World Health Organization
Global Vaccine Safety,
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Information Sheet
Observed rate of vaccine reactions
Bacille Calmette-Guérin (BCG) vaccine

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The Vaccines

The original strain of *Mycobacterium bovis* BCG strain was developed in 1921 at the Pasteur Institute with attenuation through serial passage of an isolate from a cow with tubercular mastitis. This isolate was subsequently distributed to several laboratories in the world and a number of strains developed (Oettinger et al., 1999). Currently, five main strains account for more than 90% of the vaccines in use worldwide with each strain possessing different characteristics. The agreed terminology for the strains include the Pasteur 1173 P2, the Danish 1331, the Glaxo 1077 (derived from the Danish strain), the Tokyo 172-1, the Russian BCG-I, and the Moreau RDJ strains (NIBSC and WHO, 2004).

Each strain has a different reactogenicity profile - the Pasteur 1173 P2 and Danish 1331 strains are known to induce more adverse reactions than the Glaxo 1077, Tokyo 172-1, or Moreau RDJ strains. The concentration of live particles in the vaccines ranges from 50,000 to 3 million per dose, according to the strains. The strain is one of the important factors that has been implicated in incidence of adverse events following BCG vaccination (Milstien et al., 1990, Lotte et al., 1984).

There is no standardized production of BCG vaccine between manufacturers.

The first WHO reference reagents for BCG vaccines of sub-strain Danish 1331, Tokyo 172-1 and Russian BCG-I were established in 2009 and 2010. These reference reagents cover the major proportion of BCG vaccine strains currently in production and that are supplied by UNICEF after prequalification for their use globally. The NIBSC-HPA distributes the reagents as a WHO collaborating center. This has helped to limit the strain variation within vaccine production.

Understanding the different reactogenic profiles of different BCG vaccines is important in interpreting any vaccine safety data.

Adverse events

Globally BCG vaccine is used extensively with approximately 100 million newborns being vaccinated each year. Despite this extensive use few severe adverse events have been reported. For some adverse events (such as disseminated BCG disease), the diagnosis may depend on the culturing of M. Bovis BCG to distinguish this from other forms of Mycobacterial disease.

Mild adverse events

Almost all vaccine recipients experience an injection site reaction characterized by a papule, which may be red, tender and indurated. The papule commences two or more weeks after vaccination and then may progress to become ulcerated healing after 2-5 months leaving a superficial scar. Swelling of the ipsilateral regional lymph nodes (usually axillary but may also be cervical and/or supra-clavicular) may also occur. However, the lymph nodes remain small (< 1.5cm) and do not adhere to overlying skin.

Mild local reactions occur despite correct intradermal administration and the extent of the reaction will depend on a number of factors including the strain used in the vaccine, number of viable bacilli in the batch, and variation in injection technique. No treatment is required for mild injection site reactions with or without mild regional lymphadenopathy.

Severe adverse events

Local adverse events

Injection site reactions. Reactions which have been reported include local sub-cutaneous abscess and keloids (thickened scar tissue) (Lotte et al., 1984)

Skin lesions distinct from the vaccination site. Tuberculosis infection can cause a number of cutaneous lesions (such as TB chancre, lupus vulgaris, scrofuloderma, papulonecrotic tuberculids etc). There are case reports of cutaneous lesions, distinct from the site of vaccination, thought to have occurred after BCG vaccination (Bellet et al., 2005). It is important to note that multiple cutaneous lesions may signal disseminated BCG disease usually in an immunocompromised host. There are case reports of lupus vulgaris, scrofuloderma following BCG vaccination.

Lymphadenitis. When severe, this includes nodes which become adherent to overlying skin with or without suppuration. Suppuration has been defined as "presence of fluctuation on palpation or pus on aspiration, the presence of a sinus, or large lymph node adherent to the skin with a caseous lesions on excision" (Lotte et al., 1984). If BCG is administered in the recommended site (deltoid) the ipsilateral axillary nodes are most likely to be affected but supra-clavicular or cervical nodes may also be involved (Hengster et al., 1992). The onset of suppuration may be variable with cases presenting from one week to 11 months following vaccination (de Souza et al., 1983). Lymphadenitis presenting within 2 months of vaccination and larger nodes (+ 1cm) may be less likely to resolve spontaneously (Caglayan et al., 1991). Suppurative lymphadenitis is now rare, especially when BCG inoculations are performed by well-trained staff, with a standardized freeze-dried vaccine and a clearly stated individual dose depending on the age of the vaccinated subjects.

