Program Management

To change from general to selective BCG vaccination, an efficient notification system must be in place in addition to the following criteria:
– an average annual notification rate of smear-positive pulmonary TB cases below 5 per 100 000; or
– an average annual notification rate of tuberculous meningitis in children aged under five years below 1 per 10 million population during the previous five years; or
– an average annual risk of tuberculous infection below 0.1%.

BCG vaccine (WHO position paper)

Vaccine Quality

An ADT should be conducted on each lot of BCG vaccine. The number of CPs (culturable particles) in vaccine incubated at 37°C for 28 days should be not less than 20% of that in the vaccine stored at 4°C.

Temperature sensitivity of vaccines
The BCG vaccine should be manufactured according to the current recommendations published in the report of the WHO Expert Committee on Biological Standardization.

An ADT (accelerated degradation test) should be conducted on each lot of BCG vaccine. The number of culturable particles in vaccine incubated at 37°C for 28 days should be not less than 20% of that in the vaccine stored at 4°C.

Experimental evidence indicates that (BCG vaccine) viability is unaffected by storage at -20°C or -30°C or by freezing and thawing up to 10 times.
BCG

Vaccine Handling

The recommended conditions for storing vaccines used in immunization programmes are shown in Appendix 81_1. This diagram also indicates the maximum times and temperatures in each case. At the higher levels of the cold chain, i.e., at national (primary), and regional or province level, OPV must be kept frozen between -15°C and -25°C. Freeze-dried vaccines (i.e., BCG, measles, MMR and yellow fever) may also be kept frozen at -15°C to -25°C if cold chain space permits, but this is neither essential nor recommended. At other levels of the cold chain (intermediate vaccine stores and health facilities), these vaccines should be stored between +2°C and +8°C. All other vaccines should be stored at between +2°C and +8°C at all levels of the cold chain. Liquid formulations of vaccines containing diphtheria, pertussis, tetanus, hepatitis B, Haemophilus influenzae type b, IPV and their combinations should not be frozen.

Reconstituted BCG vaccine is very unstable, must be kept cold, and must be discarded within six hours of reconstitution. The reasons for these precautions are as follows:
1. There is a risk of contamination because BCG vaccine, like other lyophilized live vaccines, does not contain any bacteriostatic agent. For this reason, WHO recommends that reconstituted lyophilized vaccine should be kept cold and discarded at the end of six hours.
2. There is a loss of potency.

Once reconstituted, all BCG vaccines should be kept cold and discarded within six hours, regardless of how many doses remain in the vial or ampoule.

Freeze-dried BCG vaccines, regardless of their substrain, are sensitive to ultraviolet and fluorescent light. They should be protected from light when used.
Freeze-dried BCG vaccines, regardless of their substrain, are sensitive to ultraviolet and fluorescent light. They should be protected from light when used.

**Temperature sensitivity of vaccines**

WHO no longer recommends that freezedried vaccines (measles, yellow fever, Hib and BCG) be shipped and stored at -20°C. Storing them at -20°C is not harmful but is unnecessary. Instead, these vaccines should be stored and transported at +2°C to +8°C.

**Administration summary: BCG vaccine (see Appendix 2_10)**

- It is essential that only the diluent supplied with the vaccine be used.
- BCG vaccine should be kept at 2°C-8°C after reconstitution.
- Any remaining reconstituted vaccine must be discarded after six hours or at the end of the immunization session, whichever comes first.
BCG, measles, MR, MMR and rubella vaccines are equally sensitive to light (as well as to heat). Normally, these vaccines are supplied in vials made from dark brown glass, which gives them some protection against light damage, but care must still be taken to keep them covered and protected from strong light at all times.

At the higher levels of the cold chain, i.e. at the national (central) and regional or provincial levels, OPV must be kept frozen between -15°C and -25°C.

Reconstituted BCG, measles and yellow fever vaccines must be kept cooled and must be discarded after 6 hours after reconstitution.

It is no longer necessary to ship and store freeze-dried vaccines (measles, yellow fever and BCG) at -20°C. Instead, they may be refrigerated at +2°C to +8°C.

WHO no longer recommends that freeze-dried vaccines (measles, yellow fever, Hib and BCG) be shipped and stored at -20°C. Storing them at -20°C is not harmful but is unnecessary and uses up valuable storage space in the deep-freeze. Instead, they should be kept in refrigeration and transported at +2°C to +8°C.
Freeze-dried BCG vaccines, regardless of their substrain, are sensitive to ultraviolet and fluorescent light. They should be packed in ampoules made from a substance of low light transmittance, such as amber glass, and should be protected from light when used.

Reconstituted BCG vaccine is very unstable and should be used during one working session of five to six hours. Residual vaccine should be discarded at the end of the session.

