diagnostics and on preventive and treatment tools for leprosy. As part of the guidelines development process the GLP held an experts' meeting in Delhi on the 30-31 May 2017 named Guidelines Development Group (GDG) meeting. The GDG discussed reviewed the findings of the literature review and developed recommendations through evidence to recommendations tables. For the role of BCG for leprosy control the feedback of the leprosy guideline development group was shared with the BCG working group and to further link the two parallel processes (BCG working group and Guidelines development).

The role of the BCG vaccine in the control of leprosy

Leprosy has important clinical, social, and public health consequence and can only partly be controlled by the antibiotic treatment. Even with the possible introduction of a chemoprophylaxis regimen, due to its partial efficacy the use of vaccine at birth remain an important tool for prevention of the disease; in addition data indicate additional protection for contacts vaccinated at birth who also receive chemoprophylaxis. Evidence on the efficacy of BCG to prevent leprosy is well established¹⁸, but there have been no WHO guideline recommendations for its use as a leprosy preventive tool. BCG is easily accessible and already part of the vaccination policy of most leprosy endemic countries. As national policy to control TB develops, however, changes in those policies may be made in response to changes in TB epidemiology without consideration of effects on leprosy prevention, which might compromise achievements in leprosy control. The GDG concluded that immune prophylaxis could be important in leprosy and wish to point out the results of the efficacy review to the BCG working group for their consideration, with a focus on efficacy of BCG for preventing leprosy when given at birth/infancy. The evidence on revaccination for adults exposed to a case (contacts) seems too limited at this stage to bring it to the attention of the working group/SAGE; however the use of BCG to prevent leprosy among adults and adults at risk (exposed contacts) cannot be excluded. Other vaccines have been shown to be effective for prevention of leprosy however data are more limited and they don't confer higher protection than BCG. Among those, only one is currently produced namely *mycobacterium indicus pranii* (formerly known as *mycobacterium w*). A current study on its efficacy is planned to be carried out in 4 districts in high burden leprosy states in India.

Therefore while the fundamental efforts to control the spread of leprosy will continue to rely on early diagnosis and multi-drug treatment, leprosy vaccines are a key element for success and the development of efficient, safe and affordable vaccines against leprosy must be a global priority.

¹⁸ Merle et al. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. Expert Review of Vaccines. Volume 9, 2010 - Issue 2.

5.4. Antimicrobial resistance in Leprosy

Since the late 80s, due to the raise of drug resistances (mainly dapsone resistance), leprosy monotherapy was replaced by combined treatment. *M. leprae* is a bacterium which cannot be grown in vitro and therefore it is difficult to assess antimicrobial resistance (AMR) with common phenotypic drug susceptibility tests. Nowadays sequencing methods are able to detect mutations in the genome of the bacterium and related resistances. Resistances to rifampicin, dapsone and ofloxacin are linked to drug resistance determining regions (DRDR) of the genes *rpoB*, *folP1* and *gyrA*.

An analysis of data from 18 endemic countries and 1,862 cases revealed that, 127 (6.8%) *M. leprae* strains bear mutations related to resistances (73 rifampicin-resistant, 59 dapsone-resistant and 19 Ofloxacin-resistant strains). Also multi-resistances were detected (20 cases had both rifampicin and dapsone resistance, while 4 cases had both ofloxacin and dapsone resistance, no cases had both rifampicin and Ofloxacin resistance). Resistances to rifampicin were observed in 12 countries. Of those, 3 countries (India, Brazil and Columbia) had more than 5 rifampicin resistant cases during the period of 2009-2015. No increasing trend was observed. Most drug resistant cases were reported in countries where more testing is carried out therefore it is important to expand the surveillance program more widely, to be able to assess trends.¹⁹

6. Non-tuberculous mycobacterial (NTM) infections

Mycobacteria are aerobic Gram positive bacteria with over 100 identified species and most of them are living in the environment e.g. water and soil. The prevalence of environmental mycobacteria is higher in hot than in cold climates. Around 20 mycobacterial species are causing human diseases.

Non-tuberculous mycobacterial (NTM) are also known under the terms atypical mycobacteria and mycobacteria other than tuberculosis (MOTT). Pathogenic NTM can cause pulmonary infections, skin disease and lymphadenitis. The incidence of NTM disease is rising in the past decades. In high-income countries the incidence of NTM lymphadenitis in children is 0.6 to 2.15 cases per 100,000 children per year, and highest rates in the age below 4 years.²⁰

The effects of BCG vaccination on NTM infections and especially Buruli ulcer disease (BUD) were recently analyzed in a systematic review.²⁰ The analysis revealed that BCG is protective against NTM lymphadenitis in children.

¹⁹ Cambau et al. Results of the global antimicrobial resistance surveillance network for leprosy 2009-2015: a call for vigilance for all communicable diseases. Submitted Article, 2017.

²⁰ Zimmermann and Curtis et al. Does BCG vaccination protect against non-tuberculous mycobacterial infection? 2017, unpublished (Department of Paediatrics, The University of Melbourne, Parkville, Australia).

The incidence of NTM infection in children in HIC countries is lower in BCG-vaccinated children (RR 0.04 (95%CI 0.01-0.21), concluding that BCG vaccination protects against NTM lymphadenitis.²⁰ European countries reported an increase in NTM infections when interrupting universal BCG vaccination.^{20,21,22}

6.2. Buruli ulcer disease

BUD is a chronic debilitating disease caused by *Mycobacterium ulcerans*, which produces the toxin – mycolactone – which causes tissue damage and inhibits the immune response. Often the bacterium affects the skin and sometimes bone, and can lead to permanent disfigurement and long-term disability.

In 2015, 2037 new cases were reported from 13 countries, most patients are children aged less than 15 years. In the last 10 years more than 42,000 BUD cases were reported.²³ BUD was reported in Africa, South America and Western Pacific regions in 34 countries.^{23,24} High endemic countries are Benin, Côte d'Ivoire, Ghana, Cameroon and Australia.²³ Three different lineages of *M. ulcerans* are described.²³ In Africa, the incidence of BUD is estimated to be between 21 and 320 cases per 100,000. Children aged below 15 years and adults aged above 49 years are at highest risk of infection.²⁵ Moreover, children below 5 years of age are less likely to be exposed to *M. ulcerans* than older children.^{23,26} Potential risk factors for contracting the disease are contact with water (e.g. presence of wetland, swimming in rivers, contact with stagnant water, and farming activities near rivers), mosquito bites, and BUD history in the family.^{23,27} Due to effective national BUD control programs the number of BUD is declining, and leading to hypothesize that humans are causative for the transmission by shedding bacteria into the environment, but the complete mechanism of transmission is not yet understood.²³

A recent systematic review of randomized controlled trials (RCTs) on effectiveness of BCG against Buruli ulcer have revealed ~50% efficacy (RR 0.5, 95%CI 0.37-0.69) in African settings.²⁰ In more detail, two RCTs from Uganda report on lower incidence of BUD in BCG vaccinated compared to not vaccinated.^{20,28} Higher protection rates were reported in low-incidence areas and only within the first year after vaccination.^{20,28} Recent case-control studies in the Democratic Republic of Congo, Ghana and Togo did not observe significant evidence of a protective effect of routine BCG vaccination on the risk of developing either any BUD or severe forms of BUD. (OR 1.34, 95% CI 0.19 to 1.51).^{20,29,30} Studies in Benin concluded that BCG vaccination at birth provides significant

²¹ Romanus V et al. Atypical mycobacteria in extrapulmonary disease among children. Incidence in Sweden from 1969 to 1990, related to changing BCG-vaccination coverage. *Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 1995;76(4):300-310.

²² Trnka L et al. 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):348-352.

²³ Röltgen K and Pluschke G. Epidemiology and disease burden of Buruli ulcer: a review. *Research and Reports in Tropical Medicine*, November 2015.

²⁴ WHO. Buruli ulcer (*Mycobacterium ulcerans* infection) Fact sheet: available: <http://www.who.int/mediacentre/factsheets/fs199/en/>, accessed June 2017.

²⁵ Debacker M et al. Risk factors for Buruli ulcer, Benin. *Emerg Infect Dis*. 2006;12(9):1325–1331.

²⁶ Röltgen K et al. Late onset of the serological response against the 18 kDa small heat shock protein of *Mycobacterium ulcerans* in children. *PLoS Negl Trop Dis*. 2014;8(5):e2904.

²⁷ Jacobsen KH and Padgett JJ. Risk factors for *Mycobacterium ulcerans* infection. *Int J Infect Dis*. 2010;14(8):e677–e681.

²⁸ Bradley DJ et al. BCG vaccination against mycobacterium ulcerans infection (Buruli ulcer). First results of a trial in Uganda. *Lancet*. 1969;1(7586):111-115.

²⁹ Phillips RO et al., Effectiveness of routine BCG vaccination on buruli ulcer disease: a case-control study in the Democratic Republic of Congo, Ghana and Togo. *PLoS Negl Trop Dis*. 2015 Jan 8;9(1):e3457.

³⁰ Smith PG et al. The protective effect of BCG against *Mycobacterium ulcerans* disease: a controlled trial in an endemic area of Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1976;70(5-6):449-457.

protection against the development of *M. ulcerans* osteomyelitis in children under 15 years of age, but does not protect adults aged ≥ 15 years³¹ and adults.^{32,33} Studies in mice, by challenging animals with *M. ulcerans* injection into the footpad, reveal that BCG may lead to a transient protection but depending on host and pathogen.^{34,35,36} Characterization of the *M. ulcerans* homologue of the mycobacterial antigen 85 (Ag85A) from BCG which is leading to the protective immune response indicated that cross-reactive protection might be possible, by demonstrating significantly reducing of the bacterial load in *M. ulcerans*- infected mice.³⁷ The evidence of BCG vaccination therefore suggests some protective effective against Buruli ulcer, but is not completely conclusive.

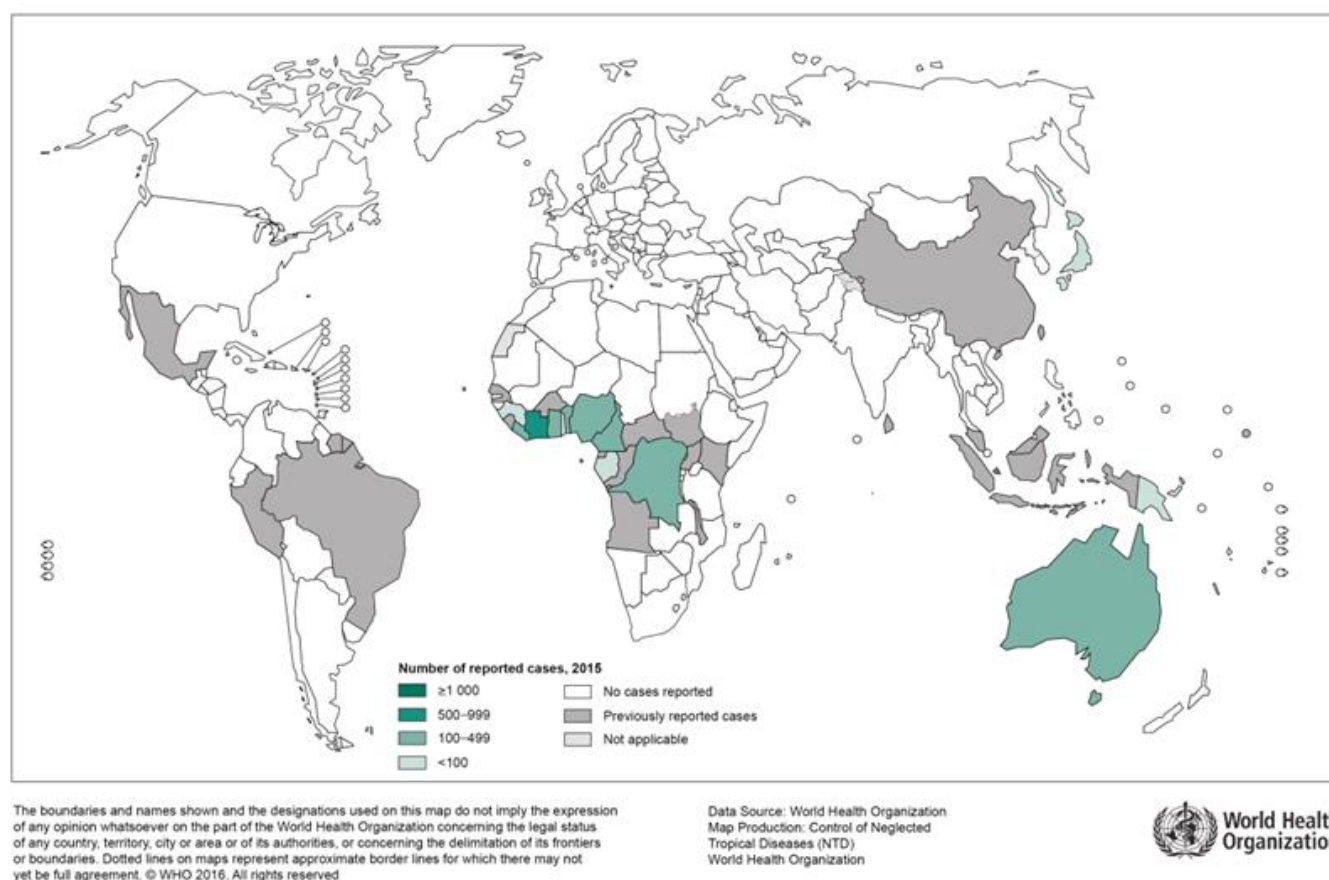


Figure 4: Distribution of Buruli ulcer worldwide, 2015. WHO.

Source: WHO. http://gamapservr.who.int/mapLibrary/Files/Maps/Buruli_2015.png?ua=1

³¹ Portaels, F et al Prophylactic effect of *Mycobacterium bovis* BCG vaccination against osteomyelitis in children with *Mycobacterium ulcerans* disease (Buruli ulcer). 2002. Clin. Diagn. Lab. Immunol. 9:1389-1391.

³² Portaels F et al. *Mycobacterium bovis* BCG vaccination as prophylaxis against *Mycobacterium ulcerans* osteomyelitis in Buruli ulcer disease. Infect Immun. 2004 Jan;72(1):62-5.

³³ Nackers F et al. BCG vaccine effectiveness against Buruli ulcer: a case-control study in Benin. Am J Trop Med Hyg. 2006 Oct;75(4):768-74.

³⁴ Converse PJ et al. BCG-mediated protection against *Mycobacterium ulcerans* infection in the mouse. PLoS Negl Trop Dis. 2011 Mar 15;5(3):e985.

³⁵ Fraga AG et al. Cellular immunity confers transient protection in experimental Buruli ulcer following BCG or mycolactone-negative *Mycobacterium ulcerans* vaccination. PLoS One. 2012;7(3):e33406.

³⁶ Tanghe A et al. A booster vaccination with *Mycobacterium bovis* BCG does not increase the protective effect of the vaccine against experimental *Mycobacterium ulcerans* infection in mice. Infect Immun. 2007 May;75(5):2642-4. Epub 2007 Feb 26.

³⁷ Tanghe A et al. Protective efficacy of a DNA vaccine encoding antigen 85A from *Mycobacterium bovis* BCG against Buruli ulcer. Infect Immun. 2001 Sep;69(9):5403-11.

7. Current WHO recommendations (2004 and addition of 2007)

The current WHO recommendations for BCG vaccination are:

- 1 BCG vaccine dose to “all infants” (all healthy neonates), as soon as possible after birth, in countries with high TB burden
- No BCG revaccination or boosters
- Low burden TB countries may limit BCG vaccination to infants in high-risk groups (or TST negative older children), and adults who are at high risk for occupational TB exposure and are tuberculin skin test negative

Low Endemicity Criteria* to change to selective vaccination

*International Union Against Tuberculosis & Lung Disease

- Efficient TB notification system in place
- Average annual notification rate of smear-positive pulmonary TB cases <5 per 100,000
- Average annual notification rate of TB meningitis in under 5 years < 1 per 10 million population during previous 5 years
- Average annual risk of TB infection below 0.1%

WHO Policy Recommendation (2007) Infants at risk of HIV infection

- Children known to be HIV+, even if asymptomatic, should **NOT** be immunized with BCG

National decision-making on BCG vaccination to be guided by local factors:

- Prevalence of TB in the general population
- Potential for infant exposure to TB
- Prevalence of HIV infection
- Coverage and efficacy of interventions to prevent MTCT of HIV
- Rates of exclusive and mixed breastfeeding
- Capacity to conduct follow-up of immunized children
- Capacity to perform early virological infant diagnosis (in the first months of life)

WHO Policy Recommendation (2004) Special Risk Groups

Adults:

- BCG vaccination NOT recommended (incl. pregnant women)
- Consider for TST negative persons in unavoidable and close contact with cases of multi-drug resistant TB

There is currently no official WHO recommendation for the use of BCG against leprosy or *M. ulcerans*.

8. Country policies and implementation

Two different sources of data were used to analyse the policy of countries, the BCG world atlas (updated in 2017)³⁸ and the WHO/UNICEF Joint Reporting (JRF) (data from 2016)³⁹

Based on the data from 180 countries in the BCG World Atlas 157 (87.2%) countries recommended universal BCG vaccination in 2016, while the remaining 23 countries recommended selective vaccination of high-risk groups or had stopped BCG vaccination altogether³⁸. Based on the JRF data in 2016 (data of 194 member states) 141 member stated that they recommended universal birth dose, 14 countries within the first week, 21 countries did not have BCG vaccination in the routine schedule and 25 countries recommend selective BCG vaccination or vaccination at a later in childhood (1 during the first month of life, 7 during the first year).

Table 3: Country practice of BCG vaccination reported in the JRF in 2016³⁹

| | | |
|--|------------|---------------|
| Total number of countries | 194 | |
| • no BCG in the routine schedule | 21 | 10.82% |
| • BCG vaccination given at birth; | 141 | 72.68% |
| • BCG vaccination given within the first week | 14 | 7.22% |
| universal vaccination given at birth and within the first week | 143 | 73.71% |
| vaccination given at birth and within the first week in high risk groups | 12 | 6.19% |
| • BCG vaccination given later during life | 18 | 9.28% |
| universal vaccination | 5 | 2.58% |
| vaccination in in high risk groups | 13 | 6.7% |

Countries which are recommending selective BCG vaccination or no BCG vaccination at all are mostly located in Western Europe. The selective vaccination approach mainly focusses on recommending BCG vaccination in high-risk infants, infants born in high-risk TB settings and individuals involved in high TB risk occupations (e.g. health care workers) or travel. Additional variations in BCG vaccination strategies include 8 countries³⁸ that recommend tuberculin skin testing post-BCG vaccination. Of note 33 countries had previously recommended multiple BCG vaccinations, but have since ceased revaccination to use a single BCG dose.³⁸ In the 2016 JRF data, 6 countries still reported practicing BCG revaccination (Bulgaria, Kazakhstan, Russian Federation (the), Tajikistan, Turkmenistan, Ukraine).³⁹ All countries are high incidence countries and use the Russian BCG strain.

8.2. Country policies on the use of BCG against leprosy

Brazil officially recommends BCG (re)vaccination (up to 2 lifetime doses of BCG) for contacts without signs or symptoms of leprosy upon examination, regardless of whether the index case is classified as paucibacillary (PB) or multibacillary (MB). Other countries recommending BCG vaccination as part of national policy to prevent leprosy among contacts of leprosy cases are Colombia (since the year 2000) and Australia (since the year 2008) for children whose parents have leprosy and/or a diagnosis of leprosy, as found in a recent survey conducted by GLP whose results have been recently published.⁴⁰

³⁸ Zwerling A, et al. The BCG World Atlas: A database of global BCG vaccination policies and practices. PLoS Med. 2011;8(3).

³⁹ WHO/UNICEF joint reporting process, Data, statistics and graphics 2016. Available at http://www.who.int/immunization/monitoring_surveillance/data/en/, accessed July 2017.

⁴⁰ Gillini et al. Global practices in regard to implementation of preventive measures for leprosy. PLoS Negl Trop Dis. 2017 May; 11(5): e0005399.

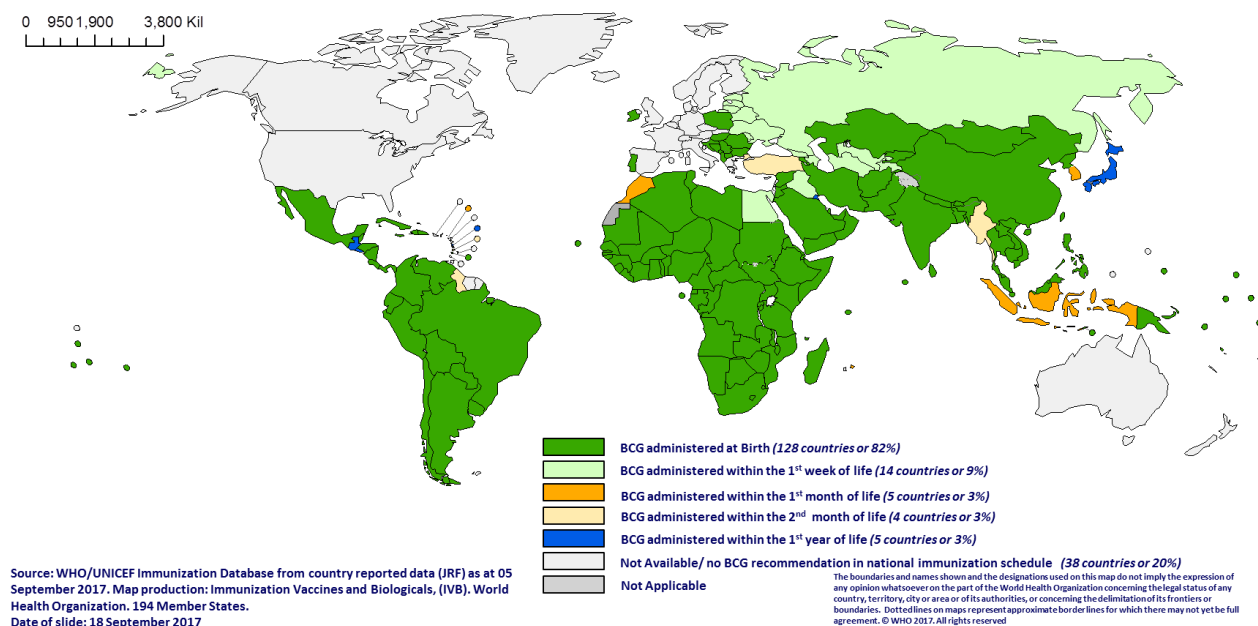


Figure 5: BCG vaccination policies by WHO member states, data from 2016.³⁹

Table 4: Summary of global practices in regard with use of immunoprophylaxis for leprosy by region.

| Region | Countries using BCG vaccination or revaccination of leprosy contacts as national policy (year) | Countries using BCG/other vaccine for leprosy contacts under research studies (Year) |
|--------|--|---|
| AFR | None | None |
| AMR | Brazil (1987), Colombia (2000), Peru (planned) | None |
| EMR | None | None |
| SEAR | None | Bangladesh (2016) India (<i>Mycobacterium indicum pranii</i> vaccine, planned for the beginning of 2017) |
| WPR | Australia (2008) | None |

Source: Gillini et al.⁴⁰

8.3. Review of BCG vaccine policies in countries with low TB burden

BCG immunization policies can vary widely in countries with low TB burden, therefore a review of BCG vaccination strategies was conducted through compilation of data from the WHO/UNICEF Joint Reporting Form, national health department websites, Vaccine European New Integrated Collaboration Effort (VENICE) documents, BCG World Atlas database, and literature review using the PubMed database. Review of these data sources showed that there were significant variations in BCG vaccination across 33 low TB incidence countries, defined by the WHO as having an annual TB notification rate of ≤ 100 cases of all TB forms per million.

