

# Complications of bacille Calmette-Guérin (BCG) vaccination and immunotherapy and their management

JM Grange

**Summary:** *Complications of bacille Calmette-Guérin (BCG) vaccination are uncommon. Fewer than one in 1000 people vaccinated develop significant local reactions, and serious disseminated disease develops in fewer than one in a million.*

*Localised complications - which include hypersensitivity reactions, abscesses at the injection site, and localised lymphadenopathy - are usually self limiting. They usually result from faulty technique, including the accidental intracutaneous injection of the stronger percutaneous vaccine, or poor selection of subjects for vaccination. Abscesses at the injection site usually respond to drainage and chemotherapy with isoniazid or erythromycin. Lymphadenopathy responds poorly to antimicrobial treatment and surgery may be needed for suppurating or discharging lesions to hasten recovery and give a good cosmetic result.*

*Disseminated disease usually occurs in people with impaired immunity, in whom it is often fatal. BCG should never be given to people who are known to be infected with HIV, but the risk of complications in children born to HIV infected mothers is low. Disseminated disease can also result from intravesical instillation of BCG to treat bladder cancer, but this responds to antituberculosis chemotherapy.*

**Key words:**

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## Introduction

Bacille Calmette-Guérin (BCG) has been used extensively as a vaccine against human tuberculosis for over 70 years. As BCG is a live attenuated vaccine, infectious complications occasionally occur. In recent years, the nature and incidence of such complications in people infected with HIV has caused concern.

BCG is usually given to children in the United Kingdom (UK) between the ages of 10 and 14 years, and about 70% of this target group receives the vaccine<sup>1</sup>. In addition, up to 50 000 neonates are vaccinated each year in selective programmes aimed at high risk groups, such as infants born to immigrants from countries where the prevalence of tuberculosis is high<sup>1</sup>. The vaccine is given to adults and children by intradermal injection, using a vaccine that contains 8-26 million colony forming units (cfu) in each 10 dose vial - that is, 0.8-2.6 million cfu in each standard 0.1 ml dose. Infants may, alternatively, be vaccinated percutaneously by a multipuncture technique, using a vaccine that contains 50 to 250 million cfu in each vial.

In addition to its role as a vaccine against tuberculosis, BCG has also been used as an immunotherapeutic agent in patients with various forms of cancer. In recent years this role has largely been restricted to the treatment of superficial cancer of the bladder by intravesical instillation. Although

BCG is used far less for immunotherapy than as a vaccine against tuberculosis, the incidence of infectious complications is very much higher when used in immunotherapy than when used as a vaccine<sup>2,3</sup>.

Adverse reactions to BCG vaccination are rare, provided that correct immunisation techniques are used and that those to be vaccinated are properly selected. The Department of Health has published full details of technique and selection<sup>1</sup>. In brief, the vaccine should be given only to those who are shown to be tuberculin negative (Heaf grades 0 and 1 and Mantoux responses of 0-4 mm), although infants up to 3 months of age may be vaccinated without prior tuberculin testing. People with a history of BCG vaccination should be revaccinated only if they are tuberculin negative and have no characteristic BCG scar. Other contraindications include malignancy, corticosteroid treatment, fever, pregnancy, generalised septic skin conditions, and immunosuppressive disorders. It has recently been recommended that BCG vaccination of children with active atopic dermatitis should be deferred until remission as the vaccine may exacerbate this skin condition<sup>4</sup>.

The World Health Organization recommends that people known to be infected with HIV should never be given BCG but that routine immunisation of infants

should continue in areas where the incidence of tuberculosis and HIV infection is high<sup>5</sup>. In the UK it is advised that BCG should not be given to infants born to mothers known or suspected to be HIV infected, unless the infants are subsequently confirmed to be HIV negative<sup>6</sup>.

**Complications of BCG vaccination**

There are two major categories of adverse reactions to BCG vaccination: non-infectious and infectious. The exact incidence of adverse reactions is difficult to estimate as their definitions are not universally accepted. Rates vary between regions and centres, but local adverse reactions usually occur at a rate of 0.1 to 0.5 per 1000 vaccinations, and serious, disseminated complications occur at a rate of less than 1 in a million vaccinations<sup>7</sup>.

