# Bacille Calmette–Guérin vaccination: the current situation in Europe

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**A WHO EURO Task Force provides the latest evidence and a coherent policy to use BCG vaccination in Europe** http://ow.ly/pusIU

Tuberculosis is a major public health priority. This is not only because of its daunting morbidity and mortality rates, both globally and in Europe (summarised in figs 1 and 2) [1, 3–5], but also because of the natural history of the disease. Active (contagious) tuberculosis disease occurs after a period of latency (or subclinical infection), and different risk factors [6–13], in combination with latent infection, introduce challenges to prevention, diagnosis and treatment of the disease. Vaccination against tuberculosis, if effective, would be therefore critical to control and elimination strategies [14–16]. The bacille Calmette–Guérin (BCG) vaccine is, from a historical perspective, a milestone of tuberculosis control (figs 3–7). During the first half of the 20th century, it was administered ubiquitously throughout Europe, but is now recommended by the World Health Organization (WHO) to be given once at birth, specifically in tuberculosis-endemic areas.

The BCG is currently the only available vaccine to provide protection against haematogenous spread and subsequent severe clinical forms of tuberculosis, including meningitis [17–19]. It is included in national childhood immunisation programmes in most high-burden countries in Europe, and is also administered to high-risk populations in nonendemic areas [17]. In western Europe, as in other low-incidence regions, discontinuation of national BCG vaccination began following initial pilot studies in the former Czechoslovakia (1961–1972) and Sweden (1975) [20–22]. These studies demonstrated the decline in risk of serious forms of tuberculosis in children, evidence of the weak protective effect of BCG in adults and lack of impact on the global incidence of tuberculosis. Usage of BCG by country in the WHO European Region is summarised in table 1.

Given that a more effective vaccine against tuberculosis does not currently exist [26], BCG remains an important prevention tool, particularly in children. Unfortunately, some countries have recently faced problems with adverse events (table 2) due to shifting from one strain of BCG to another [27]. Meanwhile, other countries are debating a shift away from national BCG vaccination to selective vaccination, although previous discontinuation experiences have produced transient increases in severe forms of tuberculosis, particularly tuberculous meningitis [20–22]. As countries weigh the impact of current and future BCG practices, guidance for BCG policy making is needed.

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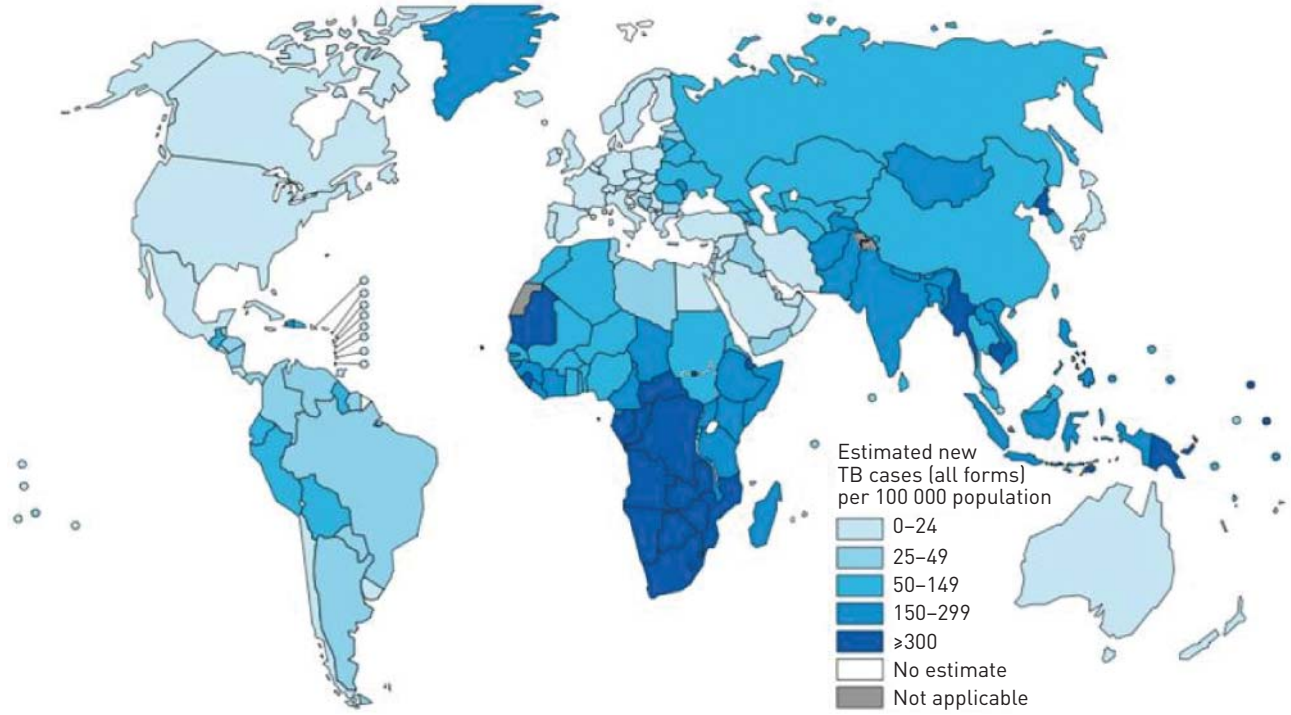