In 2016 (based on the BCG World Atlas) universal vaccination at birth was still recommended in the following 8 countries: Costa Rica, Cuba, the Czech Republic, Ireland, Jamaica, Malta, the United Arab Emirates, and West Bank and Gaza Strip. Jordan and Greece vaccinated children before school age. In Slovakia, neonatal BCG vaccination was optional and free but not mandatory. BCG vaccination of neonates and children less

than 5 years travelling to countries with high TB incidence was recommended in 7 countries: Australia, Canada, Finland, Jordan, New Zealand, Sweden, and Switzerland. Australia offered BCG vaccination for travelling children over 5 years of age as well. Finland, Ireland, Israel, and Sweden selectively vaccinated immigrant children born in high TB incidence countries, while Jordan, New Zealand, Norway, and Slovenia also vaccinated infants living with parents, household members, or caretakers from high incidence countries.

Targeted BCG vaccination in high-risk populations was recommended in several countries. Infants living in a household with persons either with current or past TB were recommended for vaccination in 9 countries: some states of Canada, Cyprus, Finland, Greece, Ireland, Jordan, New Zealand, Sweden, and the USA. Neonates born to parents with current or past leprosy were also recommended for BCG vaccination in Australia and Jordan. Indigenous Australian Aboriginals and Canadian Inuit and first nation's populations at high risk for TB were also recommended to have neonatal BCG vaccination. Health care workers at high risk of exposure to drug resistant cases were recommended for vaccination in 6 countries: Australia, France, Ireland, Italy, Jordan, and the USA.

8.4. Switching vaccination policy – from universal to selective vaccination

The generated data from the BCG World Atlas are categorizing countries into 3 main policies: (a) current recommendation for universal BCG vaccination at set age (b) previously recommended universal BCG vaccination but currently does not; or (c) BCG recommendation for selected high-risk groups or never recommended at all.

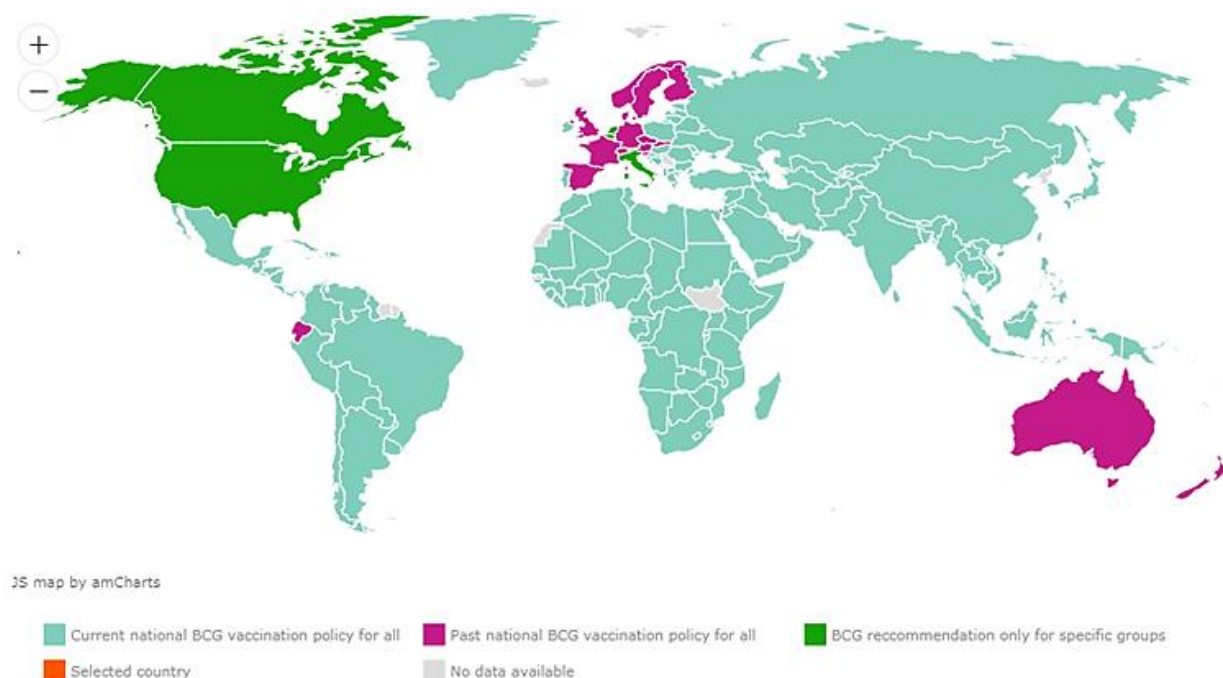


Figure 6: World map displaying BCG vaccination policies by country. Source: BCG World Atlas.

In 2016, WHO/UNICEF Estimates of National Immunization Coverage (WUENIC)⁴¹ did not have routine BCG vaccination data for the following 11 countries: Austria, the Czech Republic, Denmark, Finland, France, Greece, Israel, Italy, Malta, Slovakia, and Slovenia. All 11 countries are located in Europe and 8 (73%) countries did not have routine BCG vaccination for over a decade. Additionally, Canada, Germany, the Isle of Man, Spain, the United Kingdom, and the U.S., had also ceased universal BCG vaccination programmes and therefore not included in the coverage data³⁸. The most recent country to discontinue routine BCG vaccination was Slovakia in 2012, followed by the Czech Republic and France in 2009 and 2007 respectively. Although many countries began BCG vaccination programmes in the 1940s-1980s, WUENIC data also shows that several countries have recently adopted BCG vaccination.^{38,41}

There are established guidelines for countries shifting away from universal vaccination and towards targeted vaccination of high-risk groups.^{42,43} The 2004 WHO position paper⁴ on the use of BCG vaccine recommended that “in countries with a high burden of TB, a single dose of BCG vaccine should be given to all infants as soon as possible after birth”. However, in countries with a low burden of TB, countries may choose to “limit BCG vaccination to neonates and infants of recognized high-risk groups for the disease or to skin-test-negative older children”.

8.5. BCG vaccine coverage estimate

To determine current BCG policy implementation and vaccine uptake, WHO/UNICEF Estimate of national immunization coverage (WUENIC) was analysed by individual country practices and by WHO region.

The WUENIC vaccine coverage estimates (of countries recommending universal BCG vaccination) is 89.82% across 169 countries in 2016, and all WHO regions have average vaccine coverage greater than 86%. Africa has the lowest average BCG vaccine coverage (86.6%) by WHO region, while the highest average BCG vaccine coverage (94.7%) is in the Americas. The data show an increasing trend in BCG immunization up to 1990, after which vaccine coverage appears to plateau between 80-90% (Figure 7). Since 2000, 5 countries including Japan, Jordan, Kuwait, South Sudan, and Timor-Leste, have increased their BCG vaccine coverage dramatically.

Worldwide, the percentage of countries with BCG coverage <50% has decreased from 16% to less than 5% in the last 25 years (Figure 8). A majority of countries have BCG coverage greater than 80%, with more countries increasing their coverage every year (Figure 8). However, BCG coverage still remains low in some countries, with coverage estimates showing that 11 countries have relatively low BCG coverage (<70%). Within these countries, 4 are in Africa, 3 are in Europe, 3 are in the Eastern Mediterranean, and one is in the Western Pacific region. Although some of these countries are in low TB incidence countries without routine BCG vaccine programmes, such as Sweden, high TB incidence countries such as Equatorial Guinea, Papua New Guinea, and Somalia, also report extremely low vaccine coverage estimates of 48%, 65%, and 39% respectively.

⁴¹ WHO/UNICEF Estimates of National Immunization Coverage. Available at http://www.who.int/immunization/monitoring_surveillance/data/en/, accessed July 2017.

⁴² Dierig A, Tebruegge M, Krivec U, Heininger U, Ritz N. Current status of Bacille Calmette Guérin (BCG) immunisation in Europe - A ptbnet survey and review of current guidelines. *Vaccine*. Elsevier Ltd; 2015;33(38):4994–9. Available from: <http://dx.doi.org/10.1016/j.vaccine.2015.06.097>

⁴³ Altes HK, Dijkstra F, Lugnèr A, Cobelens F, Wallinga J. Targeted BCG Vaccination Against Severe Tuberculosis in Low-prevalence Settings. *Epidemiology*. 2009;20(4):562–8. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001648-200907000-00015>

The BCG vaccine coverage is $\geq 99\%$ in 52 countries, with America, Europe, and the Western Pacific region accounting for the majority (73%) of the high coverage countries. Interestingly, Zwerling et al.'s (2011) world map of varying BCG vaccine policies shows that countries that previously recommended universal BCG vaccination but are currently stopping routine immunization, are also in the America, Europe and the Western Pacific region.³⁸ As countries achieve high BCG vaccine coverage through improved health systems and decrease their TB incidence, policymakers are likely to modify universal vaccination practices to fit the evolving epidemiology of the local population.

Vaccine coverage of high-risk groups by selective vaccination

As the incidence of TB continues to decline in the developed countries, selective vaccination strategies in high-risk populations are increasingly being used as an alternative to universal BCG vaccination.^{44,45} However, selective immunization programmes depend heavily on the ability to identify and reach the target population.⁴⁶

Feiring *et al.* (2016) estimated BCG vaccine coverage in selected target groups in Norway and found that children targeted for selective BCG vaccination had a lower coverage of the target vaccine when compared to vaccines in the universal programme⁴⁶. This study emphasizes that improved mechanisms for identifying eligible children and subsequent vaccine delivery are essential for the success of targeted vaccine strategies.⁴⁶

In addition to immigrant populations from countries with high risk of TB, health care workers (HCWs) and travellers to high TB incidence countries are also commonly identified as high-risk groups for targeted BCG vaccination strategies.^{47,48} A literature review on European policies for BCG vaccination in HCWs revealed a wide range of policies including immunization of only high-risk sector HCWs, all unvaccinated Mantoux-negative HCWs, or not recommending the BCG vaccine for HCWs at all.⁴⁷ Analysis of 3 case studies of children who developed travel-associated TB disease highlighted an absence of information on BCG vaccine efficacy for prevention of travel-associated TB.⁴⁸ Due to the paucity of evidence, recommendations on the use of pre-travel BCG immunization were inconsistent and a low threshold for pre-travel immunization in children was advised until more evidence-based guidelines could be produced.⁴⁸

⁴⁴ Tu H-AT, Vu HD, Rozenbaum MH, Woerdenbag HJ, Postma MJ. A review of the literature on the economics of vaccination against TB. *Expert Rev Vaccines*. 2012;11(3):303–17.

⁴⁵ Hersh AL, Tala-Heikkilä M, Tala E, Tosteson ANA, Fordham von Reyn C. A cost-effectiveness analysis of universal versus selective immunization with *Mycobacterium bovis* bacille Calmette-Guérin in Finland. *Int J Tuberc Lung Dis*. 2003;7(1):22–9.

⁴⁶ Feiring B, Laake I, Molden T, Haberg SE, Nokleby H, Seterelv SS, et al. Do selective immunisation against tuberculosis and hepatitis B reach the targeted populations? A nationwide register-based study evaluating the recommendations in the Norwegian Childhood Immunisation Programme. *Vaccine*. Elsevier Ltd; 2016;34(17):2015–20. Available from: <http://dx.doi.org/10.1016/j.vaccine.2016.02.060>

⁴⁷ Bo M, Zotti CM. European policies on tuberculosis prevention in healthcare workers: Which role for BCG? A systematic review. *Hum Vaccines Immunother*. Taylor & Francis; 2016;12(11):2753–64. Available from: <http://dx.doi.org/10.1080/21645515.2016.1200776>

⁴⁸ Ritz N, Connell TG, Curtis N. To BCG or not to BCG?. *Preventing travel-associated tuberculosis in children*. *Vaccine*. 2008;26(47):5905–10.

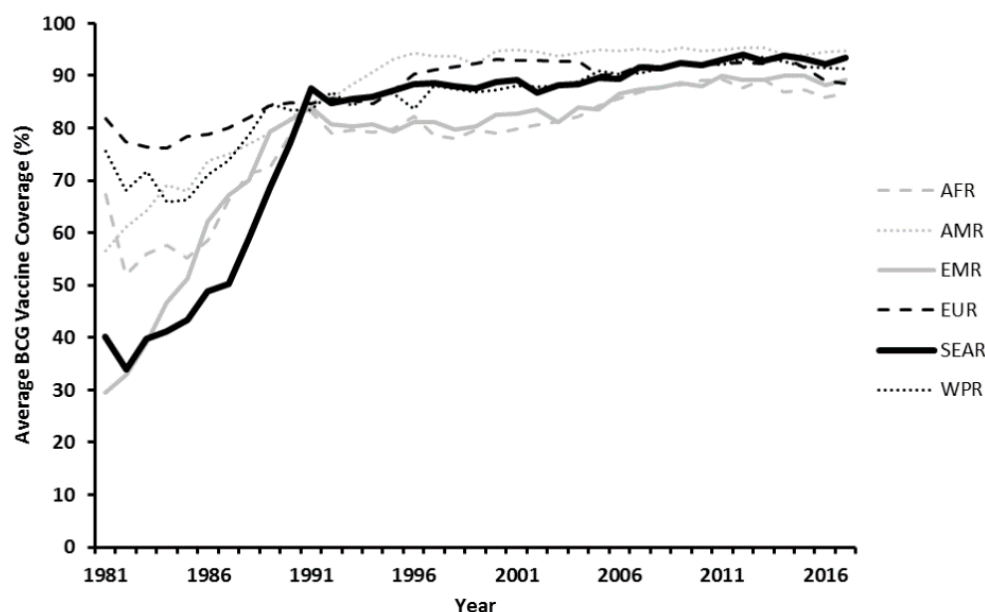


Figure 7: BCG vaccine coverage by WHO Region from 1980-2016.

Source: WUENIC

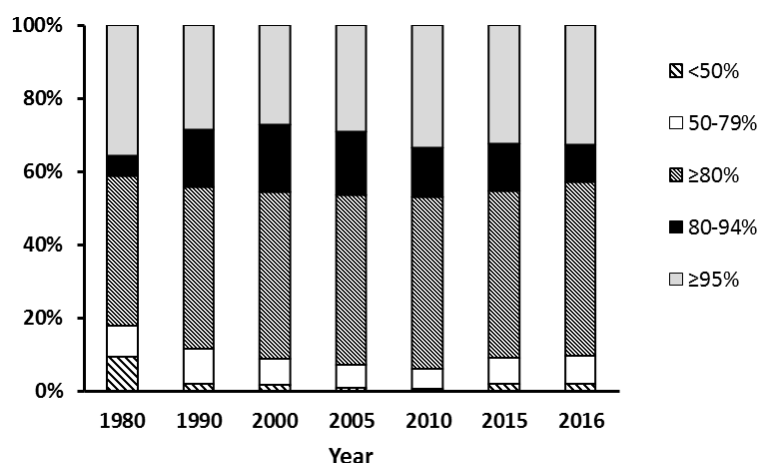


Figure 8: Percentage of countries with BCG coverage <50%, 50-79%, 80-94%, and ≥95%.

Source: WUENIC

8.6. Timeliness of BCG vaccination

BCG timeliness findings were obtained from a study examining “Doses of vaccine given out of order or on the same day in the EPI: analysis of survey data” by Colin Sanderson at the London School of Hygiene and Tropical Medicine funded by the World Health Organization Initiative for Vaccine Research. This study used Demographic Health Surveys (DHS) rounds 5 and 6, and Multiple Indicator Cluster Surveys (MICS) round 3 from 71 countries.⁴⁹ The median vaccine years covered 2004 to 2007.

⁴⁹ Afghanistan; Albania; Armenia; Azerbaijan; Bangladesh; Belize; Benin; Bolivia; Burkina Faso; Burundi; Cambodia; Cameroon; Central African Rep; Chad; Colombia; Comoros; Congo DR; Congo Rep; Costa Rica; Cote d'Ivoire; Djibouti; Dominican Rep; Egypt; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea Bissau; Guyana; Haiti; Honduras; India; Iraq; Jamaica; Jordan; Kenya; Kyrgyz Rep; Lao PDR; Lesotho; Liberia; Madagascar; Malawi; Maldives; Mali; Mauritania; Mongolia; Mozambique; Namibia; Nigeria; Pakistan; Peru; Rwanda; Senegal; Sierra Leone; Sudan; Swaziland; Tajikistan; Tanzania; Thailand; Timor Leste; Togo; Tunisia; Uganda; Ukraine; Uzbekistan; Vanuatu; Vietnam; Yemen; Zambia; Zimbabwe

Methods

To allow the same 24-month ‘follow-up’ period for each infant, the analysis was restricted to infants at least 24 months old at the time of the mother’s interview. Only data from infants with dates for all relevant vaccines given could be used. In some surveys, many dates of administration are missing. Therefore, only surveys with at least 40% of vaccine doses dated were included in the analysis. Percentages of infants administered BCG were calculated by week, up to week 130 for each country.

Findings

The median BCG coverage among infants across the 71 countries surveyed was 38% by 1 week of age; 75% by 6 weeks of age; 88% by 14 weeks of age and 93% by 52 weeks of age.

Table 5: BCG coverage among infants by week of administration in 71 countries*

| | Number of countries with BCG coverage N (%) | | |
|-------------|---|----------------|--------------|
| | <50% N(%) | 50-80% N(%) | >80% N(%) |
| At 1 week | 48 (48%) | 12 (17%) | 11 (15%) |
| At 6 weeks | 13 (18%) | 29 (41%) | 29 (41%) |
| At 14 weeks | 0 (0%) | 8 (11%) | 63 (88%) |

*Not weighted for the population

Data limitations

Only surveys with at least 40% of vaccine doses administered dated were included in the analysis.

Overall coverage for 71 countries (solid black line); coverage for Rwanda (dashed circular line); coverage for India (solid dashed line) and Nigeria (solid dashed and circular line)

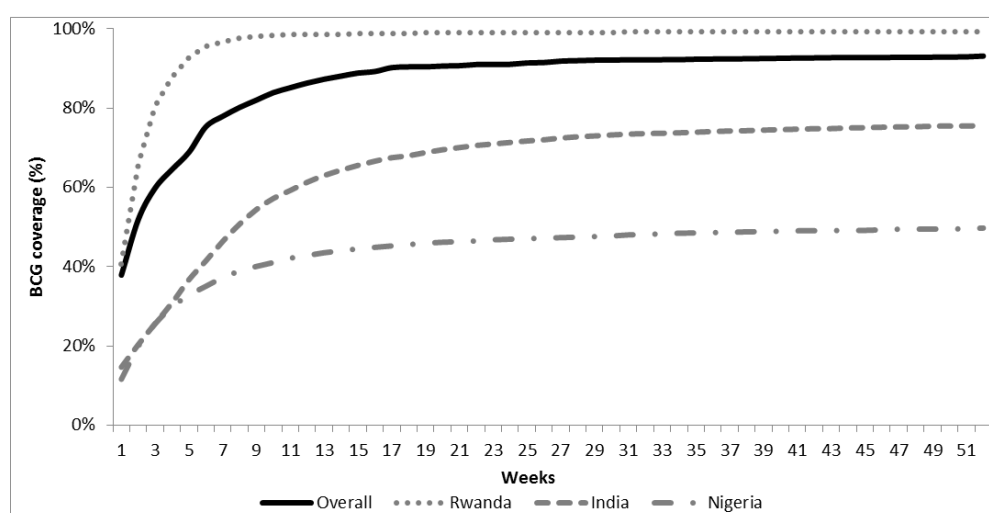


Figure 9: Median BCG coverage among infants by 1 week up to 1 year of age.

9. Vaccine strains and other factors that are influencing safety and effectiveness of BCG vaccines

BCG vaccine contains a live, attenuated strain of *M. bovis* that was originally isolated from TB infected cattle and cultured for a period of 13 years and a total of 231 passages.⁵⁰ Since the BCG vaccine was first used to immunize humans in 1921, over the years, different BCG vaccine seed strains have evolved from the original vaccine strain for production.

BCG vaccine strains that are used worldwide differ in terms of their genetic and phenotypic properties. The original BCG vaccine strain was formerly distributed by the Pasteur Institute of Paris and sub-cultured in different countries using different culture conditions that were not standardised. Over the years, more than 14 sub-strains of BCG have evolved and have been used as BCG vaccine in different parts of the world.

Table 6: List of manufacturers and vaccine strains (July 2017),

| Manu- facturer | Coun- try | Strain | Supplying beyond domestic market | PQ Status | Releasing NRA Functionality | Vial size | Route of ad- ministration | Ongoing pro- duction |
|--|----------------|---|---|--------------|-----------------------------------|---------------|------------------------------|----------------------------|
| ANLIS | Argen- tina | Pasteur 1173 P2 strain | | N | N | 10ds/ 20ds | unknown | Y |
| Fundacao Ataulpho de Paiva | Brazil | Moreau, Rio strain | x | N | Y | 10ds | unknown | N |
| BulBio- NCIPD | Bul- garia | Bulgarian substrain (Sofia) SL222 | x | Y | Y | 10ds/ 20ds | intradermal | Y |
| China National Biotech Group (Shanghai) | China | Chinese substrain Shanghai D2PB30 2 (derived from Danish strain 823) | x | N | Y | 5ds | intradermal | Y |
| China National Biotech Group (Chengdu) | China | Chinese substrain Shanghai D2PB30 2 (derived from Danish strain 823) | x | N | Y | 5ds | intradermal | Y |
| Shaanxi Pharmace- utical Holding Group Biological Products | China | Chinese substrain Shanghai D2PB30 2 (derived from Danish strain 823) | | N | Y | 20ds | unknown | Y |
| AJBiotics | Den- mark | Danish 1331 strain | x | Y | Y | 10ds/ 20ds | intradermal | N |
| Serum Institute of India | India | Russian (Moscow) - 368 | x | Y | Y | 10ds/ 20ds | intradermal | Y |
| Green Signal Biopharma | India | Danish 1331 strain | x | Y | Y | 20ds | intradermal | Y |
| BCG Vaccine Laborator, Chennai | India | Danish 1331 strain, Madras Working Seed Lot (MWSL) | x | N | Y | 10ds/ 20ds | intradermal | N |
| Taj Pharma Ltd | India | Russian (Moscow) - 368 | | N | Y | 20ds | unknown | Y |

⁵⁰ WHO. State of the art of new vaccine research and development. 2006 (WHO/IVB/06.01; available at http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.01_eng.pdf, accessed August 2017.