A total of 10 371 adverse events were recorded in an international review of BCG complications up to 1977<sup>7</sup>. Most of the complications (70.8%) were abnormal primary complexes, either lesions at the injection site or, more commonly, suppurative lymphadenitis. Lesions at the injection site were either ulcers, subcutaneous abscesses, or necrotic lesions due to excessive delayed hypersensitivity reactions. In some reports, abscesses at the injection site occur more commonly than lymphadenopathy<sup>8</sup>. Other complications were localised or generalised non-fatal persisting BCG infection (10.5%), fatal disseminated BCG infection (0.3%), and 'post-BCG syndromes', principally keloid scarring (18.2%)<sup>7</sup>.

Treatment depends on the nature (infectious or non-infectious) of the complication, its severity, and the nature of any underlying causative factor. In the UK serious complications, including abscesses and keloid scarring, should be reported to the Committee on Safety of Medicines by the yellow card system, and vaccination techniques should be reviewed<sup>1</sup>. The major categories of BCG complications and their treatment are summarised in the table.

**Non-infectious complications**

These usually manifest as hypersensitivity reactions at the injection site but occasionally as distant immune reactions, including erythema nodosum and phlyctenular conjunctivitis. Most local hypersensitivity reactions occur within a few days of vaccination and are commoner in revaccinated subjects and those who are tuberculin positive. Generalised, life threatening hypersensitivity reactions have occurred following intravesical instillation of BCG (see below). Keloid scarring is the commonest of the late non-infectious complications<sup>7</sup>. The risk of such scarring is minimised by giving the injection in the skin overlying the insertion of the deltoid muscle. Injections higher up the arm are much more likely to lead to keloid scarring.

**Management**

Large local reactions due to hypersensitivity, which may occur when those who react strongly to tuberculin

**TABLE Principal complications of BCG vaccination and their management**

Complication	Management
Local hypersensitivity reaction	None, or topical dressing
Abscess or ulcer at injection site	Drainage or needle aspiration if indicated. Isoniazid or erythromycin
Regional lymphadenitis	Surgical if there is excessive enlargement, overt suppuration, or sinus formation
Distant lesion, eg osteitis	Chemotherapy*
Disseminated BCG infection ('BCG-osis')	Chemotherapy*
Disseminated BCG infection with cardiovascular effects following intravesical instillation of BCG	Chemotherapy* plus intravenous corticosteroids

\* see text for details

are vaccinated, resolve spontaneously unless they become infected. Topical corticosteroids are sometimes prescribed, but there is no published information on their efficacy. In practice, and especially if ulceration occurs, it is difficult to distinguish between local lesions due to hypersensitivity and those due to infection. Parents may expect some form of treatment and, despite their dubious value, short courses of isoniazid or erythromycin (see below) are often prescribed<sup>9</sup>.

**Infectious complications**

These include ulcers and abscesses at the site of injection, regional lymphadenitis, and more distant lesions, such as osteitis and disseminated disease ('BCG-osis').

**Local complications: abscesses and ulcers at the injection site and regional lymphadenopathy**

Local abscesses and ulcers usually present between one and five months after vaccination, but some present even later. Lymphadenopathy occurs in the drainage area of the vaccinated site and is thus commonest in the axilla, although cervical lymph nodes may be affected if the vaccine is given in the upper deltoid region. Local cutaneous lesions and suppurative lymphadenitis seldom occur in the same patient.

Lymphadenopathy is not uncommon after percutaneous vaccination of neonates and infants. In Japan, where this form of vaccination is used extensively, lymphadenopathy was detected in 253 (0.79%) of 34 516 vaccinated children<sup>10</sup>. The great majority resolved spontaneously and only eight (0.02%) proceeded to suppuration and discharge.