FIGURE 1 Global estimated tuberculosis (TB) incidence rates, 2011. Reproduced from [1] with permission from the publisher.

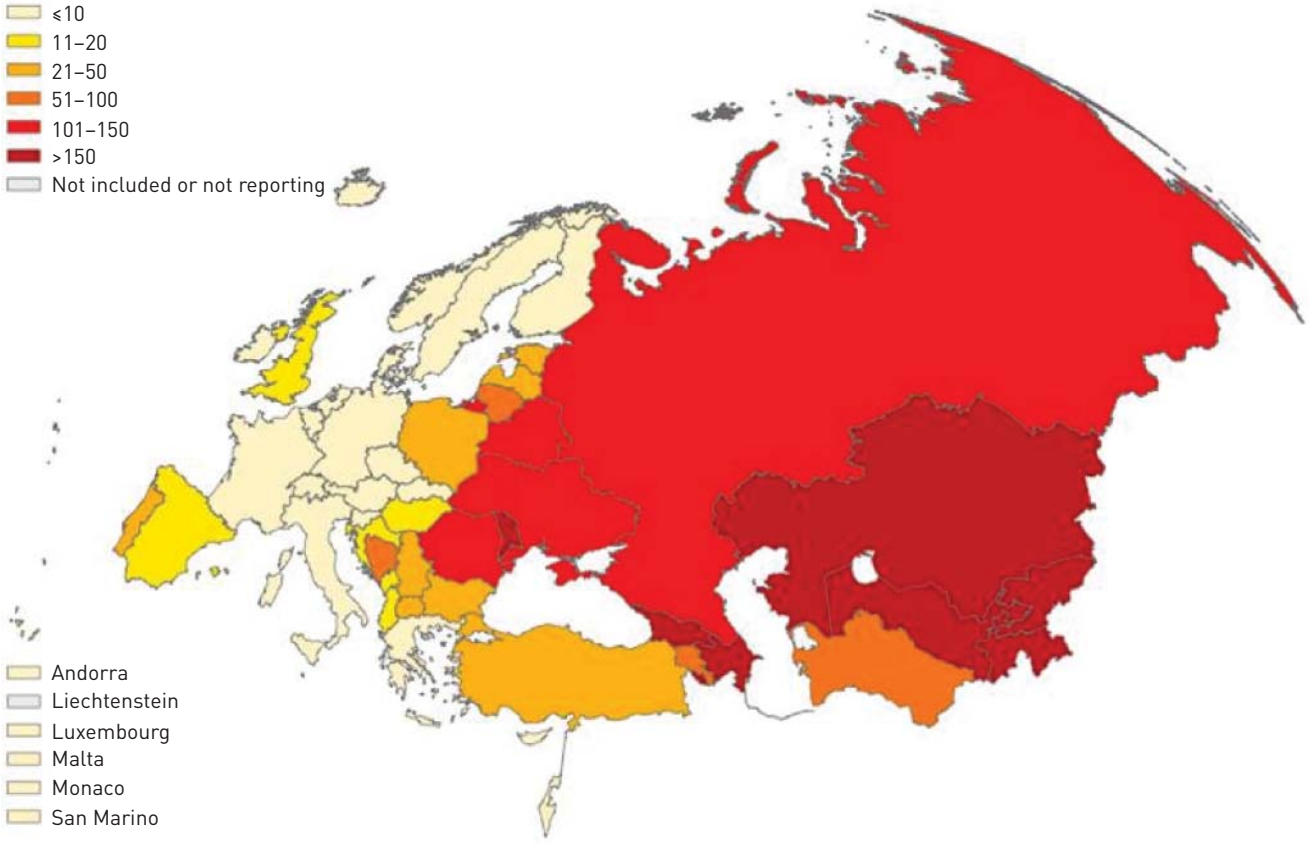


FIGURE 2 World Health Organization European Region estimated tuberculosis incidence rates per 100 000 population, 2011. Data from the United Nations Administrated Province of Kosovo (in accordance with Security Council Resolution 1244 (1999)) is not included in the figures reported for Serbia. Reproduced from [2] with permission from the publisher.

FIGURE 3 Wooden mask worn by health workers to announce a forthcoming vaccination campaign (Republic of Bénin). Image courtesy of J.P. Zellweger.

The purpose of this editorial is to summarise current policy on administration and management of adverse events of the BCG vaccine from the WHO European regional perspective. The editorial will briefly summarise what the BCG vaccine is, the history of its development and production, its safety, as well as incidence and management of adverse events. Finally, it will provide guidance on BCG policy development.

## The BCG vaccine and its history

The BCG vaccine provides protection against severe forms of tuberculosis, particularly tuberculous meningitis and disseminated tuberculosis in infants and young children [17–19]. It does not prevent primary infection and, more importantly, it does not prevent reactivation of latent pulmonary infection, the principal source of spread of *Mycobacterium tuberculosis* in the community. The impact of BCG vaccination on transmission is therefore limited.

BCG contains a live, attenuated strain of *Mycobacterium bovis*, which primarily causes tuberculosis in cattle. *M. bovis* was originally isolated in 1908 from a cow with bovine tuberculosis by Calmette and Guérin at the Pasteur Institute in Lille, France. In order to attenuate the strain, it was carefully subcultured every 3 weeks for ~13 years. During this