Systemic adverse events

Osteitis and Osteomyelitis. This is a rare and severe complication of BCG vaccination which has primarily been reported in Scandinavia and Eastern Europe and typically associated with changes in BCG vaccine strain. There was a report of an increase in osteitis to 35 per million in Czechoslovakia after a shift from the Prague to Russian strain BCG (Lotte, et al., 1988). Both Finland and Sweden reported increases in osteitis after 1971 when they shifted to a Gothenburg strain produced in Denmark. Sweden reported rates as high as 1 in 3,000 vaccine recipients, which declined rapidly when the national programme shifted to a Danish (Copenhagen, 1331) vaccine strain (Lotte et al., 1988). More recently reports of osteitis have become infrequent.

Disseminated BCG disease or systemic BCG-itis. This recognized but rare consequence of BCG vaccination traditionally has been seen in individuals with severe cellular immune deficiencies. The risk (fatal and non-fatal) is thought to be between 1.56 and 4.29 cases per million doses (Lotte et al., 1988). This is based on pre-HIV data. However, the exact incidence is debated because few centers are able to differentiate *Mycobacterium Bovis* BCG from other forms of Mycobacterium in patients presenting with disseminated disease. In a recent retrospective case series review of Mycobacteriunm tuberculosis complex 5% of cases were found to have the *M. Bovis* BCG strain (Hesseling et al., 2006). Additional data from studies in South Africa confirm the significantly high risk of disseminated BCG (dBCG) disease in HIV-positive infants, with rates approaching 1% (Hesseling et al., 2009).

As expected the cellular primary immunodeficiency predisposes to the condition. This includes severe combined immunodeficiency, chronic granulomatous disease, Di George syndrome and homozygous complete or partial interferon gamma receptor deficiency (Jouanguy et al., 1996; Jouanguy et al., 1997; Casanova et al., 1995).

In one series of 60 cases of BCG-itis the case fatality rate was approximately 50% although other smaller studies have documented a higher mortality rate (Lotte et al., 1988, Talbot et al., 1997). Early recognition and diagnosis is critical to management. In patients with primary immunodeficiency disorders the disease may be fatal without reconstitution of immunity through stem cell transplant.

Immune reconstitution inflammatory syndrome (IRIS). This has recently been identified as a BCG vaccine-related adverse event in immunocompromised individuals due to HIV started on antiretroviral therapy (ART) (DeSimone et al., 2000). It usually presents within 3 months of immune restoration and manifests as local abscesses or regional lymphadenitis usually *without* dissemination. No fatal cases have yet been documented. The etiology is unknown but postulated to be a deregulated inflammatory reaction directed against opportunistic pathogens including mycobacterial organisms following immune reconstitution.

Other rare events. A number of events have been reported as case reports or series. These include sarcoidosis, ocular lesions (conjunctivitis, choroiditis, optic neuritis), and erythema nodosum. Tuberculous meningitis (due to the BCG) has been described but is exceptionally rare (Tardieu et al., 1988)

Other safety issues

Immunization safety issues

Injection technique. Intradermal inoculation of BCG vaccine is a difficult field technique and incorrect administration may lead to local reactions including injection site reactions and lymphadenitis.

Change in vaccine strain: The Pasteur and Copenhagen strains have generally been found to be more reactogenic than the Tokyo, Glaxo or Brazilian (Moreau) strains (Milstien et al., 1990). There were several reports in the late 1980s of "outbreaks" of BCG reactions, manifested as large ulcers and local lymphadenopathy or suppurative lymphadenitis. At this time, changes in vaccine availability led many programmes to switch from the less reactogenic Glaxo1077 to the more reactogenic Pasteur 1173P2 strain without staff being notified of the necessary change in dosage it implied (in Austria: Hengster et al., 1992; in India: Kabra et al., 1993; in Jamaica: Noah et al., 1990; in Mozambique: WER, 1988; in Zimbabwe: WER, 1989).

