

NON-TUBERCULOUS MYCOBACTERIA: GENERAL

Mapping the global use of different BCG vaccine strains

Nicole Ritz^{a,b,c}, Nigel Curtis^{a,b,c,*}^a Department of Paediatrics, The University of Melbourne, Royal Children's Hospital Melbourne, Flemington Road, Parkville, VIC 3052, Australia^b Infectious Diseases Unit, Department of General Medicine, Royal Children's Hospital Melbourne, Flemington Road, Parkville, VIC 3052, Australia^c Murdoch Children's Research Institute, Royal Children's Hospital Melbourne, Flemington Road, Parkville, VIC 3052, Australia

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SUMMARY

Bacille Calmette–Guérin (BCG) vaccine is one of the oldest and most commonly administered vaccines worldwide. Different BCG vaccine strains exist as a result of genetic changes that occurred during repeated subculture in different countries before lyophilisation was introduced for storage of seed lots in the 1960s. Increasing evidence suggests that these genetically divergent BCG vaccine strains are associated with different protective efficacy against tuberculosis (TB), different rates of adverse events and variable susceptibility to anti-tuberculous drugs. Information on which BCG vaccine strains are used in each country worldwide has not previously been collated. This report summarises data from the EuroTB network and from WHO/UNICEF in the first map depicting the BCG vaccine strains used globally. In 83 (44%) of 188 countries, more than one BCG vaccine strain was used during the five year period. In the countries that used only one strain, BCG Denmark was used in 32, BCG Russia/Bulgaria in 30, BCG Japan in eight, BCG Connaught in two. Twelve countries used their locally-produced BCG vaccine strains. The considerable variation in BCG vaccine strains used worldwide highlights the importance of documenting the particular vaccine strain used on an individual, local and national level. This is important for the interpretation of changes in the epidemiology of adverse events after BCG immunisation, for the management of adverse events after BCG immunisation, to interpret differences in the protective efficacy of BCG, and to inform the design of trials investigating novel TB vaccines.

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1. Introduction

Bacille Calmette–Guérin (BCG) vaccine is one of the oldest and most commonly administered vaccines worldwide. After attenuation of *Mycobacterium bovis* over a 13-year period the vaccine was first used in humans in 1921 in France.¹ Thereafter the vaccine was distributed to different laboratories worldwide where further repeated subculture of BCG led to the emergence of phenotypically different vaccine strains.² Subsequently, the different BCG vaccine strains that had evolved were stored in each country as seed lots for future vaccine production (Table 1).² Phenotypic characteristics of these different vaccine strains were reviewed in the early 1980s³ and underlying genetic differences were investigated soon thereafter.^{4–6} The advent of DNA microarrays and the sequencing of the genome of *Mycobacterium tuberculosis* enabled the first comparative analysis of genomic diversity amongst BCG vaccine strains in

1999.⁷ Since then, several studies have further detailed the genetic variation amongst BCG vaccine strains used worldwide.^{8–13}

The importance of the genetic differences between BCG vaccine strains has been highlighted by several animal and human studies.¹¹ These strongly support the notion that genetically different BCG vaccine strains induce a quantitatively and qualitatively different immune response that leads to differences in protective efficacy against tuberculosis (TB).^{14,15} The differences between BCG vaccine strains have other important implications. Different strains have been associated with different rates of adverse events.^{16,17} In addition, susceptibility to anti-tuberculous drugs varies between different BCG vaccine strains.¹⁸ Some BCG vaccine strains are also administered via different routes (for example percutaneously as well as intradermally), also potentially influencing protection and rate of adverse events.^{19,20}

Currently there is insufficient evidence to determine which BCG vaccine strain provides better protection or which is associated with less adverse events. The particular BCG vaccine strain chosen for use in different countries worldwide is therefore based on a number of other factors, including historical precedent, logistic or cost considerations and local production. In most developed countries this results in the use of one particular BCG vaccine strain.

* Corresponding author at. Department of Paediatrics, The University of Melbourne, Royal Children's Hospital Melbourne, Flemington Road, Parkville, VIC 3052, Australia. Tel.: +61 3 9345 5161; fax: +61 3 9345 6667.

E-mail address: nigel.curtis@rch.org.au (N. Curtis).

Table 1
Commonly used and internationally distributed BCG vaccine strains.

BCG vaccine strain (name used in this manuscript)	Synonyms	Selected manufacturers
BCG Brazil	Moreau, Rio	• Instituto Butantan, São Paulo, Brazil
BCG Bulgaria	Sophia	• Bulbio-NCIPD, Sofia, Bulgaria
BCG Connaught	Toronto	• Sanofi Pasteur, Toronto, Canada
BCG Denmark	Danish, Copenhagen	• Statens Serum Institute, Copenhagen, Denmark
BCG Japan	Tokyo	• BCG Laboratory, Tokyo, Japan
BCG Pasteur	French, Paris	• Several local producers see Table 2
BCG Russia	Russian, Moscow	• Allergen, Stavropol, Russia • Gamaleya Institute, Moscow, Russia • Microgen, Russia • MPBP, Russia • Serum Institute India

In contrast, in the majority of countries with a high TB incidence, the vaccine is supplied through UNICEF/WHO and the Global Alliance for Vaccines and Immunisation (GAVI) who use a number of different BCG vaccine suppliers.