time, many genetic changes (or point mutations) occurred making the strain less virulent in animals such as cows and guinea pigs. The resulting altered strain was named BCG. After extensive safety testing in animals, BCG was first used as a vaccine in human infants in 1921 [18]. The vaccine was used extensively and for many years, as there were no other treatment options against tuberculosis until the development of isoniazid in the 1940s, and confidence in the preventive effect of BCG vaccination was high both in the medical and the patients' communities (figs 3–7).

Today, there are several different substrains of the original BCG strain. The reason for this is that during the early years of the vaccine, all BCG cultures were maintained at the Pasteur Institute in Paris, France (fig. 5). However, from 1924 to 1931, the BCG strain was distributed to several laboratories throughout the world where they were maintained by continuous subculture [18, 28]. After many years, it became clear that the


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FIGURE 4 "To defeat tuberculosis is easy with the BCG". Advertisement in a peripheral tuberculosis dispensary, dating from the time of French colonisation (*circa* 1950) (Republic of Benin). Image courtesy of J.P. Zellweger.

various strains maintained in different laboratories were no longer identical to each other. Indeed, it is likely that all the various strains maintained by continuous subculture continued to undergo genetic changes. Even the original BCG strain maintained in Paris continued to change during the subculturing needed to maintain the viability of the strain. To limit these genetic mutations, procedures used to maintain the strains were modified. Today, the strains are maintained using a seed lot production technique to limit further genetic variation using lyophilised cells so that each batch starts with the same substrain [18, 29].