Reconstituted vaccines against measles, yellow fever and tuberculosis (BCG) are unstable vaccines; they should be used as soon as possible after reconstitution, be kept in a ice bath during the immunization session and should be discarded at the end of the session.

Multi-dose Open Vials

Opened vials of measles, yellow fever and BCG vaccines MUST be discarded at the end of each immunization session or after 6 hours whichever comes first.
Opened vials of measles, yellow fever, BCG and freeze-dried Hib vaccine cannot be used after an initial immunization session, (even if the VVM has not reached the discard point.). They must be discarded within six hours of reconstitution or at the end of the session, whichever comes first. The VVMs for these vaccines are attached to the vial caps and should be discarded when the vaccine is being reconstituted.

The revised (multi-dose vial) policy does not change recommended procedures for handling vaccines that must be reconstituted, that is, BCG, measles, yellow fever, and some formulations of Hib vaccines. Once they are reconstituted, vials of these vaccines must be discarded at the end of each immunization session or at the end of six hours, whichever comes first.

Schedule

Since 1974, BCG vaccination has been included in the WHO Expanded Programme on Immunization (EPI)

WHO recommends the following schedule for infants (Appendix 39_5).
The regularly-reviewed EPI policy recommendation for BCG is to continue the use of the vaccine as it prevents severe TB in some, but not all children who have been immunized. There should be no BCG booster doses. Should countries, based on cost-effectiveness considerations, decide to discontinue the use of BCG, WHO recommends applying the criteria defined by the International Union against Tuberculosis and Lung Disease (IUATLD). The criteria essentially refer to the requirement for an efficient case-notification system against a background of very low national prevalence figures for all forms of TB.

Immunization of infants with Bacille Calmette-Guérin vaccine (BCG) can protect against TB meningitis and other severe forms of TB in children less than five years old. BCG vaccine is not recommended after 12 months of age because the protection provided is variable and less certain.

The recommended method of prevention for children who are younger than 12 months old is to immunize them as soon after birth as possible with BCG vaccine.

Typical immunization schedule for children (see Appendix 2_19.)

If the infant does not have a scar and you cannot determine whether a dose of BCG has been given, immunize the infant with BCG vaccine.
Unfortunately, the (BCG) vaccine does not fully meet the essential requirement of having a significant impact against the most common manifestation of TB, namely pulmonary disease. Despite the shortcomings of this vaccine, WHO continues to recommend that a single dose of BCG be given to neonates or as soon as possible after birth in countries with a high prevalence of TB.

Since severe adverse effects of BCG vaccination are extremely rare even in asymptomatic, HIV-positive infants, all healthy neonates should be BCG-vaccinated, even in areas endemic for HIV. However, where resources permit, long-term follow-up of BCG-vaccinated infants of known HIV-positive mothers is desirable for early treatment, should disseminated BCG disease occur in children with rapid development of immunodeficiency.

In cases where infants have been exposed to smear-positive pulmonary TB shortly after birth, BCG vaccination should be delayed until completion of 6 months of prophylactic isoniazid treatment.

Countries with a low burden of TB 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. In some low-burden populations, BCG vaccination has been largely replaced by intensified case detection and supervised early treatment.

There is no proven benefit of repeated BCG vaccination against TB. This also applies to revaccination of BCG-vaccinated individuals who remain negative by subsequent tuberculin testing.
In the absence of a scar in children in high-burden countries, BCG vaccination is indicated.

In low-burden countries, good protection against primary TB may also be achieved following vaccination of skin-test-negative adults. BCG vaccination of skin-test positive individuals, whether induced by environmental mycobacteria, Mtb or BCG does not improve immunity to TB.

BCG vaccination is indicated
– for all infants living in areas where TB is highly endemic (concerning HIV, see below);
– for infants and children at particular risk of TB exposure in otherwise low-endemic areas;
– for persons exposed to multidrug-resistant Mtb (impact not established.)

BCG vaccination is contraindicated
– for persons with impaired immunity (symptomatic HIV infection, known or suspected congenital immunodeficiency, leukaemia, lymphoma or generalized malignant disease);
– for patients under immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, radiation);
– in pregnancy.

Given the high risk of acquiring TB and the low risk of serious adverse events following BCG vaccination of HIV-exposed neonates, WHO maintains that, in HIV-infected areas, all neonates be given BCG. Older infants or children suspected of being HIV-infected should not be vaccinated if they have symptomatic disease or other evidence of immunosuppression.
There are few population-based data on the effectiveness, or otherwise, of BCG vaccine in preventing severe tuberculosis in HIV-positive infants. Given the high prevalence of HIV and tuberculosis in certain countries and of the current development of new tuberculosis vaccines, some of which are based on BCG, GACVS advises no change in the current recommendations for BCG immunization of infants in countries with a high prevalence of tuberculosis and that population-based studies should be undertaken to determine the efficacy and safety of BCG and related vaccines in HIV-negative and HIV-positive children in countries with a high endemic rate of tuberculosis.