BCG vaccines – Vaccine strains and other factors

| Manu- facturer | Coun- try | Strain | Supplying beyond domestic market | PQ Status | Releasing NRA Functionality | Vial size | Route of ad- ministration | Ongoing pro- duction |
|---|------------------|---------------------------|---|--------------|-----------------------------------|---------------|--|----------------------------|
| BioFarma | Indo- nesia | Pasteur 1173P strain | x | N | Y | 5ds/ 10ds | intradermal | Y |
| Pasteur Instiute of Iran | Iran | Pasteur 1173P2 strain | | N | Y | 20ds | intradermal | Y |
| Japan BCG Laboratory (JBL) | Japan | Tokyo 172-1 strain | x | Y | Y | 10ds/ 20ds | intradermal/ percutaneous (multipuncture device) | Y |
| Biomed Lublin | Poland | Moreau strain | x | N | Y | 10ds | intracutaneous | Y |
| Microgen | Russia | Russian (Moscow) - 368 | x | N | Y | 10ds/ 20ds | intradermal | Y |
| Inst. Of Virology, Vaccines and Sera Torlak | Serbia | Pasteur 1173P2 strain | x | N | N | 10ds/ 20ds | intradermal | Y |
| NIIDV | Taiwan | Tokyo 172 strain | | N | Y | 20ds | intradermal | Y |
| Queen Saovabha Mem. Inst (Thai Red Cross) | Thai- land | Japanese strain | | N | Y | 10ds | intradermal | Y |
| Inst. Pasteur Tunis | Tunisia | Pasteur 1173P2 strain | | N | Y | 20ds | intradermal | Y |
| Merck & Co (former Organon) | United States | TICE® strain | | N | Y | 1ds | percutaneous (multipuncture device) | Y |
| IVAC - Institute of Vaccines and Medical Biologicals | Viet- nam | Pasteur 1173P2 strain | | N | Y | 20ds | unknown | Y |

Data from April 2017

All manufacturers are in condition of serving the domestic market where the product is registered

AJ Biologics acquired the BCG production facility of Statens Serum Institute

Information for Taj Pharma and Shaanxi are derived from public available sources

Filling and finishing companies as well as distributors not included

There may be differences in protection against TB between different strains of BCG, between products made from the same strain by different manufacturers, and between batches made by individual manufacturers (perhaps caused by having more than one genotype in some seed lots).⁵¹ There is currently not a consensus. A systematic review⁵² of published trials did not find an association with vaccine strains. However, a large randomized trial in 303,092 neonates in Hong Kong however found that the risk of TB with BCG-Pasteur vaccine was 45% (95% CI 22% - 61%) less than with BCG-Glaxo but was published only in abstract form.^{53,54} In

⁵¹ Biering-Sorensen S, Jensen KJ, Aamand SH, Blok B, Andersen A, Monteiro I, et al. Variation of growth in the production of the BCG vaccine and the association with the immune response. An observational study within a randomised trial. *Vaccine*. 2015;33(17):2056-65.

⁵² Mangtani P et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014; 58: 470–80. Figure 3 and 4.

⁵³ Comstock GW. Simple, practical ways to assess the protective efficacy of a new tuberculosis vaccine. *Clin Infect Dis*. 2000;30 Suppl 3:S250-3.

⁵⁴ Shann F. Editorial Commentary: Different Strains of Bacillus Calmette-Guerin Vaccine Have Very Different Effects on Tuberculosis and on Unrelated Infections. *Clin Infect Dis*. 2015;61(6):960-2.

one observational study⁵⁵, there were large differences in the effectiveness of different BCG vaccine strains in a series of cohort studies in Kazakhstan:

| | Effectiveness against | |
|-------------------|---------------------------|----------------------|
| | Clinical TB notifications | Culture confirmed TB |
| BCG-Japan | 69% | 92% |
| BCG-Serbia | 43% | 82% |
| BCG-Russia | 22% | 51% |

The authors noted potential sources of bias in their study, including possible variations in tuberculosis incidence over time, possible changes in diagnostic and notification practices, and possible catch-up vaccination in those unvaccinated. The limitations of current studies make it difficult to draw definitive conclusions. Further research is thus needed.

The effect of differing colony forming units (CFU) concentrations in BCG vaccines is unknown. For example, a dose of BCG-Japan contains approximately 5-fold more CFU than the other WHO prequalified BCG vaccines. The number of CFU claimed by the manufacturers in each 0.05 ml infant intradermal dose is:

| Country | Manufacturer | Strain | Dose | CFU |
|-----------------|--------------|-------------|---------|----------------------------------|
| Bulgaria | Intervax | Russia-I | 0.05 ml | 0.75 - 3 x 10 ⁵ CFU |
| Denmark | SSI | Danish 1331 | 0.05 ml | 1 - 4 x 10 ⁵ CFU |
| India | Green Signal | Danish 1331 | 0.05 ml | 1 - 4 x 10 ⁵ CFU |
| India | SII | Russia-I | 0.05 ml | 1 - 4 x 10 ⁵ CFU |
| Japan | JBL | Tokyo 172 | 0.05 ml | 1.8 - 19.5 x 10 ⁵ CFU |

In addition to determining the CFUs manufacturers are also required to measure the total bacterial concentration which measures both viable and killed bacteria (WHO TRS 979 Annex 3). It is known that there can be a significant quantity of killed bacteria in the finished vaccine depending on manufacturing process⁵⁶, however it is not known whether the quantity of killed bacteria has any impact on the immunogenicity or safety/reactogenicity of the vaccine.

Very little is known about the comparative effectiveness of the WHO prequalified BCG vaccines, and deep genome sequencing has not been done to determine how many different genotypes are in each of the WHO prequalified BCG vaccines. The mixture of genotypes in individual BCG vaccines (at least 2 genotypes in BCG-Denmark and four in BCG-Japan) may contribute to the large inter-batch variation that compromises manufacture. Using a single genotype is likely to lead to more consistent production of BCG and reduce the potential for shortages. Deep genome sequencing should be used routinely for quality control during production of BCG vaccine to monitor variation in the genotypes present in the product.⁵⁷

The formulation of international requirements for freeze-dried BCG vaccine is complicated by the following:

a) a number of different strains derived from the original strain of BCG are used in vaccine manufacture;

⁵⁵ Favorov M, Ali M, Tursunbayeva A, Aitmagambetova I, Kilgore P, Ismailov S, et al. Comparative tuberculosis (TB) prevention effectiveness in children of Bacillus Calmette-Guerin (BCG) vaccines from different sources, Kazakhstan. PLoS One. 2012;7(3):e32567.

⁵⁶ Gheorghiu et al. Stabilisation of BCG Vaccines. Dev Biol Stand 87, 251-261. 1996.

⁵⁷ Wada T, Maruyama F, Iwamoto T, et al. Deep sequencing analysis of the heterogeneity of seed and commercial lots of the bacillus Calmette-Guérin (BCG) tuberculosis vaccine substrain Tokyo-172. Sci Rep. 2015;5:17827.

- b) many of the strains used in vaccine manufacture contain more than one genotype;
- c) a number of different manufacturing and testing procedures are employed;
- d) it is difficult to determine the relationship between significant differences *in vitro* and *in vivo* between different BCG vaccine strains, in one product over time and differences in protective efficacy against TB in humans;
- e) vaccines are produced with different total bacterial content and numbers of culturable particles; (e.g. BCG Tokyo contains approximately 5-fold more CFU per dose than BCG Russia)
- f) vaccines intended for administration by different routes are prepared. The WHO recommendations⁵⁸ focus on ensuring the production of consistent vaccine lots with characteristics similar to those of lots previously shown to be safe and effective. In order to avoid variation, the total number of passages from master seed lot to final product should be monitored and controlled. WHO Reference Reagent substrains (BCG Danish 1331, Tokyo 172-1, Russian BCG-I and BCG Moreau-RJ) are also available as comparators for validity and consistency monitoring in viability assays.

10. Market update BCG Vaccines⁵⁹

Summary

For 2017, BCG vaccine supply is estimated to be 1.5 times greater than forecasted demand. This excess supply is reassuring given the instability of the manufacturing process and is important progress from the restricted supply situation in recent years. However, demand flexibility is limited due to in-country product registration constraints and supply still being concentrated, with a few large suppliers with prequalified products serving most countries. Consequently, shortages may still occur.

Market highlights- Over ten years (2005–2015), short-duration stock-outs of BCG (maximum 1.5 months) have been reported across all regions, income groups and procurement methods. The African region, low income countries (LICs) and lower-middle income countries (LMICs) were most affected. In 2014 and 2015, average stock-out duration increased. Stock-outs seem to be caused by several factors: production issues, countries having only one product registered, timely availability of financing (national or external), procurement shortcomings, and inefficient vaccine management.

Global Demand- Annual global demand is forecasted at ~350M doses according to a model based on country-reported EPI schedule, UN Population Division (UNPD) population, WHO-UNICEF estimated coverage, 50% wastage, and historical procurement data. Information on past country purchases shows that countries may be over procuring BCG, possibly due to actual wastage >50%, large country stocks, or country target population greater than UNPD estimates. The greatest difference in forecasted demand and historical procurement is seen for self-procuring LMICs.

⁵⁸ WHO. Recommendations to assure the quality, safety and efficacy of BCG vaccines. Annex 3 in WHO TRS No. 979. Available at http://who.int/biologicals/areas/vaccines/TRS_979_Annex_3.pdf?ua=1.

⁵⁹ The data sources for assessing stock-outs were regional consultations (current) and the WHO/UNICEF Joint Reporting Form (JRF) reported data on stock-outs (past). The demand analysis included sources of historical procurement data (JRF and UNICEF) and global demand forecast (Linksbridge/Gates Foundation Global Vaccine Market Model). Data for the supply analysis were obtained by manufacturer interviews, PAHO Revolving Fund consultations, historical procurement data (JRF and UNICEF), and review of published articles and four policy papers concerning supply. The pricing analysis is based on review of historical data (WHO Vaccine Product, Price and Procurement database (V3P), UNICEF SD, PAHO Revolving Fund)

Global Supply- Between 2013 and 2015, manufacturing issues for most WHO prequalified (PQ'd) vaccines led to temporary reduced production or suspension of production. Additionally, some non-PQ'd vaccines exited the market. Nevertheless, supply increased significantly in 2016, as some of the manufacturers' production issues were resolved and the vaccine of a new supplier, GreenSignal, was PQ'd. In 2017, supply is estimated to reach ~500M doses from 19 suppliers. The suppliers can be split into two groups: (1) four suppliers with PQ'd products that can reach 169 countries (86% of WHO member states) that accept UN procurement or have one of the PQ'd products registered and (2) fifteen suppliers with non-PQ'd products that can serve 52 countries where they have product registered. In 2017/2018, three manufacturers are expected to be back on the market and additional capacity could be made available from one other currently active manufacturer.

Supply/Demand Balance- For 2017, BCG vaccine supply is estimated to be 1.5 times greater than forecasted demand based on historical procurement data (JRF and UNICEF) and global demand forecast.⁶⁰ This excess supply is reassuring given the instability of the manufacturing process and is important progress from the restricted supply situation in recent years. Nevertheless, the BCG market is not risk free. Two main factors contribute to the risk:

- Supply concentration: 50% of global vaccine supply is produced by two manufacturers, and, more important, those two manufacturers account for 75% of supply of products PQ'd by WHO. Though the loss of a major supplier would not lead to a supply/demand imbalance, it would certainly create a constrained supply situation. In those circumstances, vaccine requirements for self-procuring countries and countries procuring through the United Nations will need to be coordinated. Of note, these two major suppliers are released by the same National Regulatory Authority (NRA): The Central Drugs Standard Control Organization (CDESCO) of India.
- Limited demand flexibility: one-third of countries have only one product registered and, as a result, may be at risk for shortages should a production issue occur. Among those, the most at risk are countries with BCG in the EPI schedule, a large birth cohort, and those that import vaccines, and thus have less control or visibility on production issues and risks.

Pricing- Over the past ten years, the price for BCG has remained low – the median reported price in 2015 was US \$0.52 (range \$0.04–\$15.08 for 29 reporting countries, plus UNICEF and PAHO each included as a single price point). Pricing data (2015) for self-procuring countries shows that price per dose varies by income level, with high income countries (HICs) paying significantly more than middle income countries (MICs), albeit for different products/presentations. Disparity by region is also seen; notably, LMICs in the African region (AFR) reported a much higher price per dose than the European region (EUR) or the Western Pacific region (WPR) for the same product. Countries (excluding HIC WPR outlier) are paying up to 32 times more than the UNICEF price. Affordability for countries has not been raised as an issue for the BCG market. Yet, the low price may be leading to under-investment on the production side.

Areas for Action- Global immunization stakeholders, countries and manufacturers can work to enhance sustainable access to BCG supply through the following methods:

- Collect and share information on global demand, supply and price of BCG to continue risk identification
- Enhance supply management at country level, reducing procurement volumes when necessary

⁶⁰ Linksbridge SPC. Global Vaccine Market Model (GVMM) Demand Module. 2017.

- Investigate strengthening the production processes of a few key manufacturers for supply security
- Explore opportunities for registration of several BCG products in each country and following the “WHO Collaborative Procedure for Registration of Prequalified Products”

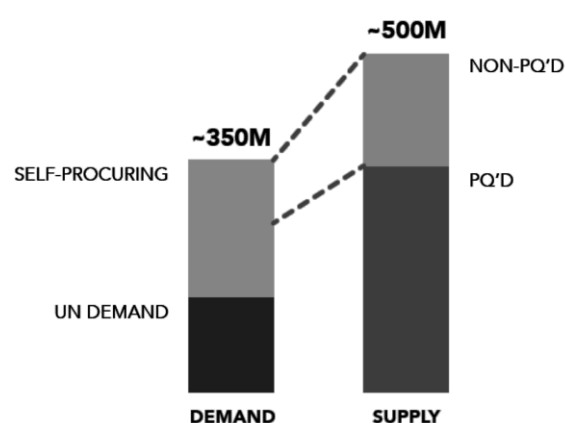


Figure 10: 2017 Estimated Supply/Demand Balance

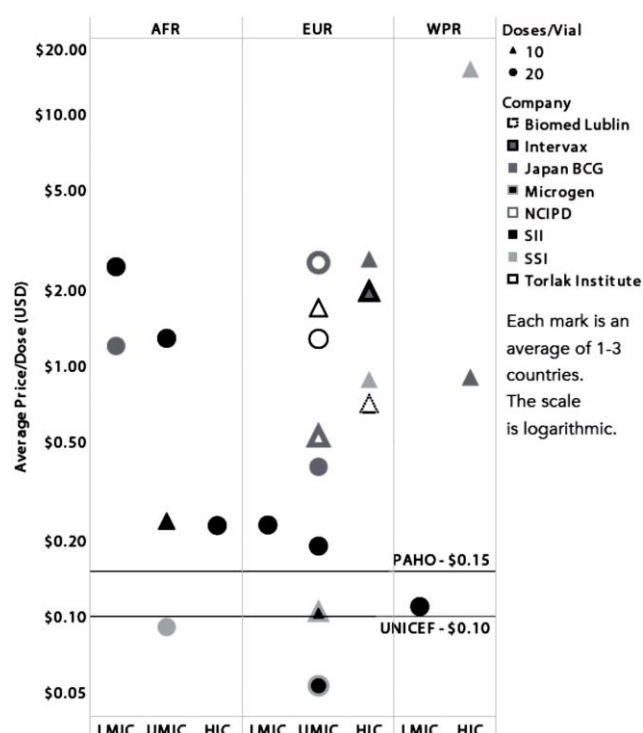


Figure 11: Average self-procuring Price/Dose by manufacturer (2015)

10.2. Impact of BCG vaccine shortages

Among countries experiencing BCG vaccine shortages, immunization policy changes included not administering the vaccine, administering the vaccine only when available, cohorting vaccinees on specific days to maximize use of multi-dose vials, and only administering the vaccine in certain populations and regions of the country.⁶¹ Mathematical modeling of pediatric TB deaths during BCG supply shortages estimated that an additional 11,713 additional TB deaths would occur in the first 15 years of life per 10% annual supply shortfall.⁶² As BCG supply shortages can result in increased pediatric TB mortality, collaboration between health agencies and vaccine manufacturers is crucial to ensure global BCG supply continuity.^{61,62}

⁶¹ Kontturi A et al. The impact of Bacille Calmette-Guerin shortage on immunisation practice and policies in Europe - A Paediatric Tuberculosis Network European Trials Group (ptbnet) survey. *Tuberculosis*. 2016;101:125–9.

⁶² Harris RC et al. The potential impact of BCG vaccine supply shortages on global paediatric tuberculosis mortality. *BMC Med*. BMC Medicine; 2016;14(1):138. Available from: <http://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0685-4>

10.3. How to mitigate the impact of BCG shortages

1. In light of the previous global shortage of BCG vaccines, WHO, with UNICEF, prepared a set of priority actions to help cope with the shortage and prioritize distribution of available doses. WHO should work with UNICEF, PAHO Revolving Fund, countries, and manufacturers to understand the cause of the shortage and attempt to resolve it
2. Careful planning of limited supply allocation should occur through collaboration between WHO, UNICEF Supply Division, PAHO Revolving Fund and BCG vaccine manufacturers to provide vaccines to priority countries. Countries/large refugee settings will be prioritized based on their TB and leprosy risk taking into consideration
 - The TB rate per 100,000 population, hence the highest TB transmission and where infants have the highest risk of being infected with TB. This of course will necessitate the updating of the development of a list of countries with the highest TB rate per 100,000 population. In particular, countries with health systems that are not able to track and provide preventive treatment to children should receive priority.
 - The risk of transmission of leprosy is reflected by the leprosy case notification rate and % of children among total notified cases for leprosy.
3. Allocation of vaccine will be deprioritized for any re-vaccination (which is not recommended).

11. BCG efficacy and effectiveness against TB

Based on previous available evidence, the efficacy of BCG vaccine was believed to mainly prevent severe forms of tuberculosis (TB) in children. Research evaluating its efficacy to prevent pulmonary TB (PTB) has revealed widely varying results, ranging from little or no protection to relatively high protection. Similarly, previous evidence has suggested that BCG does not prevent TB infection.

Recently, a more extensive evaluation has been carried out towards better understanding the effectiveness of BCG vaccine against various forms of TB and what factors contribute towards its variation in protection. New information is also emerging on BCG vaccine protection against primary TB infection in children exposed to persons with PTB.

BCG vaccine efficacy against Pulmonary Tuberculosis - evidence from randomised controlled trials

Mangtani et al., conducted an extensive systematic review and meta-analysis of randomized controlled trials with the aim of estimating efficacy of BCG against PTB, miliary and meningeal TB, as well as gaining better insight into factors associated with vaccine efficacy.⁶³ A search of 10 medical databases revealed 18 randomised or quasi-randomised trials published between 1945 and 2004, in which human study subjects were randomised to BCG versus placebo or other control. The participants were followed up to assess incidence of tuberculous disease - PTB (all 18 studies), meningeal or miliary TB (6 studies). The studies involved 309,300 participants and were conducted in various countries: USA (10 trials), Canada (1 trial), India (4 trials) and Haiti (1 trial).

Although an overall rate ratio (RR) of PTB comparing vaccinated with unvaccinated participants of 0.50 (95% CI 0.36 – 0.72) for PTB was noted in the forest plot this was not considered appropriate to use given the

⁶³ 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. Clin Infect Dis. 2014;58(4):470–80.

considerable heterogeneity noted across the trials. Vaccine protection against PTB varied by a priori defined trial subgroups: study design, age of vaccination, tuberculin skin test (TST) positivity, and distance from the equator. Analysis in the different subgroups showed VE was higher in studies with lower risk of diagnostic detection bias (60%, 95% CI 36 – 75). Among those vaccinated as neonates, RR for PTB was 0.40 (95% CI 0.28-0.56). Among school age children who were TST negative at time of intervention (mycobacterial naïve), vaccine protection was higher (RR 0.25, 95% CI 0.21 – 0.31), however protection was low among older age groups who were TST negative (RR 0.88, 95% CI 0.58 – 1.31). In studies in which TST status was not stringently determined, therefore may have included TST+ or mycobacterial exposed children, average protection from PTB was lower (school children RR 0.67, 95% CI 0.54 – 0.84, older age groups RR 0.81, 95% CI 0.55 – 1.22).

In this meta-analysis, protection against PTB appeared to be higher in settings further from the equator (latitude > 40° RR 0.32, 95% CI 0.22-0.46 versus latitude 0° - <20° RR 0.78, 95% CI 0.58 – 1.05). However, the 5 studies conducted at latitudes 0° - < 20° were mostly among school age (1 study) or older age groups (3 studies), without stringent TST testing (3 studies). Therefore, findings of lower VE at low latitude settings may be related to inclusion of individuals who were already mycobacteria (TB or non-TB) exposed among other factors such as higher TB endemicity. In contrast, the 8 studies from latitudes beyond 40° were mostly neonatal vaccination (4 studies), or stringently TST negative school age children, with 7 of the 8 studies having low risk of bias (high quality). Findings of higher VE at high latitude settings therefore may be related to inclusion of individuals who were not already mycobacteria exposed among other factors such as lower TB endemicity and general better quality of studies. The 5 studies from latitude 20° – 40° were a mixture of school age or older participants, with mixture of stringent TST testing (3 studies) and non-stringent testing (2 studies), most studies of low bias. Indeed a formal metaregression analysis noted a significant proportion of the effect of latitude on efficacy was attenuated taking into account age at vaccination and tuberculin testing stringency before vaccination. The authors suggested the remaining persistence of a latitudinal effect could be due to the fact that tuberculin testing may not exclude exposure to all environmental mycobacteria.

There is a paucity of BCG vaccine RCTs conducted in low latitudes. This meta-analysis of trials formed part of a larger systematic review that included observational studies.⁶⁴ For instance seven of eight case-control studies which were of neonatal BCG against pulmonary TB (with only one above 30° latitude) were pooled indicating a moderate protective effect. Further research and analysis of such studies with low risk of bias and low prior exposure to mycobacteria to provide clarity to this question would be useful.

BCG vaccine efficacy against Meningeal and Miliary Tuberculosis - evidence from randomised controlled trials and Case Control Studies.

The systematic review by Mangtani *et al*⁶³, identified 6 RCTs which reported on BCG protection against meningeal and miliary (disseminated) TB. These studies included 157,264 participants, largely in the USA, Canada or the United Kingdom (5 studies), and one study in Puerto Rico. Vaccination vs placebo was given in neonatal period (2 studies), school age (3 studies), and older age (1 study). Vaccine protection was substantial (RR 0.15, 95% CI 0.08 – 0.31), reducing severe TB in vaccinated individuals by 85%. Protection was highest when vaccination was done in the neonatal period, with 90% reduction of severe TB (RR 0.10, 95% CI 0.01 – 0.77), and among school age children who were TST negative, with 92% reduction of severe disease

⁶⁴ Abubakar I *et al*. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. *Health Technol Assess*. 2013 Sep;17(37):1-372. figure 30 page 66 and figure 34 page 71 page 86 case control studies, and table 12 page 78

(RR 0.08, 95% CI 0.03 – 0.25). Vaccination of school age children or older individuals who were not stringently TST tested revealed little evidence of protection against severe disease, however the numbers of cases of severe TB were small for these age groups (0 – 3 cases) resulting in wide confidence intervals and imprecise estimates.

A systematic review and meta-analysis of 14 case control studies by Trunz *et al.*⁶⁵ examined BCG VE against meningitis and against miliary TB. The studies were published between 1980 and 1996, six were conducted in Latin America, predominantly Brazil, and eight in Asian countries, predominantly India. Incidence of TB meningitis was reduced by 73% overall (95% CI 67-87%), with higher protection in the Latin American studies (VE 87%, 95% CI 78-92%) compared to Asian settings (VE 69%, 95% CI 60-76%). Incidence of miliary TB was reduced by 77% (95% CI 58 – 87%) as reported in four of the studies in Asia and Latin America.