## BCG production and substrains

The BCG vaccines that are currently in use are produced at >40 sites throughout the world [29], many for local use within the country of production. These vaccines are not identical. Some differences in molecular and genetic characteristics are known; however, the extent to which they differ in efficacy and safety in humans is not clear [18, 29]. Globally, the most widely used BCG vaccine substrains include Connaught, Danish, Glaxo, Moreau, Moscow, Pasteur and Tokyo [28]. In high-incidence eastern European countries and former Soviet states, the predominant substrain is BCG Moscow. Although BCG Danish and Pasteur have been found to be more immunogenic [27], greater efficacy of these strains has not been demonstrated in field trials [30]. Therefore, there are currently no recommendations advising the use of one strain over another [29].

Although there are no formally recommended vaccines, ~25% of the world supply of BCG is purchased by the United Nations (UN) Children's Fund and other UN agencies for distribution to developing countries [29]. These substrains are purchased according to a WHO pre-qualification process, which determines their eligibility for use in national immunisation programmes (table 3) [31]. Vaccines are added to the pre-qualification list after extensive quality control evaluations and manufacturing site audits performed by the WHO. The list is not exhaustive, and the fact that certain BCG substrains are not included in the list does


FIGURE 5 French Ministry of Health educational poster supporting bacille Calmette–Guérin vaccination. Image courtesy of J.P. Zellweger.

not mean that, if evaluated, they would not be found to comply with pre-qualification standards and operational specifications.

## Safety

The BCG vaccine is the oldest vaccine still in use. It has been administered to >4 billion people worldwide since 1921 [18, 28, 29] and the risk of adverse events has generally been considered to be low. Recently, however, it has been found that use of the vaccine in persons who are immunocompromised (such as those with HIV) may result in an infection caused by the BCG itself [18, 32, 33]. As BCG is a live vaccine, there is an increased risk of mycobacterial circulation in the absence of a competent immune response. This can lead to disseminated BCG disease [34]. There is also concern that BCG vaccination may accelerate HIV disease progression amongst HIV-infected infants by triggering an immune response that leads to the spread of the virus [35]. In addition, even among immunocompetent persons, local reactions, including ulceration at the site of vaccination, may result in shedding of live organisms, which could, in turn, infect others who may be immunocompromised.

FIGURE 6 Tuberculosis/HIV-infected children in Myanmar. ©2012 Matthieu Zellweger (with AIDSpartners.org)/ matthieuzellweger.com.


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FIGURE 7 Romania, 1974. 6-year-old children are re-vaccinated against tuberculosis (according to the guidelines available at the time; at present, no evidence of any protection of re-vaccinating with bacille Calmette–Guérin is available, so re-vaccination is not recommended by the World Health Organizaiton (WHO)). WHO image, courtesy of the United States National Library of Medicine, History of Medicine Division.

## WHO position on BCG vaccination

The core WHO policy recommendations are summarised in table 4. Currently, the WHO position is that a single dose of BCG vaccine should be given to all infants as soon as possible after birth in countries with a high burden of tuberculosis ($\geqslant$40 cases per 100 000 population). Contraindications are infants or persons known to have HIV or other immunosuppressive conditions (fig. 6) [35, 36]; in settings with adequate HIV services, BCG vaccination should be delayed for infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative. Although BCG might be potentially useful in other groups (*e.g.* health care workers, travellers to endemic areas and contacts of multidrug-resistant cases) the available evidence is not sufficient to recommend its use. The WHO does not recommend BCG revaccination as there is little or conflicting evidence of whether this confers additional protection, and revaccination may increase the risk for adverse events.

## Adverse events

Amongst immunocompetent infants and children, mild events such as localised skin reactions following BCG vaccination are common; almost all recipients of BCG develop a bluish-red pustule accompanied by pain, swelling and erythema within 2–4 weeks after vaccination [37, 38], with ulceration and drainage in ~70% of vaccinated individuals [29, 30]. Abscess and regional lymphadenitis occur in 1–2% of vaccinated individuals [29, 39]. Severe adverse events occur very rarely. The absolute risks of severe adverse events are summarised in table 2. Importantly, although there are currently no recommendations for the use of certain strains, the Pasteur and Danish strains are known to induce more adverse reactions [30, 38, 40].