SAGE strongly endorses the continued used of BCG in national immunization services as a means of minimizing the harmful effects of tuberculosis infection in the first year of life. SAGE recommends that the vaccine be used until there is an alternative improved anti-tuberculosis vaccine. In the meantime, national immunization services are encouraged to maintain the highest possible coverage of infants.

SAGE reinforces WHO’s recommendation that no booster dose of BCG be given, as there is no evidence that booster doses are efficacious.

WHO recommends intradermal application of the (BCG) vaccine, preferably on the deltoid region of the arm using syringe and needle, although other application methods such as the multiple puncture technique are practised in some countries. Newborn vaccinees normally receive half the dose given to older children. BCG vaccine can be given simultaneously with other childhood vaccines.
Contraindications

All infants should be immunized except in these three rare situations:

1. Anaphylaxis or a severe hypersensitivity reaction is an absolute contraindication to subsequent doses of a vaccine. Persons with a known allergy to a vaccine component should not be vaccinated.
2. Do not give BCG or yellow fever vaccine to an infant that exhibits the signs and symptoms of AIDS.

The following are not contraindications. Infants with these conditions should be immunized (see Appendix 6_11B)

BCG vaccine (WHO position paper)
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– for all infants living in areas where TB is highly endemic (concerning HIV, see below);
– for infants and children at particular risk of TB exposure in otherwise low-endemic areas;
– for persons exposed to multidrug-resistant Mtb (impact not established.)
BCG vaccination is contraindicated
– for persons with impaired immunity (symptomatic HIV infection, known or suspected congenital immunodeficiency, leukaemia, lymphoma or generalized malignant disease);
– for patients under immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, radiation);
– in pregnancy.

HIV-positive infants may receive BCG vaccine only when asymptomatic and living in areas where TB is highly endemic. Long-term follow-up of such children following vaccination is desirable. HIV-positive, asymptomatic infants in low-burden areas should not be BCG-vaccinated. Indications for vaccination of groups likely to contract HIV should always be considered carefully. The efficacy of BCG vaccination in HIV-infected infants is not known.

Given the high risk of acquiring TB and the low risk of serious adverse events following BCG vaccination of HIV-exposed neonates, WHO maintains that, in HIV-infected areas, all neonates be given BCG. Older infants or children suspected of being HIV-infected should not be vaccinated if they have symptomatic disease or other evidence of immunosuppression.
BCG

There are few population-based data on the effectiveness, or otherwise, of BCG vaccine in preventing severe tuberculosis in HIV-positive infants. Given the high prevalence of HIV and tuberculosis in certain countries and of the current development of new tuberculosis vaccines, some of which are based on BCG, GACVS advises no change in the current recommendations for BCG immunization of infants in countries with a high prevalence of tuberculosis and that population-based studies should be undertaken to determine the efficacy and safety of BCG and related vaccines in HIV-negative and HIV-positive children in countries with a high endemic rate of tuberculosis.

Global Advisory Committee on Vaccine Safety, 3–4 December 2003

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**Adverse Event**

The (GACVS) concluded that the isolation and identification of a low level of isoniazid resistance of BCG strains from 5 patients presenting with lymphadenitis do not justify a change in standard policy.

Global Advisory Committee on Vaccine Safety, 9–10 June 2005

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All immunization programmes should monitor at least the following AEFIs:

1. All injection site abscesses.
2. All cases of BCG lymphadenitis.
3. All deaths that are thought by health workers, or the public, to be related to immunization.
4. All cases requiring hospitalization that are thought by health workers, or the public, to be related to immunization.
5. Other severe or unusual medical incidents that are thought by health workers, or the public, to be related to immunization.

With respect to the third, fourth, and fifth events, health workers may relate the event to immunization because it occurred within a month of an immunization, as its case definition indicates. However, some medical incidents can be related to immunization even if they have a delayed onset.

Surveillance of Adverse Events Following Immunization
For mild problems, health workers should comfort and advise parents and treat the patient. It is not necessary to report these reactions, except for BCG lymphadenitis and injection site abscesses, unless parents' concerns are significant.

Research

Improved TB vaccines are widely seen as a key element for successful TB control, and the development of efficient, safe and affordable vaccines against TB must remain a global priority.

There are few population-based data on the effectiveness, or otherwise, of BCG vaccine in preventing severe tuberculosis in HIV-positive infants. Given the high prevalence of HIV and tuberculosis in certain countries and of the current development of new tuberculosis vaccines, some of which are based on BCG, GACVS advises no change in the current recommendations for BCG immunization of infants in countries with a high prevalence of tuberculosis and that population-based studies should be undertaken to determine the efficacy and safety of BCG and related vaccines in HIV-negative and HIV-positive children in countries with a high endemic rate of tuberculosis.