These studies support previous evidence that BCG vaccination confers high protection against severe forms of TB, but highlights the paucity of evidence from African high TB endemic settings.

Emerging evidence of BCG vaccine protection against primary infection with tuberculosis

Recently, the question of whether BCG vaccine provides any protection against primary infection with TB was explored in a systematic review and meta-analysis conducted by Roy *et al.*⁶⁶ Previously, it had been believed that the vaccine does not prevent TB infection, however evidence for this has been scarce, largely due to the limitations of TST which cannot distinguish if a positive response is due to *M tuberculosis* infection, or BCG vaccination, or non-tuberculous mycobacterial infection. Recently, T cell based interferon gamma release assays (IGRA) have been developed which are specific for detection of *M tuberculosis* infection, and are not reactive to BCG immune responses or non-tuberculous mycobacterial infection. Therefore, these assays make it possible to identify if an individual is MTB infected or not.

Roy *et al.*⁶⁶ examined the question of whether BCG vaccination prevents MTB infection. They searched multiple electronic databases from 1950 to 2013 for studies which satisfied the inclusion criteria. Studies were in community congregated settings and households, and BCG vaccination was determined by one or a combination of BCG scar, medical record documentation, or parental recall of vaccination. Exposure to TB was defined as close contact with person/s with active TB as identified by the treating physicians (in 13 of 14 studies index case had smear positive PTB). TB infection was defined as any positive IGRA result in a child contact, and TB disease was defined as presence of active TB as reported by study authors. Outcomes of both infection and active disease were determined at point of IGRA testing after TB exposure.

Fourteen studies with 3,855 participants were analysed. The settings included European countries (9 studies), Sub-Saharan Africa (3 studies), and Asia (2 studies).

Primary analysis of all 14 studies revealed that BCG vaccinated children exposed to persons with open pulmonary TB had 19% less TB infection than unvaccinated children (95% CI 8 – 29%), and in a subset of 6 studies that followed up exposed children to determine additional incident infection, vaccinees had 27% less TB infection (95% CI 13 – 39%). Protection against infection varied by study quality, with greater protection

⁶⁵ Trunz BB *et al.* Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006;367(9517):1173–80.

⁶⁶ Roy A *et al.* Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. *BMJ*. 2014;349(aug04_5):g4643. Available <http://www.bmj.com/content/349/bmj.g4643>, accessed September 2017.

in higher quality studies of low Newcastle-Ottawa score (VE 32%, 95% CI 16 – 45%), and in higher latitudes (latitude 0° - <20°, VE 13%, latitude 20° - < 40°, VE 12%, latitude 40°+, VE 26%).

Restricting analysis to 6 studies which gave follow-up information on progression to active TB (n=1,745), vaccinated children experienced 71% less active TB disease than non-vaccinees (95% CI 42 – 85%).^{67,68,69,70,71,72} Among children who were IGRA positive at enrolment (already infected), on follow-up vaccinees had 58% less progression to active TB disease (95% CI 23 – 77%). These findings give us new insight to previously unrecognised protective effects of BCG vaccine – up to 27% prevention of primary TB infection, and 58% prevention of progression to any active TB disease among children age up to 16 years already infected with MTB at time of enrolment into the study.

This new evidence of additional protective effects of BCG vaccination to prevent TB infection albeit modest, as well as to prevent progression to active TB disease, has implications on its overall effect on the control of TB. The infected young child will over the decades become the latent TB “carrier” who may later in life experience reactivation and contribute to TB transmission during their adult life.

The evidence from RCTs showing that BCG prevents PTB by as much as 50%, especially when given in the neonatal period, or in school age children who are TST negative on stringent testing. This evidence should be appreciated as a significant benefit of the BCG vaccine, over and above its well-known protection against severe forms of TB in children.

12. BCG efficacy and effectiveness against leprosy

In comparison to the effectiveness of BCG against TB, BCG seems to be more protective against leprosy. The effectiveness of BCG vaccination against leprosy was recently analyzed in a systematic review (5 RCTs, 6 cohort studies, 17 case-control studies).^{18,73}

It found BCG to be effective in preventing leprosy, with an overall pooled RR of 0.45 (95% CI 0.34 to 0.56). However, across studies BCG had a variable protective effect, ranging from 20-80% reduction in risk.⁷⁴ The variation in the level of protection may be partly related to the strain of BCG studied and variation in study methodology. There was limited data on the effects of age on effects of BCG vaccination efficacy. In the RCTs, BCG had a larger effect in persons vaccinated at <15 years of age compared with those older than 15 years of age. All cohort studies were conducted in persons vaccinated prior to 15 years of age and the case-control studies did not report age of vaccination. Newborns were included in the studies were not analyzed

⁶⁷ Eisenhut M et al. BCG vaccination reduces risk of infection with Mycobacterium tuberculosis as detected by gamma interferon release assay. *Vaccine* 2009;27:6116-20.

⁶⁸ Eriksen J et al. Protective effect of BCG vaccination in a nursery outbreak in 2009: time to reconsider the vaccination threshold? *Thorax* 2010;65:1067-71.

⁶⁹ Soysal A et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005;366:1443-51.

⁷⁰ Dominguez J et al. Comparison of two commercially available gamma interferon blood tests for immunodiagnosis of tuberculosis. *Clin Vaccine Immunol* 2008;15:168-71.

⁷¹ Okada K et al. Performance of an interferon-gamma release assay for diagnosing latent tuberculosis infection in children. *Epidemiol Infect* 2008;136:1179-87.

⁷² Tsolia MN et al. Whole blood interferon-gamma release assay is a useful tool for the diagnosis of tuberculosis infection particularly among Bacille Calmette Guérin-vaccinated children. *Pediatr Infect Dis J* 2010;29:1137-40.

⁷³ Poobalan et al. Systematic review on the effectiveness and efficacy of BCG against leprosy. 2017, unpublished.

⁷⁴ Setia et al. The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis*. 2006 Mar;6(3):162-70.

separately. The number of BCG doses, and whether the study evaluated a general population or focused on leprosy contacts did not significantly affect results.

For preventing leprosy among contacts of leprosy cases BCG revaccination is used as an approach. The impact of BCG revaccination on reducing disease in contacts of leprosy patients has been investigated with contradictory results. Cunha et al (2008)⁷⁵ showed no additive protection of revaccination in a RCT of almost 100,000 Brazilian school children who received their first vaccination at birth. On the other hand an RCT⁷⁶, in Malawian infants and adults showed that, a second BCG vaccination afforded an additional 49% protection compared with no revaccination. A potential explanation for these discrepant results might be that revaccination of adults is only beneficial once the initial immune response from the childhood immunization wanes. The evidence on the effectiveness of revaccination for adults exposed to a case (contacts) seems too limited at this stage, with only 2 RCTs with conflicting results, to consider it for changes in the recommendation of BCG.

Düppre et al (2008)⁷⁷ assessed the effectiveness of 1-2 doses of BCG vaccination against leprosy among the contacts of 1161 patients in Brazil over 18 years of follow up. It was noted that of the 122 cases of leprosy detected in this study, 28 (23%) occurred within the first 2-10 months following vaccination. The risk of leprosy during the initial months of exposure was highest among those vaccinated with no previous scar, and assumed not to have received BCG in infancy. However, the number of cases detected declined substantially after the first year, and in the following years the protection rate in this group reached 80%. Over the study period of 18 years, the protection conferred by BCG was 56% and was not substantially affected by previous BCG vaccination. Since 1987 in Brazil, BCG vaccination of all contacts has been considered an effective means of substantially reducing the incidence of leprosy and therefore it is part of the national guidelines on leprosy. As such, Brazil officially recommends BCG (re)vaccination (up to 2 lifetime doses of BCG) for contacts without signs or symptoms of leprosy upon examination, regardless of whether the index case is classified as paucibacillary (PB) or multibacillary (MB).

Schuring et al (2009)⁷⁸ evaluated the effects of BCG vaccination status and post-exposure prophylaxis (PEP)⁷⁹ in the form of single-dose rifampicin (SDR) on prevention of leprosy in a secondary analysis of a single centre, double blind, cluster randomized, placebo-controlled trial on rifampicin prophylaxis. Individually, BCG vaccination (given at infancy) and PEP (SDR) given to contacts of leprosy patients were each protective against leprosy disease (reduction in risk 57% [95% CI: 24–75%] and 58% [95% CI: 30–74%], respectively). The combined strategies showed a protective effect of 80% at 2 years follow up (for BCG OR: 0.43 (95% CI 0.25 to 0.76), for rifampicin OR: 0.42 (95% CI 0.26 to 0.70) and for combined OR: 0.20 (95% CI 0.08 to 0.50)).

⁷⁵ Cunha SS et al. BCG revaccination does not protect against leprosy in the Brazilian Amazon: a cluster randomised trial. *PLoS Negl Trop Dis*. 2008 Feb 13;2(2).

⁷⁶ Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet*. 1996 Jul 6;348(9019):17-24.

⁷⁷ Düppre NC et al. Effectiveness of BCG vaccination among leprosy contacts: a cohort study. *Trans R Soc Trop Med Hyg*. 2008 Jul;102(7):631-8.

⁷⁸ Schuring et al. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. *Vaccine*. 2009 Nov 23;27(50):7125-8.

⁷⁹ PEP in the form of single-dose rifampicin (SDR) has been shown to be effective at reducing the detection of leprosy over 1 to 2 years in contacts (57%) However, PEP was no more effective at reducing incidence of leprosy over a 3 to 4 year period. (Moet et al, Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*. 2008 Apr 5;336(7647):761-4.)

On the basis of the Schuring data, a large cluster randomized controlled trial (MALTALEP) has begun in Bangladesh to compare the effect of immunization with BCG alone vs BCG plus PEP in adults and children (>5 years of age) contacts of approximately 1300 new leprosy cases.⁸⁰ Recently published observational data from this RCT (after one and half year follow up) indicate that 21 of 5136 contacts developed paucibacillary leprosy within 12 weeks after receiving BCG vaccination.⁸¹ Such cases soon after BCG vaccination could be due to immune reconstitution inflammatory syndrome (IRIS), consistent with the hypothesis that BCG accelerates the natural history of *M. leprae* infection following BCG vaccination. The MALTALEP study will have a follow up over 2 years; however as in the case of the Duppre study, long term follow up (5 to 10 years) will also be needed, due to the long incubation period of the disease, which is assumed to range from around 2 to 20 years. Other whole mycobacteria have been evaluated as vaccines, but there is little evidence that they differ significantly from BCG in protective efficacy, and data are more limited. An Indian study analyzing BCG plus killed *M. leprae* and BCG alone or placebo BCG plus killed *M. leprae* reported that, *M. leprae* significantly reduced the incidence of leprosy compared with saline. The relative risk reduction was 64% (95% CI 50.4% to 73.9%).⁸² In contrast a RCT from Malawi reported no significant difference in incidence of leprosy at 5-9 years (0.09% with BCG plus killed *M. leprae* and 0.08% with BCG; RRR 1.06(95% CI 0.62-1.82)).⁷⁶

13. Non-specific ('heterologous' or 'non-targeted') effects of BCG

BCG vaccination has been reported to have non-specific ('heterologous') effects (NSE), which, like the specific effects of BCG, may differ between genotypes and manufacturers.^{51,83,84,85} The implications of these effects, and the settings and circumstances in which they are clinically important need to be more clearly defined.^{86,87,88,89,90} The NSE of BCG should not be confused with the specific and cross-protective effects of BCG vaccination against *M. leprae*, *M. ulcerans* and other non-tuberculous mycobacteria.

In April 2014, SAGE discussed the importance of NSE and stated: *"Regarding the possible non-specific effect of BCG on all-cause mortality, the epidemiological review suggested possible beneficial effects on all-cause mortality. SAGE concluded that the evidence does not support a change in policy for BCG immunization as soon as possible after birth. The available data suggest that the current WHO recommended schedule for BCG vaccine has a beneficial effect on all-cause mortality and this should be emphasized."*⁹¹

⁸⁰ Richardus et al. The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: a cluster randomized controlled trial (MALTALEP study). BMC Infect Dis. 2013 Oct 3;13:456.

⁸¹ Richardus et al. Clinical manifestations of leprosy after BCG vaccination: an observational study in Bangladesh. Vaccine. 2015 Mar 24;33(13):1562-7.

⁸² Gupte MD, Vallishayee RS, Anantharaman DS, Nagaraju B, Sreevatsa, Balasubramanyam S, et al. Comparative leprosy vaccine trial in south India. Indian J Lepr. 1998;70:369-88.

⁸³ Anderson EJ et al. The influence of BCG vaccine strain on mycobacteria-specific and non-specific immune responses in a prospective cohort of infants in Uganda. Vaccine. 2012;30(12):2083-9.

⁸⁴ Frankel H et al. Different effects of BCG strains - A natural experiment evaluating the impact of the Danish and the Russian BCG strains on morbidity and scar formation in Guinea-Bissau. Vaccine. 2016;34(38):4586-93.

⁸⁵ Rentsch CA et al. Bacillus Calmette-Guerin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. Eur Urol. 2014;66(4):677-88.

⁸⁶ Shann F. The non-specific effects of vaccines. Arch Dis Child. 2010;95(9):662-7.

⁸⁷ Shann F. The heterologous (non-specific) effects of vaccines: implications for policy in high-mortality countries. Trans R Soc Trop Med Hyg. 2015;109(1):5-8.

⁸⁸ Flanagan KL et al. Heterologous ("nonspecific") and sex-differential effects of vaccines: epidemiology, clinical trials, and emerging immunologic mechanisms. Clin Infect Dis. 2013;57(2):283-9.

⁸⁹ Higgins JP et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ. 2016;355:i5170.

⁹⁰ Pollard et al. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. Arch Dis Child. 2017 May

⁹¹ WHO. SAGE report April 2014. Weekly epidemiological record No 21, 2014, 89, 221-236.

Subsequently, SAGE has been presented with 2 proposed questions and outlines of RCT protocols to further evaluate the hypotheses relating to NSE of vaccines considered by IVIR-AC most pressing and policy relevant with respect to timing and sequencing of infant vaccines:

http://www.who.int/immunization/research/implementation/nse_protocol_comments/en/. SAGE

reiterated the value of definitive evidence to determine the existence and magnitude of the impact of vaccine NSE on susceptibility to severe childhood infection, particularly all-cause mortality, and the potential implications for national vaccination schedules (including BCG vaccination).

In addition to the WHO initiated protocols for RCTs, two additional RCTs are ongoing:

- (i) The *Calmette trial* in Denmark⁹²
- (ii) The *Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR)* in Australia.

Brief overview of the evidence for the NSE of BCG vaccination

A recent systematic review by Higgins *et al*¹⁶⁶ concluded that BCG vaccination was associated with a reduction in all-cause mortality of approximately 50%. Because TB is an infrequent cause of death in infants and young children, this reduction is unlikely to be entirely due to fewer deaths from the disease. It is postulated that, in high mortality settings, BCG's immunomodulatory effects reduce all-cause mortality by also preventing infections other than TB.⁹³ In addition, BCG-vaccination was associated with increased cellular and antibody responses to unrelated vaccines in studies in The Gambia and Australia^{164,94} but not in a recent study in Denmark.⁹⁵

BCG vaccination might also be associated with a reduction in (non-tuberculous) respiratory infections in low mortality settings.^{96,97} The results of different studies have sometimes provoked debate.^{92,98} Some observational studies suggest BCG-vaccination is also associated with protection against allergies, eczema and asthma, though the findings have been inconsistent.^{99,100,101,102,103} One RCT suggests that vaccination with BCG-Denmark of high-risk infants protects against eczema.¹⁰⁴ The *Calmette Study* recently reported that BCG vaccination did not protect against allergy in Denmark.¹⁰⁵ The *MIS BAIR Study* in Australia is ongoing and includes allergy outcomes (allergic (atopic) sensitization, eczema and lower respiratory illness at both 1-year

⁹² Stensballe LG *et al*. BCG vaccination at birth and early childhood hospitalisation: a randomised clinical multicentre trial. *Arch Dis Child*. 2017;102(3):224-31.

⁹³ Pollard A *et al*. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. *Arch Dis Child*. 2017 May 13. pii: archdischild-2015-310282.

⁹⁴ Ota MO *et al*. Influence of *Mycobacterium bovis* bacillus Calmette-Guerin on antibody and cytokine responses to human neonatal vaccination. *J Immunol*. 2002;168(2):919-25.

⁹⁵ Nissen *et al*. Bacille Calmette-Guérin (BCG) vaccination at birth and antibody responses to childhood vaccines. A randomised clinical trial.

⁹⁶ Hollm-Delgado MG *et al*. Acute lower respiratory infection among Bacille Calmette-Guerin (BCG)-vaccinated children. *Pediatrics*. 2014;133(1):e73-81.

⁹⁷ de Castro MJ *et al*. Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis. *Clin Infect Dis*. 2015;60(11):1611-9.

⁹⁸ Benn CS and Sorup S. Commentary: BCG has no beneficial non-specific effects on Greenland. An answer to the wrong question? *Int J Epidemiol*. 2016.

⁹⁹ Arnoldussen DL *et al*. BCG vaccination and allergy: a systematic review and meta-analysis. *J Allergy Clin Immunol*. 2011;127(1):246-53, 53 e1-21.

¹⁰⁰ El-Zein M *et al*. Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. *Int J Epidemiol*. 2010;39(2):469-86.

¹⁰¹ Rousseau MC *et al*. Potential health effects from non-specific stimulation of the immune function in early age: the example of BCG vaccination. *Pediatr Allergy Immunol*. 2008;19(5):438-48.

¹⁰² Freyne B and Curtis N. Does neonatal BCG vaccination prevent allergic disease in later life? *Arch Dis Child*. 2014;99(2):182-4.

¹⁰³ Linehan MF *et al*. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. *J Allergy Clin Immunol*. 2014;133(3):688-95 e14.

¹⁰⁴ Steenhuis TJ, van Aalderen WM, Bloksma N, Nijkamp FP, van der Laag J, van Loveren H, *et al*. Bacille-Calmette-Guerin vaccination and the development of allergic disease in children: a randomized, prospective, single-blind study. *Clin Exp Allergy*. 2008;38(1):79-85.

¹⁰⁵ Thøstesen LM *et al*. Neonatal BCG has no effect on allergic sensitization and suspected food allergy until 13 months. *Pediatr Allergy Immunol*. 2017 Jun 29.

of age and 5-years of age). BCG vaccination may have beneficial effects in type 1 diabetes mellitus¹⁰⁶ and multiple sclerosis.¹⁰⁷ BCG's immunomodulatory properties are routinely exploited in the treatment of bladder cancer.¹⁰⁸ BCG vaccination is associated with protection against melanoma and may play a role in treatment.^{109,110,111} A plethora of data from animal studies provide strong evidence for BCG's ability to protect against a wide range of infections other than TB, including bacteria (e.g. *Shigella flexneri*), viruses (e.g. vaccinia virus) and protozoa (e.g. malaria). This literature has recently been reviewed by Freyne *et al.*¹¹² The immunomodulatory properties of BCG have been explored in *in vitro* experiments for decades (recently reviewed by Freyne *et al.*).¹¹³ A systematic review by Kandasamy *et al.*¹¹⁴ identified 37 studies which measured non-specific immunological effects (NSIE) of BCG vaccination. The included studies had very heterogeneous study designs, which could not be conventionally meta-analysed, providing a low level of evidence quality. The authors concluded that, while some studies showed evidence suggestive of NSIE, no consistent findings were identified that provide confidence in the nature, magnitude or timing of NSIE in humans following vaccination with BCG nor the clinical importance of the findings. There are several plausible mechanisms for the NSE of BCG and other vaccines (recently reviewed by Goodridge *et al.*¹¹⁵). It is likely that the NSE of BCG are mediated partly by heterologous effects on adaptive immunity, but also by potentiating innate immune responses through epigenetic mechanisms, a process termed 'trained immunity'.^{116,117}

14. Duration of Protection

A systematic review with data up to 2009 analysed the duration of protection. The authors report that there was consistent evidence of a protection for up to 15 years. Longer durations of protection seem to be linked to stringent tuberculin testing or those vaccinating neonates. Protection declines with time at a rate which varies between studies.¹¹⁸ A few studies included in the review noted protection beyond 15 years after vaccination. One a long term follow-up of a trial reported persistent BCG vaccine efficacy for 50 to 60 years.¹¹⁹

¹⁰⁶ Faustman DL *et al.* Proof-of-concept, randomized, controlled clinical trial of Bacillus-Calmette-Guerin for treatment of longterm type 1 diabetes. *PLoS One*. 2012;7(8):e41756.

¹⁰⁷ Ristori G *et al.* Effects of Bacille Calmette-Guerin after the first demyelinating event in the CNS. *Neurology*. 2014;82(1):41-8.

¹⁰⁸ Alexandroff AB *et al.* BCG immunotherapy of bladder cancer: 20 years on. *Lancet*. 1999;353(9165):1689-94.

¹⁰⁹ Rosenthal SR. Cancer precursors and their control by BCG. *Dev Biol Stand*. 1986;58 (Pt A):401-16.29.

¹¹⁰ Pfahlberg A *et al.* Inverse association between melanoma and previous vaccinations against tuberculosis and smallpox: results of the FEBIM study. *J Invest Dermatol*. 2002;119(3):570-5.

¹¹¹ Krone B *et al.* Protection against melanoma by vaccination with Bacille Calmette-Guerin (BCG) and/or vaccinia: an epidemiology-based hypothesis on the nature of a melanoma risk factor and its immunological control. *Eur J Cancer*. 2005;41(1):104-17.

¹¹² Freyne B *et al.* BCG-associated heterologous immunity, a historical perspective: intervention studies in animal models of infectious diseases. *Trans R Soc Trop Med Hyg*. 2015;109(1):52-61.

¹¹³ Freyne B *et al.* BCG-associated heterologous immunity, a historical perspective: experimental models and immunological mechanisms. *Trans R Soc Trop Med Hyg*. 2015 Jan;109(1):46-51.

¹¹⁴ Kandasamy *et al.* Non-specific immunological effects of selected routine childhood immunisations: systematic review. *BMJ* 2016;355:i5225.

¹¹⁵ Goodridge HS, Ahmed SS, Curtis N, Kollmann TR, Levy O, Netea MG, *et al.* Harnessing the beneficial heterologous effects of vaccination. *Nat Rev Immunol*. 2016;16(6):392-400.

¹¹⁶ Netea MG, van Crevel R. BCG-induced protection: effects on innate immune memory. *Semin Immunol*. 2014 Dec;26:512-7.

¹¹⁷ Kleinnijenhuis J, Quintin J, Preijers F, Benn CS, Joosten LA, Jacobs C, *et al.* Long-Lasting Effects of BCG Vaccination on Both Heterologous Th1/Th17 Responses and Innate Trained Immunity. *J Innate Immun*. 2013.

¹¹⁸ Abubakar *et al.* Protection by Bacillus Calmette-Guérin vaccination against tuberculosis beyond 10 years: Systematic Review and Meta-Analysis, unpublished systematic review. 2017. Unpublished.

¹¹⁹ Aronson N *et al.* Long-term Efficacy of BCG Vaccine in American Indians and Alaska Natives A 60-Year Follow-up Study. *JAMA*. 2004;291(17):2086-2091.