Concern has been expressed over the risk of local infective complications after accidental intradermal administration of the stronger BCG preparation, which is intended for percutaneous use. When 19 children aged 11 to 14 years who received

the stronger vaccine intradermally were compared with 13 who received the correct vaccine, their lesions were larger and more were still discharging at six weeks than in the correctly vaccinated group, but no action - other than reassurance - was necessary<sup>11</sup>. In another instance, 857 infants were vaccinated intradermally with the preparation intended for percutaneous use and 556 attended special follow up clinics<sup>12</sup>. Sixty-one (11%) of the infants had adverse local reactions: 48 developed axillary lymphadenopathy (>20 mm in diameter in one case), six developed papules >10 mm diameter, six developed local ulcers >10 mm diameter, and one developed an abscess at the injection site that resolved after needle aspiration.

#### Management

Material - for example, swabs or aspirated pus - should be obtained from abscesses and ulcers at the site of immunisation to confirm that BCG is the cause or to identify other organisms that occasionally cause such reactions - for example, staphylococci or environmental mycobacteria<sup>1</sup>. Various interventions have been used for post injection ulcers and abscesses due to BCG, but evidence for their relative efficacy is limited and largely anecdotal. The interventions include drainage, needle aspiration, topical or systemic isoniazid, or systemic erythromycin. Although BCG is susceptible to isoniazid, some cases do not respond and the use of erythromycin has yielded good results<sup>13,14</sup>. In one small comparative study of 18 children with local cutaneous complications, responses to one month courses of treatment with isoniazid (6 mg/kg body weight daily to a maximum of 300 mg) and erythromycin (250 mg four times daily) were similar<sup>15</sup>.

Likewise, various interventions have been used to treat lymphadenopathy but it is generally agreed that antimycobacterial chemotherapy is of no value<sup>16</sup>. Practices vary from a conservative approach with no treatment other than topical dressings to surgical removal of all chronically suppurating and discharging nodes. Although in some cases surgical treatment has been unnecessarily radical, surgery hastens healing and achieves a favourable cosmetic result<sup>16</sup>.

#### BCG lesions at more distant sites

Osteitis and arthritis are the lesions most commonly encountered. Most of the cases of post-BCG osteitis reported have occurred in Finland, and may be related to the strain of vaccine used<sup>17</sup>. Between 1960 and 1970, when the Swedish strain manufactured in Sweden was used, the incidence was 7.3/100 000 vaccinated children. The incidence rose to 36.9/100 000 when the same strain was manufactured in Copenhagen but fell to 6.4/100 000 when the English (Glaxo) strain was introduced. Post-BCG osteitis is exceedingly rare outside Scandinavia.

Otitis media and retropharyngeal abscesses were common when BCG was given orally but they are seldom seen nowadays<sup>7</sup>.

#### Management

Reported cases of post-BCG osteitis responded well to various antituberculosis drug regimens (see below). Only six of 222 children reviewed had residual deformities<sup>17</sup>.

#### Widely disseminated disease

This is uncommon, but may prove fatal. Some cases are associated with a known congenital or acquired cause of immunodeficiency, including HIV infection, but in other cases no such cause is found. A survey in France between 1974 and 1994 revealed 18 childhood cases of disseminated BCG infection, representing a prevalence of 0.59 cases per million vaccinations<sup>18</sup>. Half the children had other severe chronic infections, suggesting some form of immune defect, and half of these died.

A review of over 5000 publications worldwide on BCG between 1980 and 1995 revealed 28 cases, including four adults, of disseminated disease due to BCG<sup>19</sup>. Twenty-four patients had AIDS or various congenital immune defects and, despite antituberculosis chemotherapy, 20 died. The remaining four patients had no evident immunosuppression; they received various antituberculosis drug regimens and all survived.

#### Management

Disseminated disease is treated in a similar manner as tuberculosis due to virulent *M. bovis* - that is, with rifampicin and isoniazid and a third drug selected from ethambutol, ethionamide, and streptomycin<sup>3</sup>. Pyrazinamide is not used as, in common with *M. bovis*, BCG is naturally resistant to this agent. It may be necessary to continue treatment for longer than the usual six month period in immunocompromised patients and adverse drug reactions and interactions may occur, particularly in those with AIDS. It is recommended that treatment should be conducted in close collaboration with a chest physician experienced in the treatment of tuberculosis<sup>6</sup>. As noted above, the mortality in such immunocompromised patients is high, despite treatment.