Among HIV-infected or other immunocompromised infants and children, the absolute risk of severe adverse events from BCG vaccination has been found to be hundreds of times higher compared to immunocompetent children. Rates of disseminated BCG disease are estimated to approach 1% of HIV-infected infants vaccinated with BCG [41] and has an all-cause mortality rate of 75–86% [32–34, 42]. Additionally, BCG immune reconstitution inflammatory syndrome occurs in up to 15% of HIV-infected children who receive the BCG vaccine [32–34, 43].

## Management of adverse events

Management of local lymphadenitis remains controversial, with no consensus on the best strategy [29]. Treatment strategies range from observation (wait-and-see approach), to surgical drainage or resection, to treatment with antituberculosis drugs, to a combination of these approaches [29, 44]. In general, nonsuppurative BCG-induced lymphadenitis is a benign condition and regresses spontaneously without any treatment in 4–6 months [33]. For suppurative BCG lymphadenitis, needle aspiration is recommended in some countries, and may prevent discharge and associated complications such as fistulation. A common practice in many countries is direct injection or local instillation of antituberculosis drugs to the lesion; however, there is a poor quality of evidence to demonstrate a benefit from this practice [33], which might also promote drug resistance. Surgical incision is additionally not recommended for suppurative BCG lymphadenitis. Where needle aspiration has failed to relieve symptoms and suppurative nodes have already drained surgically or spontaneously with sinus formation, surgical excision is occasionally practiced, but carries additional risks associated with general anaesthesia needed for the procedure. Literature on the

TABLE 1 Bacille Calmette–Guérin (BCG) vaccination in the World Health Organization European Region

| Country | General BCG at birth[#] | Revaccination | Selective vaccination |
|---|---|---|---|
| **High priority** | | | |
| Armenia | Birth | | |
| Azerbaijan | 4–7 days | | |
| Belarus | 3–5 days | At 7 years (in children from a TB contact, in social risk groups, without a visible BCG scar, and handicapped children without specific contraindications for live vaccines) | |
| Bulgaria | Birth | 7 months; 7, 11, 17 years (after Mantoux test negative) | |
| Estonia | 1–5 days | | |
| Georgia | 0–5 days | | |
| Kazakhstan | Birth | 6 years (after Mantoux test negative) | |
| Kyrgyzstan | Birth | | |
| Latvia | 2–5 days | | |
| Lithuania | 3 days | | |
| Moldova | 2 days | 6–7 years (after Mantoux test negative) | |
| Romania | Birth | | |
| Russia | 3 days | 7 (after Mantoux test negative), 14 years | |
| Tajikistan | 3–5 days | | |
| Turkey | 2 months | | |
| Turkmenistan | 3 days | 14 years (after Mantoux test negative) | |
| Ukraine | 3–5 days | 7 years (after Mantoux test negative during periods of TB epidemics) | |
| Uzbekistan | 3–5 days | | |
| **Low priority** | | | |
| Albania | Birth | | |
| Andorra | No | | |
| Austria | No | | Children, travellers and HCWs at high and prolonged risk |
| Belgium | No | | Children and HCWs in prolonged exposure at high risk |
| Bosnia and Herzegovina | Birth | | |
| Croatia | Birth | | |
| Cyprus | No | | Children with continuous contact with a contagious form of TB |
| Czech Republic | No | | Children 6 months or older with TB in the family, contact with TB, origin or stay >3 months of the child or parents in a country with TB incidence >40 per 100 000 or parental request |
| Denmark | No | | Young children travelling for long periods of time to endemic areas, or living in Denmark in families with TB, or HCWs caring for at-risk patients, and sometimes given to travellers to USA due to USA regulations |
| Finland | No[¶] | | TB in the family, parents originate from a country with high incidence, or moving to such a country |
| France | No | | Given at birth in infants at risk (born in a country with a high prevalence of TB or with at least one parent born in such a country, or planning to stay at ⩾1 month in such a country, or with a history of TB in his/her family, or living in the Ile-de-France, French Guyana or Mayotte region, or any child considered by a physician as living in an environment with a high risk of exposure to TB) and professionals and students involved in healthcare, revaccination at entry if TST negative |
| Germany | No | | |
| Greece | No[¶] | | |
| Greenland | Birth | | |
| Hungary | Birth | | |
| Iceland | No | | |
| Ireland | Birth | | |