A cohort study in Brazil suggested that protection lasted for 15–20 years but with no further follow up.¹²⁰ A case control study in Saudi Arabia indicated protection in 15 to 24 year olds but not in 25–34 year olds.¹²¹ Since that systematic review data from a Norwegian study has supported findings of a long duration of protection¹²² and a recent observational study from the UK reports A 20 year protection was observed in children vaccinated in school age which then declined.¹²³ Evidence of a protection against TB for at least 10 years from infant vaccination. Considerable missing vaccine record information and the small numbers unvaccinated precluded assessment of longer duration was seen.¹²³

15. Need for revaccination, vaccination in adolescent and adults

Summary

Although primary infant BCG vaccination is thought to offer durable protection for more than 10 years and there is more recent evidence it may last for 20 years, there is a potential need for BCG revaccination. BCG revaccination is safe in *Mycobacterium tuberculosis* infected and uninfected populations. The evidence from randomized controlled trials and retrospective cohort and case-control studies demonstrates a limited effectiveness of BCG revaccination in adolescents and adults after primary BCG vaccination in infancy for protection against *M. tuberculosis* infection and TB disease. BCG revaccination is not considered cost-effective.

The data were analysed based on retrieved articles from a systematized literature search in PubMed (see appendix) and were categorized into the following themes: Vaccine Safety efficacy and effectiveness and cost-effectiveness (see section on cost-effectiveness).

Safety of revaccination

In a study (Moreau strain (Rio de Janeiro substrain)) in 71,000 Brazilian schoolchildren, adverse reactions to BCG revaccination were rare; and no significant difference in the rate of adverse reactions was observed between primary BCG vaccination and BCG revaccination.¹²⁴ The incidence of adverse reactions was estimated as 1 per 2,854 vaccinations, with no deaths or BCG disease; RR of adverse reaction to BCG revaccination was reported as 2.3 (95%CI 0.69 – 7.80), compared to primary BCG vaccination. An observational study (BCG-Danish, BCG-British) of BCG revaccination in 2997 Swedish school children also reported that the reactogenicity profile is similar to that of primary BCG vaccination.¹²⁵ BCG revaccination of 82 TST positive South African adults (BCG-Danish) showed injection site erythema (68%) and induration (86%) peaked at 1 week; ulceration (76%) peaked at 2 weeks and resolved by 3 months, with diameter of

¹²⁰ Barreto ML et al. Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil. *Int J Tuberc Lung Dis* 2005;9:1171–3.

¹²¹ Al Kassimi FA et al. Does the protective effect of neonatal BCG correlate with vaccine-induced tuberculin reaction? *Am J Resp Crit Care Med* 1995;152:1575–8.

¹²² Nguipodop-Djomo P et al. Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study. *Lancet Infect Dis* 2016;16:219–26.

¹²³ Mangtani et al. Observational study to estimate the changes in the effectiveness of bacillus Calmette–Guérin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK. *HEALTH TECHNOLOGY ASSESSMENT VOLUME 21 ISSUE 39 JULY 2017*.

¹²⁴ Dourado I et al., Rates of adverse reactions to first and second doses of BCG vaccination: results of a large community trial in Brazilian schoolchildren. *Int J Tuberc Lung Dis*. 2003 Apr;7(4):399–402.

¹²⁵ Böttiger M et al., A comparative study of Danish (Statens Serum Institut), Glaxo and Behringwerke vaccines--revaccination of schoolchildren. *J Biol Stand*. 1983 Jan;11(1):1–12.

ulceration >10mm in only 8%, which is a similar reactogenicity profile to that of primary BCG vaccination of TST negative adults in the USA.^{126,127}

Effectiveness of BCG revaccination against TB

Table 7: Primary papers on BCG revaccination effectiveness

| Author /Year | Study Design | Vaccine Strain | Population | Reference Number |
|--------------------------------------|---------------------|----------------|--|------------------|
| Rodrigues et al., 2005 | RCT | BCG- Moreau | Children in Brazil | 128 |
| Barreto et al., 2011 | | | | 129 |
| Barreto et al., 2014 | | | | 130 |
| Karonga Prevention Trial Group, 1996 | RCT | BCG-Glaxo | Individuals in Malawi | 76 |
| Leung et al., 2012 | Observational study | BCG-Glaxo | Primary school children in Hong Kong | 131 |
| Tala-Heikkila et al., 1998 | Observational study | BCG-Glaxo | Children 11 to 13 years old in Finland | 132 |
| Sepulveda et al., 1992 | Observational study | BCG- Pasteur | Young adults in Chile | 133 |

A double-blind, randomised controlled trial of BCG among more than 46,000 people of all ages in Malawi showed no protective benefit of revaccination compared to placebo against confirmed TB disease (IRR 1.43; 95% CI 0.88 – 2.35). However it should be noted that, whilst both primary and BCG revaccination demonstrated added protection against leprosy, neither primary nor BCG revaccination provided protection against TB in this population.⁷⁶ The incidence of confirmed pulmonary TB disease was higher in the BCG revaccination group compared to placebo (IRR 1.74; 95% CI 1.00 – 3.03), but was attributed to an excess of HIV-associated TB in the BCG revaccination arm.

Rodrigues and Barreto *et al.*^{129,130} conducted the BCG-REVAC RCT, which took place in two Brazilian cities, Salvador and Manaus. Using TB incidence as the primary outcome, the BCG-REVAC study found that among children aged 7-14 years initially vaccinated at birth and then revaccinated with BCG at school age, overall vaccine efficacy was 9% (95% CI: -16 - 29%) after 0-5 years of follow-up and 12% (95% CI: -2 - 24%) after extended follow-up for 9 years.¹²⁹ Although no overall benefit of BCG revaccination was observed at either time-point, additional long-term protection against TB disease was observed only at the Salvador site, with a vaccine efficacy (VE) of 19% (95% CI: 3 - 33%), and confined to the subgroup of children less than 11 years of age at revaccination (VE, 33%; 95% CI: 3-54%).^{129,130} Although it has been posited that these results are due to climatic and environmental exposures, evidence of differential exposure to non-tuberculous mycobacteria at the two sites is lacking; this may be a chance finding or due to differences in prior sensitization to *M tuberculosis*.

¹²⁶ Hatherill M et al. Safety and reactogenicity of BCG revaccination with isoniazid pretreatment in TST positive adults. *Vaccine*. 2014 Jun 30;32(31):3982-8. doi: 10.1016/j.vaccine.2014.04.084. Epub 2014 May 9.

¹²⁷ Hoft DF et al. Clinical reactogenicity of intradermal bacille Calmette-Guerin vaccination. *Clin Infect Dis*, 1999. 28(4): p. 785-90.

¹²⁸ Rodrigues LC et al., Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet*. 2005 Oct 8;366(9493):1290-5. Epub 2005 Aug 31.

¹²⁹ Barreto ML 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*. Elsevier Ltd; 2011;29(31):4875–7. Available from: <http://dx.doi.org/10.1016/j.vaccine.2011.05.023>

¹³⁰ Barreto ML et al. Causes of variation in BCG vaccine efficacy: Examining evidence from the BCG REVAC cluster randomized trial to explore the masking and the blocking hypotheses. *Vaccine*. Elsevier Ltd; 2014;32(30):3759–64. Available from: <http://dx.doi.org/10.1016/j.vaccine.2014.05.042>

¹³¹ Leung CC et al. A strong tuberculin reaction in primary school children predicts tuberculosis in adolescence. *Pediatr Infect Dis J*, 2012. 31(2):150-3.

¹³² Tala-Heikkila MM et al. Bacillus Calmette-Guerin revaccination questionable with low tuberculosis incidence. *Am J Respir Crit Care Med*, 1998. 157(4 Pt 1): p. 1324-7.

¹³³ Sepulveda RL et al. Case-control study of the efficacy of BCG immunization against pulmonary tuberculosis in young adults in Santiago, Chile. *Tuber Lung Dis*, 1992. 73(6): p. 372-7.

Suliman *et al.* (2016)¹³⁴ reported the immunological effects of BCG revaccination in an RCT, in which participants were randomly allocated to isoniazid (INH) or placebo treatment before BCG revaccination, to determine if INH impacted *M tuberculosis* specific immune response from revaccination. INH treatment and preclearance of bacilli had little effect on lymphocyte responses boosted by BCG revaccination, however, BCG-reactive natural killer (NK) cell responses remained elevated up to one year post-revaccination¹³⁴. The clinical significance of these immunological findings is unclear.

A retrospective cohort study of 303,692 children in Hong Kong who participated in a programme of BCG revaccination of TST negative children at age 6-9 years, showed no protective benefit against TB disease compared to non-participants (RR 1.28; 95% CI 0.92 - 1.77).¹³¹ A retrospective case-control study in Chile also showed no added protection against TB disease from BCG revaccination, measured by number of BCG scars¹³³, and similarly, a large retrospective cohort study in Finland that analysed risk of TB disease before and after cessation of programmatic school-age revaccination of TST negative children showed no benefit of BCG revaccination.¹³²

¹³⁴ Suliman S et al. Bacillus Calmette-Guérin (BCG) Revaccination of Adults with Latent Mycobacterium tuberculosis Infection Induces Long-Lived BCG-Reactive NK Cell Responses. J Immunol.2016;197(4):1100–10.

GRADE table

What is the safety of BCG revaccination in adolescent and adults?

Population: adolescent and adults in TB endemic areas

Intervention: BCG revaccination

Comparison: Placebo

Outcome: Local, regional and systemic adverse events

| Question necessary for recommendation development: Is BCG revaccination of adolescents and adults safe? | | | | |
|--|--|--------------------------------|---|--|
| | | | Rating | Adjustment to rating |
| Quality Assessment | No of studies/starting rating | | 2 RCTs ^{124,126} 1 Observational Study ¹²⁵ | 3 |
| | Factors decreasing confidence | Limitation in study design | Moderate | -1 |
| | | Inconsistency | None serious | 0 |
| | | Indirectness | None serious | 0 |
| | | Imprecision | Minor | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Strength of association | Not applicable | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Mitigated bias and confounding | Not applicable | 0 |
| | Final numerical rating of quality of evidence | | | 2 |
| Summary of Findings | Statement on quality of evidence | | | Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome. |
| | Conclusion | | | Based on low quality evidence, BCG revaccination of adolescents and adults is safe. |

In a large cohort of Brazilian children enrolled in the BCG revaccination arm of a cluster-randomised open label trial, the incidence of adverse reactions was estimated as 1 per 2,854 vaccinations, with no deaths or BCG disease. RR of adverse reaction to BCG revaccination was reported as 2.3 (95%CI 0.69 – 7.80), compared to primary BCG vaccination.¹³⁵ A subset of eligible participants (68%) was included; and adverse reactions were reported to study staff by passive surveillance with risk of underestimation of the true rate of adverse reactions. A small randomized controlled trial of isoniazid pre-treatment before open label BCG revaccination in TST positive South African adults showed a reactogenicity profile similar to that reported for primary BCG vaccination¹³⁶; as did an observational study among Swedish schoolchildren.¹³⁷

¹³⁵ Dourado, I., et al., Rates of adverse reactions to first and second doses of BCG vaccination: results of a large community trial in Brazilian schoolchildren. *Int J Tuberc Lung Dis*, 2003. **7**(4): p. 399-402.

¹³⁶ Hatherill, M., et al., Safety and reactogenicity of BCG revaccination with isoniazid pretreatment in TST positive adults. *Vaccine*, 2014. **32**(31): p. 3982-8.

¹³⁷ Bottiger, M., et al., A comparative study of Danish (Statens Seruminstitut), Glaxo and Behringwerke vaccines--revaccination of schoolchildren. *J Biol Stand*, 1983. **11**(1): p. 1-12.

GRADE table

What is the efficacy of BCG revaccination in preventing TB disease in adolescent and adults?

Population: adolescent and adults in TB endemic areas

Intervention: BCG revaccination

Comparison: only primary immunization

Outcome: TB disease

| Question necessary for recommendation development: | | | | |
|--|--|--------------------------------|----------------------------------|--|
| Should adolescents and adults who received BCG in infancy be revaccinated against tuberculosis? | | | | |
| | | | Rating | Adjustment to rating |
| Quality Assessment | No of studies/starting rating | | 2 RCT 3 Observational Studies | 3 |
| | Factors decreasing confidence | Limitation in study design | Moderate | -1 |
| | | Inconsistency | Minor | 0 |
| | | Indirectness | None serious | 0 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Strength of association | Not applicable | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Mitigated bias and confounding | Not applicable | 0 |
| | Final numerical rating of quality of evidence | | | 2 |
| Summary of Findings | Statement on quality of evidence | | | Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome. |
| | Conclusion | | | Based on low quality evidence, BCG revaccination of adolescents and adults who received BCG in infancy is not recommended. |

Two randomised controlled trials showed no overall benefit of BCG revaccination in providing additional protection against TB^{138,139}. One very large, cluster-randomised trial of school-age Brazilian children was open-label with no placebo; and the TB endpoint was determined by linkage to health service records.¹³⁸ Extended trial follow-up showed no overall benefit, but modest reduction in TB incidence was observed in the sub-group of younger children receiving BCG vaccination at one study centre.¹⁴⁰ A large, randomised, double-blind, placebo-controlled trial in Malawi showed no benefit of BCG revaccination against all forms of confirmed TB.¹³⁹ The incidence of confirmed pulmonary TB was slightly higher in the BCG revaccination group compared to placebo, but was attributed to an excess of HIV-associated TB.¹³⁹ A small case-control study in Chile¹⁴¹ and two retrospective cohort studies, in Hong Kong and Finland, showed no benefit of BCG revaccination^{142,143}.

¹³⁸ Rodrigues, L.C., et al., Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet*, 2005. 366(9493): p. 1290-5.

¹³⁹ Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga Prevention Trial Group. *Lancet*, 1996. 348(9019): p. 17-24.

¹⁴⁰ Barreto, M.L., 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): p. 4875-7.

¹⁴¹ Sepulveda, R.L., C. Pacha, and R.U. Sorensen, Case-control study of the efficacy of BCG immunization against pulmonary tuberculosis in young adults in Santiago, Chile. *Tuber Lung Dis*, 1992. 73(6): p. 372-7.

¹⁴² Leung, C.C., et al., Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. *Int J Tuberc Lung Dis*, 2001. 5(8): p. 717-23.

¹⁴³ Tala-Heikkila, M., et al., Evaluation of the BCG revaccination programme of schoolchildren in Finland. *Bull Int Union Tuberc Lung Dis*, 1991. 66(1): p. 57-9.

16. Safety of BCG vaccination

Adverse events following immunization (AEFIs) associated with BCG vaccines include local reactions such as injection site abscess or severe ulceration, regional adverse reactions such as ipsilateral regional lymph node enlargement with rare instances of suppuration and fistulae formation and distant disease, in the skin, gut, osteitis (bone) or osteomyelitis (bone marrow). Distal BCG disease may occur more than 12 months after vaccination.

BCG is a live vaccine that has never been cloned and there are now several different seed strains in use that have different phenotypic and genotypic differences. Clusters of AEFIs have been associated with a change in the manufacturing process and/or strain. Between 1971 and 1978 for example, osteitis outbreaks were seen in Finland and Sweden with the highest rates being 72.9 per 100,000 after the manufacture of BCG moved from Sweden to Denmark still based on the Gothenburg strain. The osteitis rates declined when the strain was changed to the Danish (Copenhagen 1331) strain. In the former Czechoslovakia, osteitis rates increased on moving from the Prague to the Moscow strain 2-4 per 100,000). Osteitis as an AEFI is now much rarer.

Rare events, such as disseminated BCG disease, are seen and are more identifiable nowadays with advent of molecular tests. It has a high case fatality rate, requiring urgent medical care and is mostly associated with immunodeficiency both acquired (HIV) and primary immune deficiency syndromes. BCG Immune Reconstitution Inflammatory Syndrome (IRIS)-is also seen with HIV infection. Other BCG syndromes noted have included uveitis and skin lesions such as lupus vulgaris.

WHO commissioned a systematic literature review in early 2017 to review the safety of BCG vaccines so as to obtain sufficient scientific evidence to make public health decisions.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of evidence. Attempts were made to categorise the key findings of the review for all vaccines and for the different products. For PICO questions, the comparator used was no vaccine or another comparator vaccine.

The findings from the systematic review (by Uthman *et al.*¹⁴⁴) was presented at the GACVS meeting in June 2017, the SAGE BCG Working Group in August 2017 and the WHO secretariat.

The systematic review analysed adverse events following BCG immunization. A total of 287 articles met inclusion criteria. However, only 52 studies reported rates of adverse events, the rest were mainly case reports and case series studies. There was substantial variation in the reported rate of lymphadenitis across countries and across periods, ranging from as low as 0.41 per 1,000 vaccinated children in Saudi Arabia in 2012 to as much as 308 per 1,000 in HIV positive vaccinated children in Haiti in 1994. Evidence was limited on rates of osteomyelitis following BCG immunization.

There was substantial variation in the reported rate of disseminated BCG across countries and across periods, ranging from 1.81 per 1,000 in South Africa to 167 per 1,000 in France. Twelve studies reported not-specified AEFIs between 1979 and 2014 from seven countries. There was variation in the reported rate of not-

¹⁴⁴Uthman et al. Adverse events following Bacillus Calmette-Guérin (BCG) immunization: A systematic review, unpublished, 2017.

specified AEFI across the studies, ranging from as low as 0.01 per 1,000 vaccinated children in Brazil in 2013 to as much as 177.82 per 1,000 in France in 2009.

The systematic review analysed the evidence taking into consideration the age of vaccine administration to address the important policy question of differences in AEFI rates for children vaccinated at birth or at the age of 6 weeks. However, no evidence was available.

Moreover, the systematic review also attempted to analyse strain specific adverse reaction rates. However, there is a paucity of evidence on this issue, due to the inadequate reporting of the specific vaccine strains used in the various products.

Uthman *et al.*¹⁴⁴ analysed data on AEFIs related to leprosy. Three different groups were analysed: 1) healthy population, 2) leprosy contacts and 3) leprosy patients. Two studies reported rates of adverse events following antileprosy BCG in healthy population (adenitis: 13.0 per 1,000) and at risk population (recent contacts that developed leprosy after BCG revaccination at 4.0 per 1,000).

The reviewers indicated that, the results of the literature review should be interpreted with caution as many of the studies initially identified were case reports. Those studies were from a variety of surveillance systems or hospital based audits, which are prone to selection and reporting bias.

A short report¹⁴⁵ on adverse events following immunisation with BCG vaccine was made available to the BCG safety subgroup from the Therapeutic Goods Administration Australia for vaccinations between 1 January 2009 – 31 December 2014 in children aged less than 7 years. From this report, the type of AEFI in the descending order of frequency was found to be abscess, injection site reaction, lymphadenopathy, infection, skin reaction, rash, erythema, impaired healing, pyrexia, vaccine error, pain, decreased appetite, hypotonic-hyporesponsive episode, irritability, Kawasaki disease, meningoencephalitis herpetic and osteomyelitis. The BCG vaccine-related AEFI rate per 100,000 doses in children aged less than 7 years are shown in Table 8.¹⁴⁵

Table 8: Age at vaccination and BCG vaccine-related AEFI rate per 100,000 doses (includes any passive reports following BCG including reactogenicity seen after most BCG vaccinations)

| Age | BCG AEFI rate | 95% CI |
|-----------|---------------|------------|
| 0 - <3 m | 56 | (37-81) |
| 3 - <6 m | 204 | (132-300) |
| 6 - <9 m | 459 | (251-769) |
| 9 - <12 m | 520 | (224-1024) |
| 1-<7 yrs | 706 | (492-981) |
| Total | 153 | (126-184) |

¹⁴⁵ Adverse events following immunisation with Bacille Calmette-Guérin vaccination: baseline data to inform monitoring in Australia following introduction of new unregistered BCG vaccine. Alexandra Hendry, Aditi Dey, Frank Beard, Gulam Khandaker, Richard Hill and Kristine Macartney. CDI 2016; 40(4):E470-E474.

17. Route of administration

Summary: The route of administration is intradermal or percutaneous administration with a multipuncture device or intradermal injection with the Mantoux method. Evidence is not sufficient to favour one of the mentioned methods.

Originally, the BCG vaccine was developed as an oral vaccine by Calmette and Guérin. After the Lübeck disaster in 1930¹⁴⁶, oral administration has been completely replaced by intradermal administration. Brazil continued oral BCG administration until the 1970s.¹⁴⁷ BCG has been delivered intradermally by multiple methods, including needle injection using the Mantoux technique, multiple puncture devices, scarification, jet injectors, bifurcated needles and multitine devices.¹⁴⁸ WHO recommends intradermal application of the vaccine, preferably on the deltoid region of the arm using syringe and needle, although other application methods such as the multiple puncture technique are practiced in some countries.⁴ Today the most conventional administration technique for BCG is the Mantoux method.¹⁴⁸

The percutaneous administration with the multiple puncture technique is practiced in some countries due to concerns of adverse events by intradermal vaccination.^{149,159,160} South Africa could not confirm the concerns of unacceptable high rates of adverse events when reporting on their transition of percutaneous administration to intradermal.¹⁵⁰ The BCG vaccine manufacturers Merck (USA) former Organon, Korea Vaccine and Japan BCG Laboratory produce vaccine for percutaneous BCG administration (see Table 6). In countries where both methods are available, a growing preference of parents for the vaccines by the multipuncture method is noticed.¹⁵¹

A literature review compared the intradermal with the percutaneous vaccination. Evidence indicates that the percutaneous is not as precise in administered dose (lower dosages) and accordingly leading to a lower rate of protection especially against the more severe forms of the disease.¹⁵⁷ Comparisons in a RCT between multiple puncture and intradermal methods revealed that intradermal administration led to a tuberculin conversion rate of 93% and administration with the multipuncture instrument to 79% and 86%, depending on the pressure which was required to engage the catch.¹⁵⁹ Nevertheless, the transition from using Tokyo 172 BCG given percutaneously to Danish 1331 BCG given intradermal in South Africa did not prevent more TB cases in children overall but reduced the proportion with disseminated disease. A recently conducted RCT in South African infants vaccinated at birth and followed up for two years showed no significant difference between intradermal BCG vaccine and percutaneous in the incidence of TB for efficacy and safety.¹⁶⁰ The same study reported on higher frequencies of BCG specific IFN γ T cells, CD4+ and CD8+ T cell proliferation,

¹⁴⁶ Fox GJ et al. Tuberculosis in Newborns: The Lessons of the "Lübeck Disaster" (1929–1933). *PLoS Pathog.* 2016 Jan 21;12(1):e1005271.

¹⁴⁷ Monteiro-Maia and Teixeira de Pinho, Oral bacillus Calmette-Guérin vaccine against tuberculosis: why not? *Mem Inst Oswaldo Cruz.* 2014 Sep;109(6):838-45.

¹⁴⁸ Plotkin's Vaccines, 7th edition, 2017. Chapter 68 New Technologies for Vaccine Administration: Vaccine Macrodistribution Systems at the Points of Care.

¹⁴⁹ Yamamoto S and Yamamoto T. Historical review of BCG vaccine in Japan. *Jpn J Infect Dis.* 2007 Nov;60(6):331-6.

¹⁵⁰ Jeena PM et al., Safety of the intradermal Copenhagen 1331 BCG vaccine in neonates in Durban, South Africa. *Bull World Health Organ.* 2001;79(4):337-43.