Effect of local BCG reactions on the acceptability of other vaccines: The duration of suppuration may alter the willingness of mothers to allow their children to receive other antigens (Loevinsohn et al., 1990).

Effect of age at the time of administration: Infants have a higher risk of lymphadenitis and for this reason a reduced dose of the vaccine is recommended (Milstien, 1990).

BCG vaccination in an individual with TB infection: This may result in an accelerated response to BCG vaccination with papule formation within 1-2 days and healing within 10-15 days.

Adverse events following BCG immunotherapy: There are several observations of adverse events following BCG administration as a therapy for bladder cancer. The vaccine is administered intravesically and the doses used in this indication are much higher than those used for infant immunization. The most frequent complications are pulmonary, hepatic, bone marrow, and joint infections, but a laryngeal tumor has also been reported. General signs such as fever and inflammatory signs are common (Sicard et al., 1992)

BCG vaccination and HIV-infection

Infants known to be HIV-infected:

There has been particular concern over the implications of HIV for the safety of BCG vaccination. In the early 1980's there were case reports of systemic BCG-itis in individuals with AIDS (Anon, 1985). A series of studies were initiated in Africa to compare reactogenicity in infants born to HIV-positive and HIV-negative women (O'Brien et al., 1995, WER, 1992, Moss et al., 2003)). In general, the data available at this time supported the WHO policy of exempting only individuals with symptomatic HIV infection (AIDS) from routine BCG vaccination at birth (WHO, 1987). Only one study found a significant excess of reactions amongst HIV exposed and HIV positive infants. This occurred following wrongful administration of more than twice the recommended dose of BCG Pasteur vaccine. Recent reviews of the literature and observational studies have resulted in a review of this policy. Talbot et al. reviewed the literature published between 1980 and 1996 and gathered 28 cases of generalized infection following BCG; 24 of them occurred in immunocompromised children, and 9 of them were AIDS cases. The mortality was 78%, but it has not been possible to estimate the part attributable to AIDS in these deaths. Hesseling et al. (2007) conducted a prospective hospital based surveillance study of laboratory confirmed cases of disseminated cases of TB and estimated that the risk of BCG disease in HIV-infected individuals was increased several hundred fold. A recent retrospective study documented a high frequency of BCG infection with complications in HIV-infected infants (Fallo et al., 2007). In the light of this the WHO has reviewed the recommendation for BCG vaccination in infants known to be HIV-infected. The current recommendation is that routine BCG vaccination is no longer recommended for infants known to be HIV-infected with or without symptoms of HIV infection.

Infants whose HIV status is unknown:

In infants symptoms of HIV-infection rarely appear before several months of age. BCG vaccination should be administered to those infants regardless of HIV exposure, especially considering the high endemicity of tuberculosis in populations with high HIV prevalence. Close follow up of infants known to be born to HIV-infected mothers and who received BCG at birth is recommended in order to provide early identification and treatment of any BCG-related complication. In settings with adequate HIV services that could allow for early identification and administration of antiretroviral therapy to HIV-infected children, consideration should be given to delaying BCG vaccination in infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative. Infants who demonstrate signs or reported symptoms of HIV-infection and who are born to women known to have HIV infection should not be vaccinated.

Summary of mild and severe adverse events

Nature of Adverse event	Description	Rate/doses
Mild	Injection site papule (onset 2-4 weeks) Mild ulceration (1-2 months) Scar (2-5 months)	Almost all vaccinees
Severe	Local Local abscess Keloid Lymphadenitis Suppuration (onset 2-6 months) Systemic (1-12 months onset time) Cutaneous skin lesions Osteitis Disseminated BCG Immune Reconstitution Syndrome	1 per 1,000-10,000 Case reports only 1 per 3,333 - 10^8 1 per 230,000 - 640,000 1 per 640,000

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al 2008, Institute of Medicine of the National Academies 2011) and from data derived from a literature search on Pubmed in 2008 using key words "vaccine antigen", "Safety" and "adverse events". An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomised controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: **http://www.who.int/vaccine_safety/vaccrates/en/index.html**

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