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TABLE 1 Continued

| Country | General BCG at birth[#] | Revaccination | Selective vaccination |
|---|---|---|---|
| Israel | No | | Newborns (BCG given at birth) and children with high risk, *e.g.* babies from families that immigrated from endemic countries |
| Italy | No | | HCWs at high risk |
| Kosovo[+] | | | |
| Luxembourg | No | | |
| Malta | No[¶] | | |
| Monaco | Birth | | |
| Montenegro | Birth | | |
| The Netherlands | No | | Children with one or two parents originating from high-incidence countries (BCG given at 5 months); long-term travellers and expatriates to high-incidence countries |
| Norway | No | | Newborns with parents from high-prevalence countries and health/birth professional students |
| Poland | Birth | | |
| Portugal | Birth | | |
| San Marino[+] | | | |
| Serbia | Birth | | |
| Slovakia | No | | |
| Slovenia | Birth | | HCWs, medical students, military (BCG given at start of work/study) |
| Spain | No | | Newborns in Basque country (BCG given at birth), and children in close and long-term contact with smear-positive adults; foreign-born children (<5 years) returning to their country (high burden) for >3 months; children (<5 years) whose parents are working in high-burden countries and have to stay with them for >3 months |
| Sweden | No | | Children born to parents from countries with a TB incidence >25 per 100 000 at the age of 6 months |
| Switzerland | No | | Children at high risk of exposure (BCG given at birth) |
| Macedonia | Birth | 7 years | |
| UK | No | | High risk areas (BCG given at birth) |

Countries listed in alphabetical order and according to tuberculosis (TB) priority [23–25]. High-priority countries are those defined in [5]. HCW: healthcare worker; TST: tuberculin skin test. [#]: entire country. [¶]: general BCG vaccination performed after birth, at the age of: Finland, >7 years; Greece, 6 years; Malta, 12 years. [+]: no information.

TABLE 2 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) | Almost all vaccinees |
| | Scar (2–5 months) | |
| **Severe** | Local | |
| | Local abscess | |
| | Keloid | |
| | Lymphadenitis | |
| | Suppuration (onset 2–6 months) | 1 per 1000–10 000 |
| | Systemic (onset 1–12 months) | |
| | Cutaneous skin lesions | Case reports only |
| | Osteitis | 1 per 3333–10[8] |
| | Disseminated BCG | 1 per 230 000–640 000 |
| | Immune reconstitution syndrome | 1 per 640 000 |

BCG: bacille Calmette–Guérin. Modified from [12].

TABLE 3 Guidelines for bacille Calmette–Guérin (BCG) vaccine

| | |
|---|---|
| **WHO** | Revised BCG vaccination guidelines for infants at risk for HIV infection www.who.int/immunization/wer8221bcg_May07_position_paper.pdf<br>Information Sheet, Observed rate of vaccine reactions of Bacillus Calmette-Guérin (BCG) vaccine, April 2012 www.who.int/vaccine_safety/initiative/tools/BCG_Vaccine_rates_information_sheet.pdf<br>Prequalification of vaccines – further information www.who.int/immunization_standards/vaccine_quality/vq_index/en/index.html |
| **CDC** | Fact sheets, BCG Vaccine www.cdc.gov/tb/publications/factsheets/prevention/BCG.htm |
| **IUATLD** | Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants www.theunion.org/images/stories/resources/RESS_BCG_Working_Group_Statement_IJTLD_December_2008.pdf |
| **Stop-TB** | Management of TB in the HIV-infected child www.stoptb.org/wg/dots_expansion/assets/documents/IJTLD_OS_ChildhoodTB_Chapter3.pdf |
| **The BCG World Atlas** | A database of global BCG vaccination policies and practices<br>If your country profile needs to be updated, please contact A. Zwerling (alice.zwerling@mail.mcgill.ca) or M. Pai (madhukar.pai@mcgill.ca)<br>www.bcgatlas.org/index.php |

WHO: World Health Organization; CDC: US Centers for Disease Control and Prevention; IUATLD: International Union Against Tuberculosis and Lung Disease.