¹⁵¹ Lee H et al., The Current Status of BCG Vaccination in Young Children in South Korea. *Tuberc Respir Dis (Seoul).* 2012 Apr;72(4):374-80. doi: 10.4046/trd.2012.72.4.374.

more secretion of IFN γ , TNF α and IL2 and less secretion of IL4 by percutaneous vaccination in comparison with intradermal vaccination.^{152,153}

Disposable-syringe jet injectors (DSJI) use needle-free technology, delivering the vaccine through a small nozzle, and is intended to be less dependent on user skill and experience.^{154,155} A RCT¹⁵⁸ in South Africa compared administration with DSJI and vaccination with the conventional technique with needle and syringe. The study population consisted of 30 adults and 66 newborns that were randomized to receive the BCG vaccine intradermal through either the standard needle and syringe (NS) method or experimental DSJI method. The majority of adverse events were characteristic BCG-associated lesions at the injection site and there were no differences in adverse event frequencies between DSJI and NS study arms. A literature review¹⁶² on adverse events in Iran identified studies that reported increased risk of adenitis with administration in the right arm compared to the left arm and also when administering in the upper third of the arm.

These studies show that correct vaccine administration technique by a trained health worker is important for the correct dosage and optimal BCG vaccine efficacy and safety.

Table 9: Primary papers on BCG vaccine administration technique

| Author/Year | Study Design | Vaccination strain | Population | Reference Number |
|---------------------------------|---------------------|----------------------------------|-------------------------------------|------------------|
| Al Jarad N <i>et al.</i> , 1999 | Observational study | No information | Schoolchildren in London | 156 |
| Bricks LF, 2004 | Literature Review | different | different | 157 |
| Geldenhuys <i>et al.</i> , 2015 | RCT | Danish strain 1331 | Children and adults in South Africa | 158 |
| Griffith <i>et al.</i> , 1963 | RCT | BCG-Glaxo | schoolchildren in Cardiff | 159 |
| Hawkrige A <i>et al.</i> , 2008 | RCT | Tokyo 172 | South African infants | 160 |
| Mahomed H <i>et al.</i> , 2006 | Observational study | Tokyo 172 and Danish strain 1331 | South African infants | 161 |
| Mostaan <i>et al.</i> , 2016 | Literature review | French 1173-P2 | Infants and children in Iran | 162 |

¹⁵² Davids V *et al.*, Dose-dependent immune response to Mycobacterium bovis BCG vaccination in neonates. Clin Vaccine Immunol. 2007 Feb;14(2):198-200.

¹⁵³ Davids V *et al.*, The effect of bacille Calmette-Guérin vaccine strain and route of administration on induced immune responses in vaccinated infants. J Infect Dis. 2006 Feb 15;193(4):531-6.

¹⁵⁴ Hickling JK *et al.* Intradermal delivery of vaccines: potential benefits and current challenges. Bulletin of the World Health Organization 2011;89:221-226. doi: 10.2471/BLT.10.079426. Available at <http://www.who.int/bulletin/volumes/89/3/10-079426/en/>, accessed July 2017.

¹⁵⁵ ten Dam HG *et al.* The use of jet-injectors in BCG vaccination. Bull World Health Organ. 43 (5):707-720 1970.

¹⁵⁶ Al Jarad N *et al.* Administration of the BCG vaccination using the multipuncture method in schoolchildren: a comparison with the intradermal method. Thorax. 1999 Sep;54(9):762-4.

¹⁵⁷ Bricks LF. Percutaneous or intradermal BCG vaccine? J Pediatr (Rio J). 2004 Mar-Apr;80(2):93-8.

¹⁵⁸ Geldenhuys HD, Mearns H, Foster J, Saxon E, Kagina B, Saganic L, *et al.* A randomized clinical trial in adults and newborns in South Africa to compare the safety and immunogenicity of bacille Calmette-Guérin (BCG) vaccine administration via a disposable-syringe jet injector to conventional technique with needle and syringe. Vaccine. Elsevier Ltd; 2015;33(37):4719–26. Available from: <http://dx.doi.org/10.1016/j.vaccine.2015.03.074>

¹⁵⁹ Griffith *et al.* A comparison between multiple puncture and intradermal methods of BCG vaccination. Tubercle. 1963 Sep;44:372-7.

¹⁶⁰ Hawkrige A Efficacy of percutaneous versus intradermal BCG in the prevention of tuberculosis in South African infants: randomised trial. Rev Port Pneumol. 2009 Jul-Aug;15(4):747-9.

¹⁶¹ Mahomed H *et al.* The impact of a change in bacille Calmette-Guérin vaccine policy on tuberculosis incidence in children in Cape Town, South Africa. Pediatr Infect Dis J. 2006 Dec;25(12):1167-72.

¹⁶² Mostaan S, Yazdanpanah B, Moukhah R, Hozouri H, Rostami M, Khorashadizadeh M, *et al.* Adverse effects of BCG vaccine 1173 P2 in Iran: A meta-analysis. Adv Biomed Res. 2016;5(1):99. Available from: <http://www.advbiomed.net/text.asp?2016/5/1/99/183659>

18. Co-administration with other vaccines

Summary

BCG co-administration with OPV and hepatitis B vaccines is safe. Even when in many settings DPT containing vaccines are administered after 6 weeks of age, a concomitant or a co-administration has proved to be safe. No evidence was retrieved on co-administration with rotavirus, PCV, and bOPV vaccination.

Due to the paucity of primary literature, BCG manufacturers were contacted (Table 10) to collect information of BCG co-administration. Some of the literature on co-administration reports on potential NSE of BCG administered alone or with other administered vaccinations.^{163,164} However, there is currently insufficient robust data to draw firm conclusions: for detailed analysis please see WHO draft protocols of clinical trials to assess the non-specific effects of vaccines¹⁶⁵ and Higgins *et al.*¹⁶⁶

In a study examining antibody response to hepatitis B surface antigen (HBsAg) in 60 infants in Turkey¹⁶⁷, simultaneous administration of BCG and hepatitis B vaccines did not influence the immune response to HBsAg when compared to administration of hepatitis B vaccine alone. This finding aligns with an older study in Senegal¹⁶⁸, which also showed that the serological response to HBsAg and poliovirus and cellular response to BCG did not differ between simultaneous administration of hepatitis B, BCG and oral polio vaccine (tOPV) vaccines compared to separate administration groups. One study in India found that BCG vaccine given first followed by hepatitis B vaccination caused less pain, as assessed by the neonatal infant pain scale, than the other order and thus recommends this order of administration.¹⁶⁹ One RCT compared the immunogenicity of a combined intradermal BCG and hepatitis B vaccine with the standard intradermal BCG and intramuscular hepatitis B vaccine in 548 infants in Brazil, and found there to be no difference in the serological response to HBV after the third hepatitis B vaccine dose at 6 months.¹⁷⁰ This cohort was followed up at 7 months, to investigate the BCG specific T-cell proliferation and cytokine production, and there was no difference between the groups.¹⁷¹

Table 10 presents the approved co-administration for the various BCG products. Information was collected by from communication with manufacturer and package inserts.

¹⁶³ Biai S, Rodrigues A, Nielsen J, Sodemann M, Aaby P. Vaccination status and sequence of vaccinations as risk factors for hospitalisation among outpatients in a high mortality country. *Vaccine*. 2011;29(20):3662-9.

¹⁶⁴ Ritz N, Mui M, Balloch A, Curtis N. Non-specific effect of Bacille Calmette-Guérin vaccine on the immune response to routine immunisations. *Vaccine*. 2013;31(30):3098.

¹⁶⁵ WHO. Call for public comments on draft protocols of clinical trials to assess the non-specific effects of vaccines. Available at http://www.who.int/immunization/research/implementation/nse_protocol_comments/en/, accessed August 2017.

¹⁶⁶ Higgins et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016;355:i5170

¹⁶⁷ Artan R et al. The effect of concurrent use of hepatitis B and Bacille Calmette-Guérin vaccination on anti-hepatitis B response. *Saudi medical journal*. 2004;25:1939.

¹⁶⁸ Coursaget P et al. Simultaneous injection of hepatitis B vaccine with BCG and killed poliovirus vaccine. *Vaccine*. 1992;10:319-21.

¹⁶⁹ Ravikiran SR et al. Pain Response in Newborns to the Order of Injecting BCG and Hepatitis-B Vaccines: A Randomized Trial. *The Indian Journal of Pediatrics*. 2011;78:693-7.

¹⁷⁰ Carniel EF et al. Immunogenicity and safety of combined intradermal recombinant Hepatitis B with BCG vaccines at birth. *Vaccine*. 2008;26:647-52.

¹⁷¹ Mazzola TN et al. Robust $\gamma\delta$ + T cell expansion in infants immunized at birth with BCG vaccine. *Vaccine*. 2007;25:6313-20.

Table 10: Information of BCG manufacturers regarding co-administration

*WHO prequalified vaccines

AJBiologics*Product information of the prequalification process.¹⁷²**Country of manufacturing:** Malaysia; **Used Strain:** Danish strain**Approved co-administration:** With DPT, DT, TT, measles, polio vaccines (OPV and IPV), Hepatitis B, Haemophilus**BCG Vaccine Laboratory**Product information of the manufacturer.¹⁷³**Country of manufacturing:** India; **Used Strain:** Danish strain**Approved co-administration:** with DPT, DT, TT, measles, polio vaccines (OPV & IPV), Hepatitis-B and Yellow Fever.**BioFarma**Product information of the manufacturer.¹⁷⁴**Country of manufacturing:** Indonesia; **Used Strain:** Paris strain**Approved co-administration:** with DTP, Measles, polio (OPV & IPV) vaccines, Hepatitis B, Haemophilus influenzae type b, yellow fever, and vitamin A supplements.**BioMed Lublin**Product information of the manufacturer.¹⁷⁵**Country of manufacturing:** Poland; **Used Strain:** Moreau strain**Approved co-administration:** The interval between BCG and Hepatitis type B vaccinations in newborn infants should not exceed 24 hours.

Individuals vaccinated against pertussis, diphtheria, tetanus, typhoid, rabies, influenza, ixodic brain fever or cholera can be vaccinated with BCG vaccine 4 weeks from the previous vaccination.

After the BCG vaccination the break interval should be 4 weeks, after that time the individual can be vaccinated against: pertussis, diphtheria, tetanus, typhoid, rabies, influenza, ixodic brain fever and cholera.

Vaccines against: poliomyelitis, measles, rubella, mumps - can be administered after a period of 6 weeks from the BCG vaccination. If the vaccine against poliomyelitis is administered simultaneously with the DTP vaccine (diphtheria-tetanus-pertussis) an interval of at least 6 weeks from the BCG vaccination should also be obligatory.

BulBIO LTD*Product information of the prequalification process.¹⁷⁶**Country of manufacturing:** Bulgaria; **Used Strain:** Moscow or Russian BCG-I**Approved co-administration:** with DPT, Measles, Polio vaccines (OPV and IPV), Hepatitis B, Haemophilus influenzae type B, and yellow fever vaccine and vitamin D supplementation**China National Biotech Group (Chengdu)**

Communication with the manufacturer on country practice in China.

Country of manufacturing: China; **Used Strain:** Shanghai D2PB302 strain**Approved co-administration:** Hepatitis B**China National Biotech Group (Shanghai)**

Communication with the manufacturer on country practice in China.

Country of manufacturing: China; **Used Strain:** Shanghai D2PB302 strain**Approved co-administration:** Hepatitis B**Green Signal Biopharma***Product information of the prequalification process.¹⁷⁷**Country of manufacturing:** India; **Used Strain:** Danish strain**Approved co-administration:** with DTP, DT, TT, Measles, Polio and Hepatitis B vaccines**Inst. Of Virology, Vaccines and Sera Torlak**Product information of the manufacturer.¹⁷⁸**Country of manufacturing:** Serbia; **Used Strain:** unknown**Approved co-administration:** -with other inactivated live vaccines

-Other vaccines to be given at the same time as BCG vaccine or during the next three months should not be given into the same (left) arm because of the risk of regional lymphadenitis.

-BCG vaccine is not recommended to be administered in the period of 4 weeks after the administration of any live vaccine.

Japan BCG Laboratory*Product information of the prequalification process.¹⁷⁹**Country of manufacturing:** Japan; **Used Strain:** Tokyo 172-1 strain**Approved co-administration:** with DTP, measles, polio (OPV and IPV), hepatitis B, Haemophilus influenzae type b, and yellow fever vaccines and vitamin A supplementation.**Pasteur Institute of Iran**

Communication with the manufacturer on country practice in Iran.

Country of manufacturing: Iran; **Used Strain:** Pasteur 1173P2 strain**Approved co-administration:** Hepatitis B**Serum Institute of India***Product information of the prequalification process.¹⁸⁰**Country of manufacturing:** India; **Used Strain:** Russian BCG-I**Approved co-administration:** with DTP, DT, TT, Measles, Polio, Hepatitis B, Haemophilus influenzae type b, yellow fever vaccines and vitamin A supplementation**Vaccins et Sérums Institut Pasteur de Tunis**

Communication with the manufacturer on country practice in Tunis.

Country of manufacturing: Tunisia; **Used Strain:** Pasteur 1173P2 strain**Approved co-administration:** Hepatitis B¹⁷² WHO prequalified vaccine AJVaccines. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=164, accessed August 2017.¹⁷³ BCG Vaccine Laboratory, Chennai. BCG VACCINE (10 DOSES) I.P. Available at <http://www.dirbcglab.gov.in/aboutproduct.html>, accessed July 2017.¹⁷⁴ BioFarma. Available at <http://www.biofarma.co.id/en/produk/vaksin-bcg-beku-kering/>, accessed July 2017.¹⁷⁵ BioMed Lublin. Antitubercle vaccine BCG 10. Available at http://www.biomed.lublin.pl/en/index.php?option=com_content&view=article&id=102%3Aszczepionka-przeciwgruczna-bcg-10&catid=40%3Alek-na-recepte&Itemid=1, accessed July 2017.¹⁷⁶ WHO prequalified vaccine BulBIO LTD. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=74, accessed August 2017.¹⁷⁷ WHO prequalified vaccine Green Signal Biopharma. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=294, accessed August 2017.¹⁷⁸ Inst. Of Virology, Vaccines and Sera Torlak Patient information leaflet, BCG vaccine, freeze dried. Available at <http://www.torlakinstitut.com/pdf/BCG-en.pdf>, accessed July 2017.¹⁷⁹ WHO prequalified vaccine JBL. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=67, accessed August 2017.¹⁸⁰ WHO prequalified vaccine SSI. Available at https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=117, accessed August 2017.

19. Update on the status of the pediatric HIV epidemic and implications for BCG administration policies in countries with high burden of HIV

Summary

- New pediatric infections are decreasing and therefore the probability that a child born to HIV- infected mothers is HIV-infected at the time of BCG vaccination is lower than it used to be (at least in context where PMTCT interventions have been scale up effectively).
- While progress was made in scaling up early infant HIV diagnosis (EID), coverage of diagnosis by 2 months is still low. Therefore, at the programmatic level, waiting for HIV diagnosis to administer BCG would still significantly delay administration in a large proportion of HIV-infected infants
- Innovations such as HIV testing at birth and use of point-of-care (POC) technologies may allow more rapid identification of HIV-infected infants in the near future, but there is currently very limited implementation. Provision of HIV testing with POC at the BCG delivery point has been considered as a potential implementation strategy, but this has not yet been piloted.
- Early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis. As countries move to implement more rapid ART initiation, occurrence of BCGemia and BCG-IRIS is less and less likely.
- The most appropriate timing for BCG vaccination that maximizes both specific and possible NSEs, particularly in HIV-1-exposed children, is thus presently unknown and studies are ongoing.

What's the likelihood of an HIV-exposed infant to be HIV infected?

Global efforts to stop new HIV infections among children has led to tangible progress. Around 76% of pregnant women living with HIV had access to antiretroviral medicines in 2016, up from 47% in 2010. New HIV infections among children globally have halved, from 300 000 in 2010 to 160 000 in 2016. Five-high burden countries—Botswana, Namibia, South Africa, Swaziland and Uganda—have already met the milestone of diagnosing and providing lifelong antiretroviral therapy to 95% of pregnant and breastfeeding women living with HIV.¹⁸²

Gains have been especially impressive in the 23 “Start Free Stay Free AIDS Free” priority countries¹⁸¹, where 88% of pregnant women living with HIV reside. Several of those countries have managed to reduce mother-to-child transmission rates to under 5%, including throughout breastfeeding¹⁸². A growing number of countries with relatively low HIV prevalence have validated the elimination of mother-to-child transmission of HIV and congenital syphilis. A major milestone on the way to the elimination of mother-to-child transmission of HIV is diagnosing and providing lifelong antiretroviral therapy to at least 95% of pregnant and breastfeeding women living with HIV.

Despite these encouraging figures, one in five women are either not tested for HIV or not started on ART during pregnancy. Moreover, these coverage estimates are based only on ART initiation and do not account

¹⁸¹ Angola, Botswana, Burundi, Cameroon, Chad, Cote d'Ivoire, DRC, Ethiopia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, South Africa, Swaziland, Tanzania, Uganda, Zambia, Zimbabwe, Indonesia and India

¹⁸² UNAIDS. GLOBAL AIDS UPDATE | 2017. http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf

for women who are lost to follow-up.¹⁸³ Furthermore, the coverage estimates do not capture the proportion of pregnant/breastfeeding women who are virally suppressed.

Transmission rates following incident infection are 2–3 times higher than in women with chronic HIV infection, and the number of children acquiring infection postnatally and in-utero are proportionally increasing.¹⁸⁴ Although policies are in place for partner testing as well as repeat testing of women during pregnancy and breastfeeding, in practice this does not always happen and/or is not systematically documented. As an intervention, partner testing is especially valuable because it can identify HIV-negative women in serodiscordant relationships who should receive HIV prevention interventions. Implementation of maternal HIV screening in immunization clinics is another important strategy for ensuring that women who were HIV-negative at their first antenatal clinic visit have received a repeat HIV test to identify incident HIV infection. National-level programme data are limited in their ability to capture true maternal and infant outcomes due to loss to follow-up or data quality issues. As a result, current global models are likely to underestimate the numbers of new infections in children as well as the true extent of pediatric HIV-related mortality¹⁸⁵.

According to the most recent estimates, only 43% of infants born to HIV-infected mothers receive virological testing before their 2nd month of age. In several countries, access to early infant diagnosis continues to rise.

Earlier testing¹⁸⁶ and testing at the point of care¹⁸⁷ along with strategies to ensure rapid turnaround of results have shown potential for enabling initiation of ART in the first weeks of life and, maximizing the effect on early morbidity and mortality. Technau *et al.*¹⁸⁶ describes the first experience with point-of-care testing (POCT) to diagnose HIV at birth and provide evidence of good performance for these new technologies around the time of birth. They show that despite the challenges and additional resources needed, combining POCT with birth testing could significantly improve time to treatment initiation and have potential to reduce early mortality and optimize infants' outcomes.

Are we able to identify infected infants in a timely manner?

In settings with a high proportion of attended deliveries, adding virological testing at birth to the existing testing algorithm can enable an earlier and wider provision of HIV testing services to mothers and babies who may not return to the health facility.¹⁸² However, a number of operational issues remain to be resolved, such as the need for additional human resources, active tracking of infants tested and messages that guarantee uptake of repeat testing at six weeks. It is also important to strengthen the overall uptake, retention and linkages in the testing-to-treatment cascade for birth testing to have the expected impact. After South Africa introduced virologic testing at birth and at 10 weeks for all HIV-exposed infants in 2015, the number of HIV-exposed infants receiving virologic testing within seven days of birth increased 15-fold in only three months, while the number of HIV-diagnosed children rose more than six-fold.¹⁸² A number of countries—including Ghana, Kenya, Namibia, Swaziland and Zimbabwe—are in the process of undertaking

¹⁸³ Woelk GB *et al.* Retention of mothers and infants in the prevention of mother-to child transmission of HIV programme is associated with individual and facility-level factors in Rwanda. *J Int AIDS Soc*, 19 (2016), p. 20837

¹⁸⁴ Drake AL *et al.* Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS Med*, 11 (2014), p. e1001608

¹⁸⁵ Mahy M *et al.* Improving estimates of children living with HIV from the Spectrum AIDS Impact Model. *AIDS*, 31 (2017), pp. S13–S22.

¹⁸⁶ Technau KG *et al.* HIV-1 point-of-care test for neonatal diagnosis of HIV in the birth testing programme of a maternity hospital: a field evaluation study *Lancet HIV* (2017) published online July 12. [http://dx.doi.org/10.1016/S2352-3018\(17\)30097-8](http://dx.doi.org/10.1016/S2352-3018(17)30097-8)

¹⁸⁷ Jani I *et al.* Effect of point-of-care technology on antiretroviral therapy initiation rates in infants. Conference on Retroviruses and Opportunistic Infections. Seattle, WA, USA; Feb 13–16, 2017. Abstract 26.

pilots of virological testing at birth to inform future national scale-up. Provision of HIV testing in conjunction with BCG administration has been considered as a potential implementation strategy to maximize access to HIV testing even for those that don't deliver at facility. However, to our knowledge, no countries have so far piloted this model.

Figure 12 New HIV infections among children (aged 0–14 years) and coverage of antiretroviral regimens to prevent mother-to-child transmission, global, 2000–2016. Source: UNAIDS 2017 estimates.

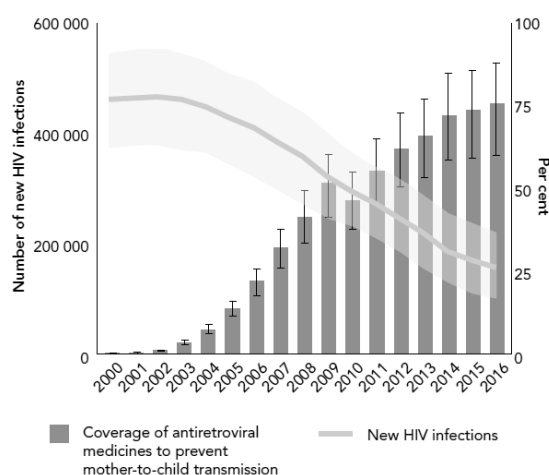
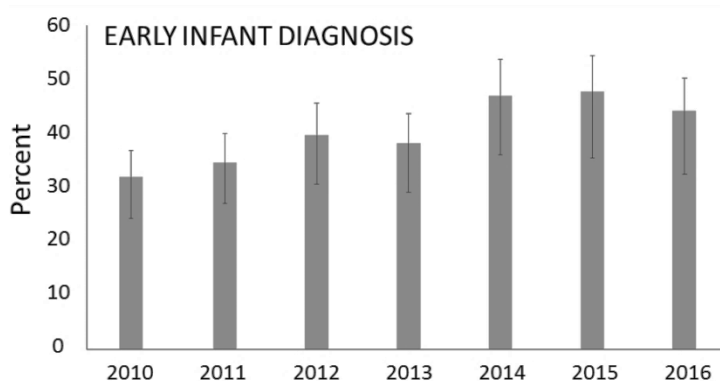


Figure 13 Percentage of HIV-exposed infants who have been diagnosed within two months of birth, 21 high-burden countries, 2013 and 2016. Source: Global AIDS Monitoring, 2017; UNAIDS 2017 estimates.