Although there is much information on BCG immunisation policies and coverage rates worldwide,^{21–23} data on which BCG vaccine strains are used in different countries is very limited. We have previously reported the particular BCG vaccine strains used in European countries.¹⁴ An online resource called the “BCG World Atlas” was launched in October 2008 and aims to collect information about BCG immunisation policies.²¹ This currently has limited information on BCG vaccine strains from information collected using an online questionnaire.

Documenting the use of different strains is important to interpret changes in the epidemiology of adverse events after BCG immunisation and for selecting anti-tuberculous drugs for the treatment of BCG-related local or disseminated complications.¹⁸ Accurate information about the particular BCG vaccine strains used in different countries is also important to inform the design of trials investigating novel TB vaccines and to interpret differences in the protective efficacy of BCG. It may also inform potential changes in

the future use of particular BCG vaccine strains based on the results of studies comparing the immune response to different BCG vaccine strains.²⁴

2. Methods

Information about BCG vaccine strains used in different countries worldwide was collected from three sources: (i) the most recent data available from the WHO/UNICEF Joint Reporting Form on Immunisation (2007 for WHO Western Pacific Region; 2003–2006 for all other countries); (ii) personal communications with representatives of all member states of the EuroTB network (a WHO collaborating centre) in 2007; and (iii) Sanofi Pasteur (for Australia and Canada only). A colour coded world map was created from this data. For all countries that produce BCG locally, the manufacturer was contacted for further information about the original BCG vaccine strain from which the current vaccine is derived.

3. Results

Data specifying the BCG vaccine strain used was available for 188 countries (Figure 1). This data was available for a mean of three (range 1–5) years per country from the WHO/UNICEF database. For 16 countries, data for only one year was available from this database, and these were therefore categorised as ‘insufficient data’ and left blank in the map (Figure 1). More than one BCG vaccine strain was used in 83 (44%) countries during the five years (Figure 1). In countries that used only one strain, BCG Denmark was used in 32, BCG Russia/Bulgaria in 30, BCG Japan in eight and BCG Connaught in two countries (for BCG Connaught, personal communication from Dr Glen Mason, Medical and Regulatory Affairs Director Sanofi Pasteur ANZ, Australia). Twelve countries use their locally-produced BCG vaccine strain during this period (Table 2). More than one BCG vaccine strain was used in 45/75 (60%) high incidence TB countries, in 22/42 (52%) intermediate incidence TB countries and 14/68 (20%) low incidence TB countries (Table 3).