TABLE 4 Summary of the World Health Organization policy recommendations on bacille Calmette–Guérin (BCG) vaccination

| | |
|---|---|
| **1** | A single dose of BCG vaccine should be given to all infants as soon as possible after birth in countries with a high burden of tuberculosis |
| **2** | Contraindications are infants or persons known to have HIV or other immunosuppressive conditions<br>In settings with adequate HIV services, BCG vaccination should be delayed for infants born to mothers known to be infected with HIV until these infants are confirmed to be HIV negative |
| **3** | BCG revaccination is not recommended, as there is little or conflicting evidence of whether this confers additional protection, and revaccination may increase the risk for adverse events. |

TABLE 5 Contact information for the World Health Organization Regional Office for Europe: communicable diseases, health security and environment

| **TB and MDR/XDR-TB control programme** | **Vaccine-preventable diseases and immunisation** |
|---|---|
| E-mail: tuberculosis@euro.who.int<br>www.euro.who.int/en/what-we-do/health-topics/communicable-diseases/tuberculosis | E-mail: vaccine@euro.who.int<br>www.euro.who.int/en/what-we-do/health-topics/disease-prevention/vaccines-and-immunization |

benefit of oral/systemic antituberculosis drug treatment without surgical drainage is conflicting, and a recent Cochrane review found no evidence of any benefit of using oral antibiotics to treat local or regional BCG-induced disease [33].

In general, oral antituberculosis medications should be reserved for infants developing rare systemic adverse reactions, such as disseminated BCG disease. In these cases, the criteria for *M. tuberculosis* should be used and the strain should be considered to be of intermediate susceptibility. Management should therefore include the appropriate combination of antituberculosis drugs; however, pyrazinamide should not be included in the drug regimen as all BCG strains have inherent resistance to this drug [29]. In addition, there is variable BCG resistance to isoniazid, which is one of the main antimycobacterial drugs available in tuberculosis-endemic settings, as well as possible acquired resistance to other first-line antituberculosis drugs [45–47]. Single-drug therapy, particularly with isoniazid, is therefore not recommended. It should also be noted that the clinical features of disseminated BCG disease are similar to those of severe


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tuberculosis, and sophisticated laboratory facilities may be needed to distinguish between *M. tuberculosis* and *M. bovis* BCG [42], as well as to test drug susceptibility.

### When to stop BCG blanket vaccination

The risk of stopping BCG vaccination in a low-incidence country should be carefully balanced against the risk of an increase in tuberculosis among children. There is no evidence of a threshold incidence; however, International Union Against Tuberculosis and Lung Disease expert opinion suggests less than five in 100 000 new sputum smear positive pulmonary cases as a threshold for stopping herd BCG vaccination [48]. It is noteworthy that even in low-incidence countries, there may be a subset of the population with a higher risk of tuberculosis; therefore, BCG vaccination should be made available to this group [49]. In low-incidence settings, it is advisable to make BCG available for children who are born of parents coming from high-incidence countries or who may have lived for prolonged periods in a high-burden country.

## Conclusions

In summary, BCG is currently the only available vaccine against tuberculosis. Despite its limitations, it offers reasonable protection against severe forms of tuberculous disease among children. The current policy document offers a rapid guidance on how to procure BCG, plan its use based on the epidemiological situation in the country and manage adverse events (tables 2–5).

This document also represents a further step in the collaboration between the European Respiratory Society (ERS) (and the *European Respiratory Journal* (*ERJ*)) and WHO on tuberculosis-related activities. Started in 1999 with the development of the ERS tuberculosis guidelines [50] and the publication of the entire series of Wolfheze documents (which helped to modernise the present system of tuberculosis control in Europe) [16], it continued with the publication of two core documents on tuberculosis elimination in Europe [15, 51], guidance on tuberculosis trans-border migration control [52], the ERS/WHO Consilium [4], and a series of important articles on multidrug-resistant tuberculosis [53–55]. In addition, two other important European Centre for Disease Prevention and Control documents reflecting collaboration with WHO have been published in the *ERJ*, including the European standards for tuberculosis care [56, 57] and the Tuberculosis in Children roadmap documents [58].

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