The main benefit of early HIV diagnosis is the potential for rapid initiation of ART to prevent early mortality, particularly in perinatally-infected infants, and future morbidity. However, even when EID is available, linkage to care and treatment initiation occurs only in a small proportion of infected infants. Globally, an estimated 919 000 children were on antiretroviral therapy in 2016, about 43% of all children living with HIV. The rate of increase in the number of children on treatment has slowed in recent years, falling to an annual increase of 6% in 2016 from an annual increase of over 10% in previous years.

In the context of earlier identification and ART initiation, how frequent is BCGemia and BCG-IRIS in HIV infected infants that received BCG?

In South Africa, all neonates are still vaccinated, regardless of HIV exposure, as the prevalence of TB and HIV is high and HIV diagnosis before 6 weeks of age has not been feasible for long time. Complications occurring soon after initiation of antiretroviral treatment (ART) are usually ascribed to immune reconstitution inflammatory syndrome (IRIS). BCG-related regional adenitis due to IRIS (BCG-IRIS) was described in respectively 6% and 15% of children in two South African cohorts.^{188,189} However, these and other reports only included children starting ART following immunological or clinical decline. As immunosuppression is a risk factor for IRIS, early ART initiation in infants should lower the risk of BCG-IRIS. A recently published study

¹⁸⁸ Smith K, Kuhn L, Coovadia A, Meyers T. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS*. 2009; 23:1097–1107. [PubMed: 19417581]

¹⁸⁹ Nuttall JJ, Davies M, Hussey G, et al. Bacillus Calmette-Guérin (BCG) vaccine-induced complications in children treated with highly active antiretroviral therapy. *Int J Infect Dis*. 2008; 12:e99–e105. [PubMed: 18799339]

by Rabie *et al.*¹⁹⁰ showed that early ART initiation before immunological and/or clinical progression substantially reduces the risk of BCG-IRIS regional adenitis. As countries move to implement a more rapid ART initiation occurrence of BCGemia and BCG-IRIS are less and less likely. This appears to be confirmed by observational data from the leDea Southern Africa cohort (Mary Ann Davies personal communication) where lymphadenitis happened in around 0.6% of the 12748 children vaccinated and started on ART with the majority of the cases happening in the 1st year.

What's the implication for “delaying” or “missing” BCG for HIV infected children?

To overcome the concerns regarding administration of BCG in HIV-infected infants, delaying BCG until these infants are diagnosed as not having HIV-1 infection has been considered. Delaying BCG vaccination could have an unintended consequence of lowering vaccination coverage. There is also some uncertainty regarding whether vaccinating HIV-1-exposed babies with BCG at birth provides protection against serious infections other than TB, i.e., through NSEs, delaying vaccination could result in increased morbidity and even mortality. The most appropriate timing for BCG vaccination that maximizes both specific and possible NSEs, particularly in HIV-1-exposed children, is unknown. A study undergoing in Uganda lead by Nankabirwa *et al.*¹⁹¹ will address this important question.

20. Vaccination of low birth weight and premature infants

Observational cohort studies describe that low birth weight (LBW) infants often receive BCG immunization late compared to normal birth weight infants.^{192,193} This policy of not vaccinating low birth weight infants at birth had a negative impact on vaccination coverage for LBW children in Guinea Bissau.¹⁹⁴ An Indian study describes no significant difference in the scar formation in infants studied with varying birth weights after 12 weeks of BCG vaccination.¹⁹⁵ A recent RCT assessed the effects of BCG vaccination on low birth weight infants in Gambia. No effect of early BCG on growth in the first year of life was observed.^{196,197} The same study concluded, that early BCG vaccination had no large negative impact on TST and BCG scarring.

Okan *et al.*¹⁹⁸ reported in their study that BCG vaccination in preterm infants at months 2-3 of postnatal life results in a high percentage of BCG scarring and 57% TST conversion. Additionally they reported, that a positive tuberculin response was significantly related to the postnatal weight gain of the preterm infants. Results from other studies suggest also that the preterm infants born at 32-36 weeks of gestation can be

¹⁹⁰ Early antiretroviral treatment reduces risk of bacille Calmette-Guérin immune reconstitution adenitis.

Rabie H, Violarì A, Duong T, Madhi SA, Josipovic D, Innes S, Dobbels E, Lazarus E, Panchia R, Babiker AG, Gibb DM, Cotton MF; CHER team. *Int J Tuberc Lung Dis.* 2011 Sep;15(9):1194-200. i. doi: 10.5588/ijtld.10.0721.

¹⁹¹ Nankabirwa V *et al.* Early versus late BCG vaccination in HIV-1-exposed infants in Uganda: study protocol for a randomized controlled trial. *Trials.* 2017 Mar 31;18(1):152.

¹⁹² Mutua *et al.* Effects of low birth weight on time to BCG vaccination in an urban poor settlement in Nairobi, Kenya: an observational cohort study. *BMC Pediatr.* 2015 Apr 18;15:45. doi: 10.1186/s12887-015-0360-5.

¹⁹³ O'Leary *et al.* Neonatal vaccination of low birthweight infants in Ghana. *Arch Dis Child.* 2017 Feb;102(2):145-151.

¹⁹⁴ Roth *et al.* Low birth weight infants and Calmette-Guérin bacillus vaccination at birth: community study from Guinea-Bissau. *Pediatr Infect Dis J.* 2004 Jun;23(6):544-50.

¹⁹⁵ Kaur *et al.* BCG vaccination reaction in low birth weight infants. *Indian J Med Res.* 2002 Aug;116:64-9.

¹⁹⁶ Biering-Sørensen *et al.* Early BCG vaccine to low-birth-weight infants and the effects on growth in the first year of life: a randomised controlled trial. *BMC Pediatr.* 2015 Sep 28;15:137. doi: 10.1186/s12887-015-0452-2.

¹⁹⁷ Biering-Sørensen *et al.* Small randomized trial among low-birth-weight children receiving bacillus Calmette-Guérin vaccination at first health center contact. *Pediatr Infect Dis J.* 2012 Mar;31(3):306-8.

¹⁹⁸ Okan *et al.* Bacillus Calmette-Guerin vaccination in preterm infants. *Int J Tuberc Lung Dis.* 2006 Dec;10(12):1337-41.

effectively immunized with BCG at birth.^{199,200,201,202} In a Brazilian study a typical BCG scar was verified in 96.9% of the control group and in 90.0% of the preterm infants.²⁰³ In contrast a study which evaluated the efficacy of BCG vaccine in pre-term infants in UAE concluded that male pre-term infants of lower gestational ages (<33 weeks) are less likely to develop BCG scar and a reactive PPD tuberculin test after BCG vaccination.²⁰⁴

21. Vaccination of travelers from non TB endemic countries to TB endemic countries

National and international guidelines and recommendations for the use of BCG vaccination for the prevention of travel-associated TB vary widely, reflecting the lack of data on the both the risk of TB and the effectiveness of BCG in this setting. Numerous case reports and case series document the acquisition of TB disease after travel but no studies provide a risk estimate. However, the incidence of TST conversion in adults after prolonged travel to high TB incidence countries has been reported as 0.35% (95% CI 0.2–0.62%) per month of travel.²⁰⁵ In addition, two studies in children in the US reported an increased prevalence of TST positivity in children who have travelled overseas.^{206,207}

The risk of travel-associated TB depends on several factors, including the TB incidence in the country visited, the duration of travel, the degree of contact with the local population and, in particular, the age of the traveler. Those visiting relatives are at higher risk. Infants and young children, especially those under 1 year of age, are at higher risk as they are more likely to develop severe and disseminated forms of TB.²⁰⁸

22. Cost-effectiveness of BCG vaccination

Summary

Review of economic analyses of BCG in the literature show that universal BCG vaccination remains cost-effective in LMICs where TB incidence is high. However, in countries where TB incidence is low, selective BCG vaccination of high-risk populations should be considered. There is insufficient data on the effectiveness of BCG revaccination. No studies were found on cost-effectiveness of BCG vaccination for leprosy however considering the double protection against TB and leprosy the BCG vaccination is cost-effective.

¹⁹⁹ Saroha et al. Immunogenicity and safety of early vs delayed BCG vaccination in moderately preterm (31–33 weeks) infants. *Hum Vaccin Immunother.* 2015;11(12):2864–71.

²⁰⁰ Dawodu et al. Tuberculin conversion following BCG vaccination in preterm infants. *Acta Paediatr Scand.* 1985 Jul;74(4):564–7.

²⁰¹ Thayyil-Sudhan S et al. Safety and effectiveness of BCG vaccination in preterm babies. *Arch Dis Child Fetal Neonatal Ed.* 1999 Jul;81(1):F64–6.

²⁰² Negrete-Esqueda L and Vargas-Origel A. Response to Bacillus Calmette-Guérin vaccine in full-term and preterm infants. *Am J Perinatol.* 2007 Mar;24(3):183–9.

²⁰³ Camargos et al. Tuberculin skin reactivity after neonatal BCG vaccination in preterm infants in Minas Gerais, Brazil, 2001–2002. *Rev Panam Salud Publica.* 2006

²⁰⁴ Sedaghatian et al. Bacille Calmette Guérin vaccination in pre-term infants. *Int J Tuberc Lung Dis.* 1998 Aug;2(8):679–82.

²⁰⁵ Cobelens FG, van Deutekom H, Draayer-Jansen IW, Schepp-Beelen AC, van Ger-ven PJ, van Kessel RP, et al. Risk of infection with *Mycobacterium tuberculosis* in travellers to areas of high tuberculosis endemicity. *Lancet* 2000;356(9228):461–5.

²⁰⁶ Lobato MN, Hopewell PC. *Mycobacterium tuberculosis* infection after travel to or contact with visitors from countries with a high prevalence of tuberculosis. *Am J Respir Crit Care Med* 1998;158(6): 1871–5.

²⁰⁷ Saiman L, San Gabriel P, Schulte J, Vargas MP, Kenyon T, Onorato I. Risk factors for latent tuberculosis infection among children in New York City. *Pediatrics* 2001;107(5):999–1003.

²⁰⁸ Ritz N, Connell TG, Curtis N. To BCG or not to BCG? Preventing travel-associated tuberculosis in children. *Vaccine* 2008;26:5904–9.

A literature review of economic analyses of the BCG vaccine for protection against TB was performed. Studies modelling the economic benefits of future TB vaccines or immunotherapeutic effects of BCG vaccine on bladder cancer, arthritis, and non-tuberculous mycobacteria, were excluded. Studies concerning non-human subjects were also excluded. Data on the economic analyses, population of interest and geography, methods, model assumptions, and main conclusions were extracted and summarized.

An initial search was limited to identifying systematic reviews published after January 1st, 2003, to capture information published following the 2004 WHO BCG position paper. A primary literature review was then undertaken to capture all studies published after January 1st, 2008 up to January 20th, 2017.

Using the search strategy described in the Appendix, a total of 89 articles were identified from the initial search and data from two systematic reviews on the economic evaluation and cost-effectiveness of the BCG vaccine were extracted. The primary literature review resulted in identifying 2,624 articles and data from six primary papers relevant to BCG vaccine economics were extracted.

Both systematic reviews by Trunz *et al.*, (2006)²⁰⁹ and Tu *et al.*, (2012)²¹⁰ provided a worldwide perspective on the costs and benefits of the BCG vaccine and concluded that vaccination was cost-effective in high TB incidence settings. Tu *et al.*, (2012) concluded that revaccination of children in developed countries is not considered cost-effective.

From the primary literature review, three studies from low incidence countries in Europe; the Netherlands²¹¹, Italy²¹² and Ireland²¹³ examined the costs of universal and selective BCG vaccination strategies. Results from these studies found that although universal BCG vaccination in countries with low TB incidence does offer protection in pediatric populations, the additional protection conferred by universal strategies is comparatively small and less cost-effective when compared to targeted vaccination of high-risk groups.

Three studies from high TB incidence settings were reviewed. In South Africa, a study examining the cost-effectiveness of BCG revaccination in adolescents found the incremental cost per year of healthy life recovered ranged from 116-9,237 USD²¹⁴. In Cameroon, a study which didn't directly address BCG vaccine cost-effectiveness found that BCG vaccination in the context of routine EPI services was lower in outreach strategies. In addition, they found that BCG coverage was low (70%), however, BCG accounted for a relatively small amount of vaccine wastage (1.1%) when compared to newer, expensive vaccines such as the pentavalent and yellow fever vaccine. Finally, a study from Brazil²¹⁵ explored the cost-effectiveness of BCG vaccination in children 7-14 years of age using a subpopulation of the BCG REVAC cluster-randomized trial.

²⁰⁹ Trunz BB et al. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006 Apr 8;367(9517):1173-80.

²¹⁰ Tu H-AT, Vu HD, Rozenbaum MH, Woerdenbag HJ, Postma MJ. A review of the literature on the economics of vaccination against TB. *Expert Rev Vaccines*. 2012;11(3):303-17.

²¹¹ Altes HK, Dijkstra F, Lugn  r A, Cobelens F, Wallinga J. Targeted BCG Vaccination Against Severe Tuberculosis in Low-prevalence Settings. *Epidemiology*. 2009;20(4):562-8. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001648-200907000-00015>

²¹² Bellini I, Nastasi A, Boccalini S. Clinical and economic impact of a specific BCG vaccination program implemented in Prato, central Italy, involving foreign newborns on hospitalizations. *Hum Vaccin Immunother*. Taylor & Francis; 2016;12(9):2383-90. Available from: <https://www.tandfonline.com/doi/full/10.1080/21645515.2016.1182274>

²¹³ Usher C, Adams R, Schmitz S, Kieran J, O'Flanagan D, O'Donnell J, et al. Evaluating the neonatal BCG vaccination programme in Ireland. *Arch Public Heal*. Archives of Public Health; 2016;74(1):28. Available from: <http://archpublichealth.biomedcentral.com/articles/10.1186/s13690-016-0141-0>

²¹⁴ Dye C. Making wider use of the world's most widely used vaccine: Bacille Calmette-Gu  rin revaccination reconsidered. *J. R. Soc. Interface* 2013 Jul 31;10(87)

²¹⁵ 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 Infect Dis*. Elsevier Ltd; 2012;12(4):300-6.

The study found that the average cost of treating one patient with TB was higher than the cost of vaccinating 381 children. This suggested that vaccination of school-age children can be cost-effective in a high TB incidence setting.

The working group concluded that publications related to BCG cost-effectiveness are scarce and of low quality. However, BCG vaccination at infancy is cost-effective in developing countries or settings with TB incidence rates $>20/100,000$ population or $>5/100,000$ smear-positive cases per year.²¹⁰ Studies show that universal BCG vaccination was no longer cost-effective in countries with low TB incidence and that targeted or selective vaccination strategies are favoured in these settings. Therefore, as the incidence of TB declines in developed countries, discontinuation of universal vaccination or targeted vaccination of high-risk populations will need to be considered. However, it is important to consider how effective implementation of this strategy is dependent on a strong surveillance system to ensure accuracy of data and better defining of high risk group infants and children ≤ 5 years with high risk for exposure to individuals with active pulmonary TB.²¹⁰ Although studies show potential for revaccination to be cost-effective in specific populations, estimates of BCG vaccine efficacy remain a controversial factor.²¹⁰

The cost-effectiveness of NSE is currently not included in the summary of evidence and is hard to address. It was concluded that this area should be targeted in the research specific section of the recommendation. In the future, novel vaccine candidates should improve cost-effectiveness.

23. Innovations and new vaccines under development

23.2. Innovations and research are critical to break the trajectory of the TB epidemic

The 10% per year fall in incidence that is needed by 2025 to achieve the goal of the end TB strategy has been previously achieved only within the wider context of universal health coverage (UHC) and broader social and economic development. To lower cases to 10 per 100,000 population by 2035 ("end the global TB epidemic") and achieve a 95% reduction in TB deaths by 2035 will need a technological breakthrough is necessary by 2025 that will allow an unprecedented acceleration in the rate at which TB incidence falls between 2025 and 2035. This will only happen with substantial investment in R&D, so that new tools such as a post-exposure vaccine or a short, efficacious and safe treatment for latent infection, are developed. For this to happen, at least 2 billion \$USD per year are needed for research. In the TAG TB R&D report 2016, TAG (the Treatment Action Group) estimates that 621 million \$USD were available in 2015 for research. This means that in 2015 there was a funding gap of \$USD 1.3 billion. International donor funding has grown for TB, however it is much less than the available funding for HIV and Malaria. To implement the Global Plan to Stop TB 2016-2020, it was estimated that in 8.3 billion \$USD were needed in 2016 alone. Only 6.6 billion \$USD was available in 2016.

23.3. Diagnostic and treatment tools on the horizon

Nine new diagnostics have been endorsed by WHO since 2007. Several are currently in development including whole genome sequencing on sputum. By 2020, it is expected that a rapid and sensitive point-of-care diagnostic test will be available as well as a triage, predictive latent TB infection (LTBI) test, and rapid drug susceptibility tests (DST). Two new drugs, bedaquiline and delamanid, and a nine-month regimen for MDR-TB were endorsed since 2012. A shorter 12-week regimen for LTBI is now available. In addition, by

2020, we expect a 4 months regimen for Drug Sensitive-TB; 6-9 months regimens for MDR-TB; and, additional new drugs.

23.4. What research is required to end the TB epidemic and eliminate TB?

A radical intensification of efforts is needed across the full spectrum of research: Basic science (immunology, pathogenesis) to prompt discovery of new tools; R&D pipeline for testing and validating new tools; Innovative strategic approaches adapted to specific country needs; Factors influencing health-related practices of patients and health care workers; and, social determinants of health and financial protection.

The Global TB Programme has developed a Global Action Framework on TB research with two main objectives: (i) To promote, enhance and intensify TB research and innovation at country level; and, (ii) To promote, enhance and catalyze TB research at global level. It is fundamental that all countries pursue national research strategies, plans and networks.

To mobilize high-level multisectoral action to accelerate country implementation of the WHO End TB Strategy in order to reach the End TB targets set by the World Health Assembly and the United Nations (UN) SDGs, on 15-16 November 2017 in Moscow, WHO and the Ministry of Health of the Russian Federation are hosting the First Global Ministerial Conference on Ending TB in the Sustainable Development Era: a Multi-sectoral Response. The Ministerial Conference will inform the UN General Assembly High-level Meeting on TB in 2018.²¹⁶

In summary, during the MDG era, the TB response saved 49 million lives. The UN SDGs call to “end the TB epidemic” in an equitable way by 2030. By optimizing and modernizing care and prevention and by enforcing bold policies we can advance and evolve, but up to a certain point only. Discovery, translational research and innovations are crucial to reach the global targets. Intensified efforts and much greater resources in both implementation and research are necessary, and the UN SDGs are an opportunity for all.

23.5. New vaccines under development

23.5.1. Status of TB Vaccine Development - highlights

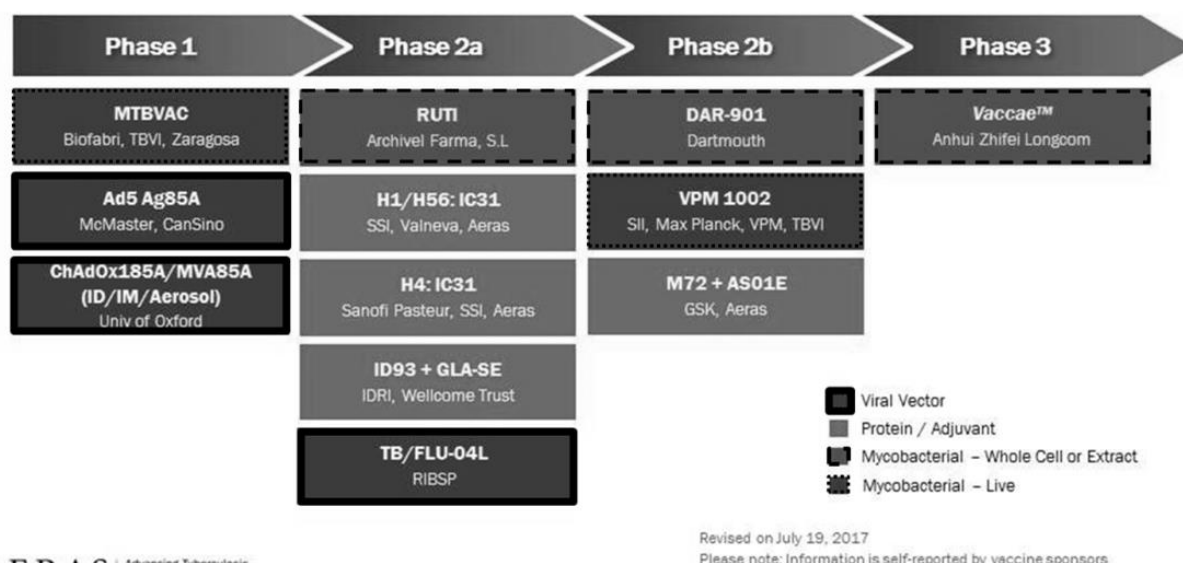
Twelve vaccine candidate approaches are currently in clinical evaluation (see Figure 14). Since a robust cellular response is believed to be required for protection against *M tuberculosis* infection and disease, the majority of candidates are based on components that induce TH1 cytokines such as IFN γ or TNF α through induction of CD4⁺ or CD8⁺ responses.

Prevention of pulmonary TB in adolescents and adults, considering that they are the major source of transmission, is a primary strategic goal in the field of TB vaccine development.

BCG is the only licensed vaccine for TB and is only partially protective in infants. As a live bacterial vaccine, BCG can cause severe disease in immune-compromised individuals, including those who are HIV-infected. Developing safer, more effective (with longer protective duration and more consistent levels of protection) vaccines for BCG replacement is considered an important strategic goal.

²¹⁶ Resolution A/RES/71/159 available at http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/71/159, accessed September 2017.

Global Clinical Pipeline of TB Vaccine Candidates



AERAS Advancing Tuberculosis
Vaccines for the World

Figure 14: Global Clinical TB Vaccine Pipeline

(According to Aeras: <http://www.aeras.org/pages/global-portfolio>)

Innovative study designs are considered, in absence of established immune correlates of protection, to establish early proof of relevant biological activity. Prevention of infection (POI) studies recruit participants who do not show evidence of past TB infection and monitor conversion to a positive infection diagnostic test. Prevention of recurrence (PoR) studies target patients who have been diagnosed with TB, at various time post diagnosis and treatment. Patients previously treated for TB have a higher incidence of TB disease compared to those with no prior history of the disease, and approximately 90% of these recurrences occur within 12 month of the initial infection. These innovative design aim to reduce the need for large, long and expensive prevention of disease (PoD) trials without evidence of significant biological effect, and thereby reduce investment risks.

Considering the BCG vaccine shortages over the recent years, transfer to liquid culture manufacturing process that is more scalable, reliable and cost effective would be highly desirable. The VPM 1002 vaccine candidate is currently being manufactured in this way. The liquid fermentation for legacy BCG is also being investigated, for what would be a more risk adverse strategy to securing BCG supplies in the mid-term.

The estimated costs of developing a safe and effective TB vaccine are approximately \$1 billion over the next 10-15 years. This cost is small compared to the \$8 billion per year that is required to respond to the TB epidemic with the current tools – and this cost is likely to increase with worsening drug resistance.²¹⁷ Hand in hand with vaccine development efforts, WHO will advocate for the need of a TB vaccine in general. The importance is also to be considered in light of the prioritized agenda on antimicrobial resistance (AMR). More candidate vaccines are in early clinical testing.