#### BCG complications in people with HIV infection

As outlined above, people with HIV infection who are given BCG are at risk of developing disseminated infection. In view of this risk, the risk of vaccinating asymptomatic HIV infected children has been debated. A review of published evidence revealed that there is a small increase in the incidence of adverse effects of BCG in children born to HIV infected women but that almost all are mild<sup>20</sup>. One outbreak of complications was traced to the accidental administration of more than twice the standard dose of BCG<sup>20</sup>. In another report, nine out of 68 HIV infected children vaccinated as neonates developed BCG related complications three to 35 months later: seven developed regional lymphadenopathy with or without fistula formation and two developed systemic disease<sup>21</sup>. In eight of the nine children the course of the HIV disease was rapid, but this was not the result of the BCG vaccination.

### Management

The treatment described above for localised or disseminated disease in patients not infected with HIV is appropriate.

### Complications associated with the intravesical instillation of BCG for the treatment of superficial bladder tumours

This therapeutic procedure is associated with a relatively high incidence of complications<sup>2,3</sup>. Cystitis is very common and is regarded as an unavoidable effect of the treatment<sup>2,3</sup>. Transient fever occurs in 3% of patients but may be due to hypersensitivity rather than systemic infection<sup>2,3</sup>. Disseminated, life threatening infection occurs in 0.4% of patients and often causes cardiovascular instability, which may lead to collapse. It is not clear whether this instability is due to anaphylactic hypersensitivity reactions or to adrenal dysfunction, or both<sup>22</sup>.

Pneumonitis, granulomatous hepatitis, or arthralgia occur in about 0.7% of patients. They are generally regarded as manifestations of hypersensitivity, but in one case of granulomatous hepatitis acid fast bacilli were seen in the liver tissue on microscopy and mycobacterial DNA was detected by the polymerase chain reaction<sup>23</sup>.

### Management

Treatment of complications of the intravesical instillation of BCG have been reviewed<sup>2,3,24</sup>. Transient fevers exceeding 38.5°C are not treated specifically but isoniazid (300 mg daily) is given for three months if the fever lasts over 12 hours. In either case BCG therapy is withheld but resumed when symptoms have resolved. Hypersensitivity reactions are likewise treated with isoniazid (300 mg daily) for three months and BCG therapy is resumed only if benefits exceed risks.

The IRP (isoniazid-rifampicin-prednisolone) regimen has been advocated for acute severe illnesses and suspected or definite generalised infection, particularly if there are cardiovascular symptoms or signs<sup>22,24</sup>. This regimen consists of isoniazid 300 mg and rifampicin 600 mg daily for six months and prednisolone 40 mg intravenously daily until symptoms subside. The addition of cycloserine, 250-500 mg twice daily, has been recommended for the first three days or until acute symptoms subside if there is evidence of generalised infection<sup>22</sup>, but it should be noted that BCG is more resistant to this agent than *M. bovis* or *M. tuberculosis*. As BCG is usually susceptible to erythromycin, and as tuberculosis has been successfully treated with newer macrolides such as clarithromycin, it would seem logical to use a macrolide if an additional drug is required to treat generalised disease due to BCG.

### Conclusions

Complications arising from the use of the live attenuated BCG vaccine are uncommon and most are either self limiting or respond to straightforward

management. Many are preventable by correct selection of those to be vaccinated. Serious complications are rare and are often the result of vaccination of immunocompromised patients. Intravesical instillation of BCG for the treatment of bladder cancer is a special case, which carries a higher risk of complications. Despite the complications described BCG remains one of the safest vaccines in use and the benefits resulting from its use for the prevention of tuberculosis and the treatment of bladder cancer greatly outweigh its disadvantages.

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- J M Grange, reader in clinical microbiology  
Imperial College School of Medicine  
and visiting professor,  
University College London Medical School
- Address for correspondence:  
Dr John M Grange  
Imperial College School of Medicine  
National Heart and Lung Institute  
Dovehouse Street  
London SW3 6LY  
tel: 0171 351 8456  
fax: 0171 376 3442  
email: j.grange@ic.ac.uk