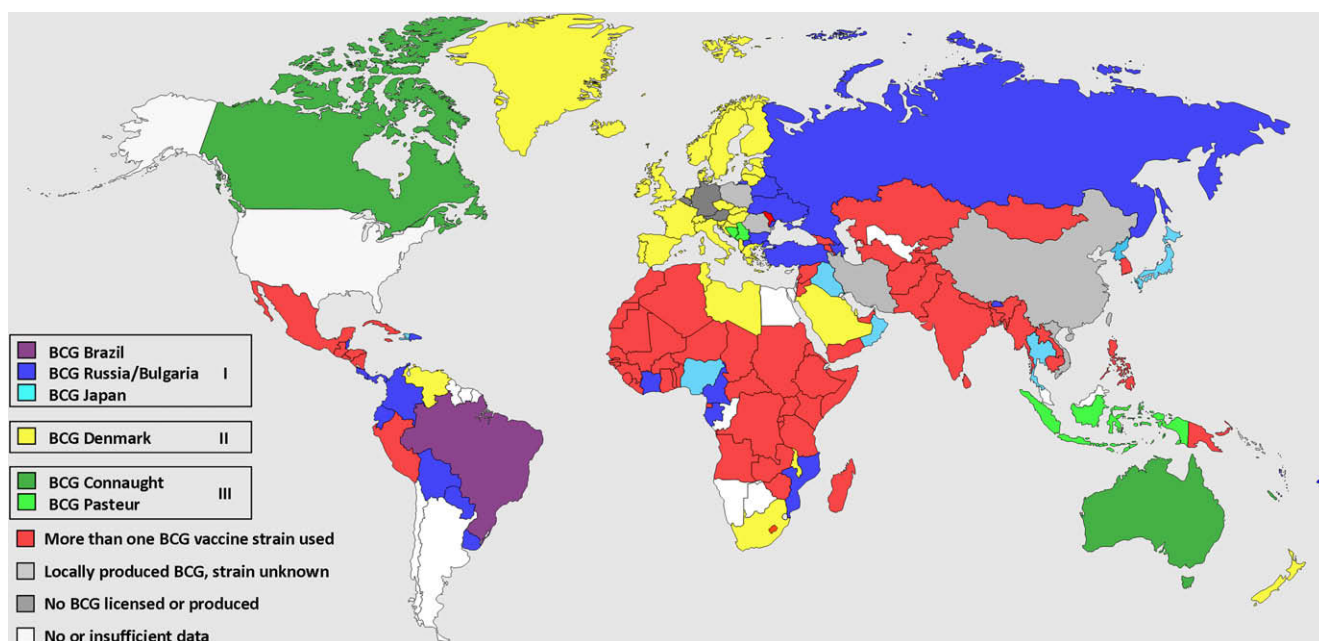


Figure 1. BCG vaccine strains used between 2003 and 2007 worldwide. Boxes surround BCG vaccines strains that are most genetically similar. Box I includes BCG vaccine strains that were obtained from the Pasteur Institute before 1926. Boxes II are III are strains obtained at later dates.

Table 2
Details of locally-produced BCG vaccine strains.

Country	Manufacturer	Original BCG strain from which local strain derived
China	Chengdu biomanufacture Shanghai biomanufacture	D2PD302*
Guyana	No information available	No information available
India	BCG vaccine laboratory Guindy	BCG Madras
Indonesia	PT. Bio Farma	Pasteur 1173
Iran	Razi Institute	No information available
Poland	Lubelska Wytownia Surowici Szczepionek, Lublin	BCG Brazil
Republic of Korea	Korean Institute of Tuberculosis	BCG Pasteur 1173P2†
Romania	Romanian National Institute for Research and Development in Microbiology and Immunology "Ion Cantacuzino"	Pasteur (192) obtained in 1925
Serbia	Torlak Institute	Pasteur 1173P2
Thailand	Queen Saovabha Memorial Institute, Thai Red Cross	BCG Japan
Uzbekistan	Uzbiopharma	No information available
Vietnam	IVAC Institute Pasteur HCM City	No information available

* Personal communication from Dr Liang Xiaofeng, Director National Immunisation Program China (no further information about the BCG vaccine strain available).

† Personal communication from Hyejon Lee, Chief of The International Cooperation Department, Korean Institute of Tuberculosis.

Table 3
BCG vaccine strains used in different countries in relation to TB incidence.

TB incidence*	Mixed	BCG-Denmark	BCG-Russia/Bulgaria	BCG-Japan	BCG-Connaught	Local BCG	No BCG licensed	Data not available	Total
High (> 100/100,000)	45	3	14	3	0	6	0	4	75
Intermediate (40–100/100,000)	22†	6	9	2	0	2†	0	2	42
Low (> 40/100,000)	14	23	7	3	2	3	3	13	68
Incidence data unavailable	2					1			3
Total	83	32	30	8	2	12	3	19	188

* TB incidence data from WHO²⁶, no data on incidence available for Marshall Islands (Mixed), Republic of Moldova (Mixed) and Serbia (Local BCG).

† One country (Republic of Korea) used both locally produced and other BCG vaccine strains (personal communication from Hyejon Lee).

4. Discussion

Differences between BCG vaccine strains have previously attracted only limited attention and the various strains manufactured worldwide are generally considered interchangeable. However, the increasing recognition of the influence of vaccine strain on the immune response and protective efficacy induced by BCG immunisation as well as on adverse events and antibiotic susceptibility means it is important to document the strains currently used in each country.

To our knowledge this is the first time that comprehensive information detailing the global use of different BCG vaccine strains has been collated. It shows that there is considerable variation in the BCG vaccine strain used worldwide and almost half of all countries used more than one BCG vaccine strain in the five years reported. This is mainly a consequence of the current system used by UNICEF/WHO/GAVI to supply developing countries with BCG vaccine. There are currently four BCG vaccine suppliers for UNICEF/WHO/GAVI producing three different BCG vaccine strains: BCG-Denmark produced by the Statens Serum Institute in Denmark, BCG-Russia (which is genetically identical to BCG-Bulgaria) by Bulbio (BB-NCIPD) in Bulgaria and by the Serum Institute in India,²⁵ and BCG-Japan by the Japan BCG Laboratory (personal communication from Katinka Rosenbom, UNICEF Supply Division, Copenhagen, Denmark).

In addition to the considerable variation in BCG vaccine strains used worldwide, this study is the first to detail the use of locally-produced BCG vaccine strains. The majority of these strains have not been genetically-characterised, and for many there is no information available about the strain from which they originate. Molecular characterisation of these strains will be necessary to determine their providence and the genetic changes that have occurred.

The information included in this study is based on vaccines delivered through the WHO expanded program on immunisation (EPI) and therefore may not include vaccines used as part of research studies or outside the EPI.

In the light of the implications discussed above, the considerable variation in BCG vaccine strains used worldwide highlights the importance of documenting the particular vaccine strain used on an individual, local and national level.

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