²¹⁷ AERAS. TB Vaccine Research & Development: A Business Case for Investment, http://www.aeras.org/pdf/TB_RD_Business_Case_Draft_3.pdf

23.5.2. Status of Leprosy Vaccine Development

As previously described the incidence of leprosy can be reduced due to vaccination with BCG or in combination with killed *M leprae*. Approaches to develop safer, more reproducible BCG based vaccines are under development; referred to as 'BCG improvement strategies'. Several studies, especially from high burden countries, have examined the efficacy of other vaccines and of the combination of post-exposure prophylaxis with BCG at birth and/or with BCG revaccination. Evidence indicates that several other mycobacterial vaccines show similar or slightly lower efficacy compared to BCG vaccination interventions; however, only the M.w (*Mycobacterium indicus pranii*) vaccine remains in production.²¹⁸ A new vaccine, the LepVax, is based on a fusion protein and an adjuvant. In animal studies the LepVax appeared to delay and reduce nerve injury. Phase I studies are beginning in America and a phase Ib study is planned to start shortly.²¹⁹

24. Additional research needs on BCG

TB control might be improved if a strain of BCG could be identified that provides better protection. This could be done at very low cost with 'ABAB' studies in which all neonates in a defined region would be vaccinated with one strain (A) of BCG for a year and another strain (B) the next year, with the alternation continued for another 2 years (AB). Providing TB were recognised similarly in odd and even years, this design would approach true randomisation but at low cost.^{54,55}

25. Working Group members, other experts and WHO secretariat

SAGE Working Group on BCG vaccines (established October 2016)

Terms of Reference

The Working Group will be requested to review the scientific evidence and relevant programmatic considerations to formulate proposed recommendations on the use of BCG vaccines for consideration by SAGE to inform a revision of the global policy on the use of BCG, and for subsequent updating of the WHO Position Paper on BCG and related materials.

Specifically the Working Group (WG) will be asked to review the following elements:

1. country practices in the use of BCG including that of targeted vaccination in low TB prevalence countries as well as the threshold applied to decide on stopping vaccination;
2. TB epidemiology as well as the epidemiology of leprosy;
3. trends in antibiotic resistance and their implications for BCG use;
4. the safety and effectiveness of BCG (in a strain specific analysis) in different age groups and according to HIV status and for different outcomes (i.e. death, pulmonary disease and infection);
5. assessment of the duration of protection and need for revaccination (including a comparison of the effect of revaccination with that of alternative protective approaches e.g. isoniazid preventive therapy);
6. the effect of BCG co-administration with other vaccines administered at birth (OPV, hepatitis B) or later (e.g. co-administration with DTP containing and specifically pentavalent vaccine);

²¹⁸ Crains et al. Leprosy. Clinical Evidence 2010;06:915

²¹⁹ Smith et al. 19th International Leprosy Congress: the Plenary Sessions. Lepr Rev (2016) 87, 564–569.

7. the economic burden of TB and cost-effectiveness of vaccination as well as modelling data to inform BCG vaccination strategies (including vaccination in the context of other control strategies);
8. the potential role of BCG in the control of leprosy.

In addition the WG will be briefed for their information on the TB vaccine candidates' development status, including BCG improvement strategies that may have implications for beneficial non-specific vaccine effects of the current BCG.

The vaccine has several non-specific effects (NSE) which should be discussed, but which should not be the immediate focus of the Working Group since this issue of NSE is being addressed by the Immunization and Vaccines-Related Implementation Research Advisory Committee (IVIR-AC).

Composition

SAGE Members

- Charles Shey Wiysonge: South African Medical Research Council, South Africa (Chair of the Working Group)
- Kari Johansen: European Centre for Disease Prevention and Control, Sweden

Experts

- Safaa Al-Khawaja: Ministry of Health, Bahrain
- Pamela Bakkabulindi: Ministry of Health, Uganda
- Sang Nae Cho: Yonsei University College of Medicine, South Korea
- Nigel Curtis: University of Melbourne, Australia
- Mark Hatherill: University of Cape Town, South Africa
- Guangxue He: Chinese Center for Disease Control and Prevention, China
- Helen McShane: University of Oxford, England
- Elizabeth Maleche Obimbo: University of Nairobi, Kenya
- Jeffrey Starke: Baylor College of Medicine, USA

WHO Secretariat

- Philippe Duclos
- Malin Finkernagel
- Tracey Goodman

Declaration of interests

Four members reported relevant interests. All interests were assessed to not constitute a conflict of interest. It was concluded that all members could take part in full in all of the discussions. The reported relevant interests are summarized below:

Helen McShane

Her research institution¹ receives a grant from the US National Institutes of Health (NIH) for the characterization of mycobacterial induced immunity in HIV-infected and uninfected individuals (2016-2019). This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from the Biotechnology and Biological Sciences Research Council for a reverse vaccinology approach to a bTB vaccine (2015-2019). This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives 2 grants from the Bill & Melinda Gates Foundation for an experimental medicine study to assess feasibility of pulmonary administration of BCG for vaccination and human challenge models (2015-2018). The second grant is for research on the heterologous effects of BCG (2014-2016).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from the National Centre for the Replacement, Refinement and Reduction of Animals in Research for the developing and validating an *in-vitro* mycobacterial challenge model to facilitate TB vaccine research and minimise *in-vivo* challenge experiments (2015-2018).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from the Tuberculosis Vaccine Initiative (TBVI) for a phase I trial to compare the safety and immunogenicity in *M. tuberculosis* infected adult subjects of MVA85A vaccination given by the aerosolized and intramuscular route (2015-2017).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from Medical Research Council Confidence in Concept (MRC CiC)/ Liverpool School of Tropical Medicine (LSTM) for the evaluation of new antigens for subunit vaccines against *Mycobacterium tuberculosis* (2015-2016).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from The EU Framework Programme for Research and Innovation Horizon 2020 (EC H2020) on TBVAC2020 for the vaccine development for poverty-related and neglected infectious diseases (2015-2019).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from Tuberculosis Vaccine Initiative (TBVI)/ Norwegian Agency for Development Cooperation (NORAD) for the preclinical clinical development of new promising TB vaccine candidates (2015-2016).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from Aeras for the investigation of mycobacterial growth inhibition assays (MGIA) in TB animal models (2014-2016).

This interest was assessed as non-personal, non-specific and financially significant*.

Her research institution¹ received two grants from Aeras for a BCG challenge trial (2013-2015) and for a mycobacterial assay for growth inhibition (2010-2013).

This interest was assessed as non-personal, non-specific and financially significant*.

Her research institution¹ received a grant from by Aeras/FDA for a novel approach for identifying biological and immunological biomarkers for TB vaccines (2010-2013).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ currently receives a grant from European Research Infrastructures for Poverty Related Diseases (EURIPRED FP7) for the analysis of the European Research Infrastructures for Poverty Related Diseases (2015-2019).

This interest was assessed as non-personal, non-specific and financially significant*.

Her research institution¹ currently receives a grant from Wellcome Trust for a clinical Research Fellowship on the evaluation of innovative TB vaccination strategies in preclinical and clinical models (2011-2016).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ received a grant from Wellcome Trust for a Phase IIb proof-of-concept efficacy trial with MVA85A in infants in South Africa (Strategic Award) (2008-2014).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ received a grant from TBVI/NORAD for research of Biomarkers (2013-2015).

This interest was assessed as non-personal, non-specific and financially significant*.

Her research institution¹ received 2 grants from The European & Developing Countries Clinical Trials Partnership (EDCTP), for the collaboration and integration of tuberculosis vaccine trials in Europe & Africa (TBTEA) (2011-2013) and for a proof-of-concept study on a phase IIb clinical trial to evaluate the protective efficacy of a booster MVA85A vaccination administered to healthy, HIV-infected adults in South Africa, Senegal and the Gambia (2009-2014).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ received a grant from the discovery and preclinical development of new generation tuberculosis vaccines (NEWTBAC 2, EU 7th Framework) in the framework of an EU TB Consortium on the discovery and preclinical development of new generation tuberculosis vaccines (2010-2014).

This interest was assessed as non-personal, specific and financially significant*.

Her research institution¹ received a grant from the European Network of Vaccine Research and Development (TRANSVAC, EU 7th Framework) with a grant on EU Vaccine Consortium: European network of vaccine research and development (2009-2013).

This interest was assessed as non-personal, specific and financially significant*.

Mark Hatherill

Mark Hatherill reported that he was reimbursed as a consultant for his work on the Advisory Board on therapeutic tuberculosis vaccines of GSK in 2014.

This interest was assessed as personal, specific and financially significant*.

His research institution² currently receives 3 grants from the Bill & Melinda Gates Foundation for the validation of correlates of risk of TB disease in high risk populations (2016-2019), for a clinical trial on a correlate of risk targeted screen and treat strategy to impact TB control (2015-2019) and for a project entitled, “Systems Immunology Consortium: Systems Biology” (2013-2016).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² received a grant from the Bill & Melinda Gates Foundation for a project on the planning for a risk-targeted intervention to reduce TB transmission (2014-2015).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² currently receives a grant from the National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS) / Medical Research Council of South Africa (SA MRC) for the analysis of the advancement of TB biomarker targeted interventions (TBTI) (2016-2018).

This interest was assessed as non-personal, non-specific and financially significant*.

His research institution² currently receives a grant from United Kingdom Department for International Development (DFID)/ Medical Research Council (MRC)/ Wellcome Trust Joint Global Health Trials for the investigation of MVA85A tuberculosis vaccine prime and selective delayed BCG boost in infants of HIV infected mothers, a randomized controlled, double blind, safety and immunogenicity trial of newborn MVA85A prime and selective, delayed BCG boost in HIV exposed uninfected infants (2012-2016).

This interest was assessed as personal, specific and financially significant*.

His research institution² currently receives two grants from Aeras for a randomized, placebo controlled, partially blinded phase II study to evaluate safety, immunogenicity, and prevention of infection with *Mycobacterium*

tuberculosis of AERAS-404 and BCG revaccination in healthy adolescents (2014-2016) and for a phase IIb, double-blind, randomised, placebo controlled study to evaluate the efficacy, safety and immunogenicity of GSK Biologicals' candidate tuberculosis (TB) vaccine GSK 692342 against TB disease, in healthy adults aged 18- 50 years, living in a TB endemic region (2014-2018).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² received a grant from Aeras for a phase 1b, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety and immunogenicity of the ID93 + GLA-SE vaccine in BCG-vaccinated healthy adults, and a phase I/IIa double-blind, randomized, placebo-controlled, dose-finding study to evaluate the safety and immunogenicity of AERAS-456 in HIV-negative adults with and without latent tuberculosis infection (2013-2015).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² currently receives a grant from Wellcome Trust for a Clinical development of a therapeutic vaccine for tuberculosis (a phase 2a, randomized, double-blind, placebo-controlled, clinical trial to evaluate the safety and immunogenicity of the ID93 + GLA-SE vaccine in HIV uninfected adult TB patients after treatment completion) (2014-2018).

This interest was assessed as non-personal, specific and financially significant*.

The University of Cape Town Clinical Trials Unit (UCTCTU) currently receives a grant from NIH for HIV clinical trials related to new prevention modalities and new strategies for the management of HIV, tuberculosis and related infections (2013-2020).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² currently receives a grant from MRC Clinical Sciences Centre for the project entitled "Systems immunology of ID93 vaccine---induced protection against recurrent TB disease" (2014-2017).

This interest was assessed as non-personal, non-specific and financially significant*.

His research institution² received a grant from NIH, NIAID for a project on the biology and biosignatures of anti-tuberculosis treatment response (2015).

This interest was assessed as non-personal, non-specific and financially significant*.

His research institution² received a grant from NIH, NIAID/ Division of Microbiology and Infectious Diseases (DMID) for a phase I study of whether pre-clearance of latent *M. tuberculosis* (MTB) infection with isoniazid (INH) enhances specific immune responses to MTB following subsequent BCG revaccination in healthy, HIV-uninfected, tuberculin skin test positive adults (2010-2014).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² received a grant from NIH, NIAID for a double-blind, randomised controlled phase IIb trial of safety and immunogenicity of MVA85A, given as an adjunctive TB vaccine for prevention of recurrent TB disease, in HIV uninfected adults (R34 planning grant) (2013-2014).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² currently receives a grant from AIDS Clinical Trials Group (ACTG) and International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) for a study of MDR TB cases and their household contacts: Operational feasibility to inform PHOENIX trial design (2015-2016).

This interest was assessed as non-personal, specific and financially significant*.

His research institution² received a grant from the InterTB Consortium (EDCTP) for an international multicentre controlled clinical trial to evaluate high dose Rifampentine and a quinolone in the treatment of pulmonary tuberculosis (2010-2013).

This interest was assessed as non-personal, non-specific and financially significant*.

Nigel Curtis

His research institution³ currently receives three grants from the Australian National Health & Medical Research Council (NHMRC) for extending the Melbourne Infant Study: BCG for Allergy & Infection Reduction randomised trial of BCG to prevent childhood allergy and infection (2016-2020), for a systems-biology approach to understanding the beneficial heterologous effects of neonatal BCG vaccination in a Melbourne-based randomised controlled trial (2016-2018), and for a BCG immunisation to prevent the development of allergy in infants: a randomised trial (2013-2016).

This interest was assessed as non-personal, specific and financial significant*.

Sang Nae Cho

Sang Nae Cho reported that he received a Research Service Contract from the Green Cross Company (South Korea) on the “Evaluation of protective efficacy of the secondary seed lot K-1 of BCG Pasteur 1173P2 in a mouse model of M. tuberculosis infection” in 2015.

This interest was assessed as personal, specific and financially significant*.

¹ University of Oxford, Jenner Institute, Research Group on Tuberculosis

² University of Cape Town, South African Tuberculosis Vaccine Initiative

³ University of Melbourne, Murdoch Childrens Research Institute, Research Group on Infectious Diseases & Microbiology

* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

Additional experts

- Olatunji Adetokunboh: Stellenbosch University, South Africa
- Rebecca Harris: London School of Hygiene & Tropical Medicine, UK
- Alexandra Hendry, The Children's Hospital at Westmead, New South Wales, UK
- Stefano Malvolti, MMGH Consulting, Zürich, Switzerland
- Punam Mangtani: London School of Hygiene & Tropical Medicine, UK
- Kristine Macartney, The University of Sydney, Australia
- Emily Nickels: Linksbrige, USA
- Amudha S. Poobalan: University Aberdeen, UK
- Maarten Postma: University of Groningen, Netherlands
- Partho Roy: London School of Hygiene & Tropical Medicine, UK
- Paul Saunderson: American Leprosy Missions, USA
- Muki S. Shey : University of Cape Town, South Africa
- Olalekan Uthman: Liverpool School of Tropical Medicine and University of Warwick, UK
- Richard White: London School of Hygiene & Tropical Medicine, UK

WHO

- Madhava Balakrishnan: EMP/RHT/SAV
- Annemieke Brands: GTB/TSC
- Tania Cernuschi: IVB/EPI
- Erwin Aime Willy D. Cooreman: RGO/GLP
- Rolando Dominguez Morales: EMP/RHT/PQT
- Philippe Duclos: IVB/ICP
- Malin Finkernagel: IVB/ICP
- Martin Friede: IVB/IVR
- Michael Gold: EMP/RHT/SAV
- Laura Gillini: RGO/GLP
- Birgitte Giersing: IVB/IVR
- Tracey Goodman: IVB/EPI
- Malgorzata Grzemska: GTB/TSC
- Ana Maria Henao Restrepo: IVB/IVR
- Raymond Christiaan W. Hutubessy: IVB/IVR
- Hye-na Kang: EMP/RHT/TSN
- Ivana Knezevic: EMP/RHT/TSN
- Laura Nic Lochlainn: IVB/EPI
- Martina Penazzato: HIV/TAC
- Carmen A. Rodriguez Hernandez: EMP/RHT/PQT
- Kefas Samson: GTB/TSC
- Patrick Seitzinger: IVB/ICP
- Johan Vekemans: IVB/IVR
- Mandy Wang: GTB/TSC
- Melody Wang: IVB/ICP
- Patrick Zuber: EMP/RHT/SAV

26. Appendix

26.2. Methodology and Search Strategy for BCG Vaccine Cost-effectiveness

Methodology

Selection Criteria

Literature review on economic analysis of the current BCG vaccine for protection against tuberculosis excluded studies modelling the economic benefits of future TB vaccines or immunotherapeutic effects of BCG vaccine on bladder cancer, arthritis, and nontuberculous mycobacteria, were excluded. Studies concerning non-human subjects, such as cattle and possums, were also excluded. Data on the economic analysis conducted, population of interest and geography, methods, model assumptions, and main conclusions were extracted and summarized.

Article selection and extraction

A number of systematic reviews exist on the economic impact of BCG vaccination, thus, collection of information consisted of first identifying systematic reviews to determine the current research landscape. The search was limited to articles published after January 1st, 2003, since the objective was to capture information published after the 2004 BCG vaccine policy paper. A total of 89 articles were screened and 2 systematic reviews on the cost-effectiveness of the BCG vaccine were identified for data abstraction.

Following the literature search of systematic review articles, a primary literature review was undertaken to ensure all studies from January 1st, 2008 published up to January 20th, 2017 were captured. Using the search strategy described in Appendix A, 2,624 articles were identified and after further selection using date of publication (i.e. excluding articles published before January 1st, 2008), 589 studies were obtained for abstract screening (Figure 15). All titles and necessary abstracts were read and 6 primary papers relevant to BCG vaccine economics were categorized and extracted.

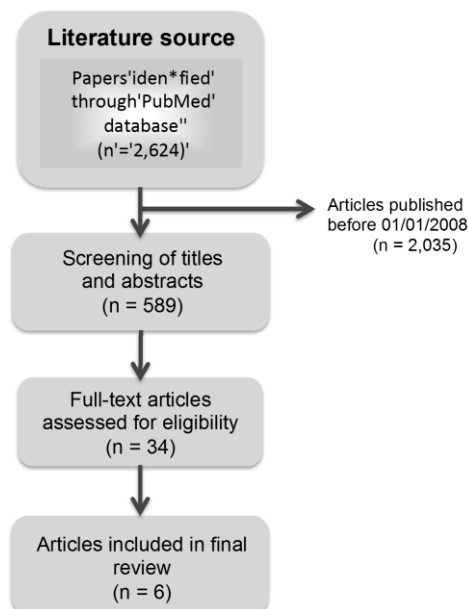


Figure 15: Workflow for primary literature search of economic evaluations on the BCG vaccine.

Database: PubMed

Systematic reviews from 2003/01/01 to 2017/01/20

89 screened, 2 deemed relevant

Dates: 2008/01/01 to 2017/01/20.

Search Terms:

("BCG Vaccine"[Mesh]) AND (((("Cost-Benefit Analysis/economics"[Mesh]) OR ("Cost-Benefit Analysis/methods"[Mesh]) OR ("Cost-Benefit Analysis/classification"[Mesh]) OR "Cost-Benefit Analysis/organization and administration"[Mesh] OR "Cost-Benefit Analysis/standards"[Mesh] OR "Cost-Benefit Analysis/statistics and numerical data"[Mesh] OR "Cost-Benefit Analysis/trends"[Mesh] OR "Cost-Benefit Analysis/utilization"[Mesh]) OR ("BCG Vaccine/administration and dosage"[Mesh] OR "BCG Vaccine/analysis"[Mesh] OR "BCG Vaccine/economics"[Mesh] OR "BCG Vaccine/statistics and numerical data"[Mesh])) NOT "bladder"

Results: 589 articles retrieved and screened.

26.3. Search Strategy for BCG Vaccine Co-administration

Literature search strategy

Database – PubMed

Dates searched (inclusive): from 2003/01/01

Specification: humans

Base Search Strategy: BCG Vaccine

"BCG Vaccine"[Mesh] OR (BCG[TW] AND (vaccin*[TW] OR immuni*[TW])) OR "Bacillus Calmette Gueri" OR OR (Calmette*[TW] AND (vaccin*[TW] OR immuni*[TW])) OR "antituberculosis vaccine"[TW] OR "b.c.g. vaccine"[TW] OR "bacille Calmette Guerin vaccine"[TW] OR "bacillus calmette guerin vaccine"[TW] OR "bcg cell wall vaccine"[TW] OR "bcg test"[TW] OR "Calmette Guerin bacille vaccine"[TW] OR "calmette vaccine"[TW] OR "eurocrine L3"[TW] OR "immun bcg pasteur"[TW] OR "monovax"[TW] OR "mycobax"[TW] OR "bcg vaccine"[TW] OR "tubercle bacilli vaccine"[TW] OR "tuberculosis vaccine"[TW] OR "tuberculosis vaccines"[TW])

Base Search Strategy: Hepatitis B Vaccine

"Hepatitis B Vaccines"[Mesh] OR (("Hepatitis B"[TW] OR "Hep B"[TW]) AND (vaccin*[TW] OR immuni*[TW]))

Base Search Strategy: Polio Vaccine

"Poliovirus Vaccine, Inactivated"[Mesh] OR "Poliovirus Vaccine, Oral"[Mesh] OR (Polio*[TW] AND (vaccin*[TW] OR immuni*[TW])) OR "attenuated live polio*[TW]

Base Search Strategy: DTP Vaccine

"Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR ((DTP[TW] OR DTaP[TW] OR diphtheria[TW] OR tetanus[TW] OR pertussis[TW]) AND (vaccin*[TW] OR immuni*[TW])) OR "diphtheria toxoid"[TW] OR "tetanus toxoid"[TW] OR "whole cell pertussis"[TW] OR "acellular pertussis"[TW]

Base Search Strategy: MMR Vaccine

"Measles Vaccine"[Mesh] OR "Measles-Mumps-Rubella Vaccine"[Mesh] OR MMR[TW]

Base Search Strategy: Hib Vaccine

"Haemophilus influenzae type b"[Mesh] OR "Haemophilus influenzae"[Mesh] OR Hib[TW]

Base Search Strategy: co-administration

"vaccine co-administration"[TW] OR "concurrent adj2 vaccination"[TW]

Search Strategy: BCG Vaccine AND (Hepatitis B Vaccine OR Polio Vaccine OR DTP Vaccine OR MMR Vaccine OR Hib vaccine OR co-administration)

26.4. Search Strategy for BCG Revaccination

Database: PubMed

Dates: 2015/12/01 to 2017/01/20.

Search Terms:

("BCG Vaccine"[Mesh]) AND (((("BCG Vaccine/organization and administration"[Mesh]) OR ("BCG Vaccine/administration and dosage"[Mesh]) OR (BCG [TW] AND ((secondary immuni*[TW]) OR (booster immuni* [TW]) OR (revaccin*[TW]) OR ("booster" [TW]) OR ("Immunization, Secondary"[Mesh])))) NOT "bladder"

Results: 3141 total articles

45 articles retrieved; no additional articles identified separate from base search

26.5. Search Strategy immunoprophylaxis of eff. search of leprosy

- exp Leprosy/
- exp Leprosy, Multibacillary/
- exp Leprosy, Paucibacillary/
- exp Leprosy, Tuberculoid/
- exp Leprosy, Borderline/
- exp Leprosy, Lepromatous/
- (hansen\$ or hansen's or hansens).tw.
- leprosy.tw.
- or/1-8
- (immune-prophylaxis or immunoprophylaxis).tw.
- exp Chemoprevention/
- ICRC.tw.
- IDRI.tw.
- (mycobacterium adj1 w).tw.
- or/10-14
- 9 and 15
- limit 16 to yr="2010 -Current"