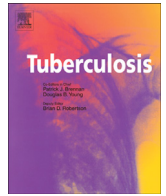




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EPIDEMIOLOGY

The impact of Bacille Calmette-Guérin shortage on immunisation practice and policies in Europe – A Paediatric Tuberculosis Network European Trials Group (ptbnet) survey[☆]



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SUMMARY

Background: Recent reports indicate an ongoing BCG shortage that may influence immunisation practice. This study aimed to determine current availability of BCG vaccine across Europe, and implications on immunisation practices and policies in Europe.

Methods: Web-based survey among Paediatric Tuberculosis Network European Trials Group (ptbnet) members, between May and October 2015.

Results: Twenty individuals from 13 European countries participated. Ongoing shortages were reported in eight countries routinely using BCG (8/11, 73%). As a consequence of the shortage, BCG was not given as completely unavailable in some countries (2/8, 25%), was given only whenever available (1/8, 13%), or only in certain regions of the country (1/8, 13%). Strategies reported to reduce loss of immunisation were administration to selected high-risk individuals (2/8, 25%), or cohorting vaccinees on specific days to maximise the use of multi-dose vials (3/8, 38%). Authorities in two countries each were considering a change of manufacturer/supplier (2/8, 25%).

Conclusions: The BCG shortage in Europe leads to significant changes in immunisation policies including changes of BCG vaccine strain and manufacturer. In addition, infants and children eligible for immunisation are at risk of not receiving BCG. To ensure necessary BCG immunisations, collaboration between national health agencies and vaccine manufacturers is crucial.

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Abbreviations: AE, adverse event; BCG, Bacille Calmette-Guérin; ECDC, European Centre for Disease Prevention and Control (the); TB, tuberculosis; MDR, multidrug-resistance; ptbnet, Paediatric Tuberculosis Network European Trials group (the); SSI, Statens Serum Institut (the); UNICEF, United Nations Children's Emergency Fund (the); WHO, World Health Organization (the); XDR, extensive drug resistance.

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1. Introduction

Globally, tuberculosis (TB) is one of the most important infectious diseases and children are especially vulnerable [1,2]. Compared to adults, children infected with *Mycobacterium tuberculosis* are more likely to develop active TB disease within a short period of time. In 2014, an estimated 1 million new TB cases and 140,000 TB deaths occurred globally among children below 15 years of age [1]. Although the overall TB incidence in Europe is decreasing, TB remains a major public health concern [3]. The World Health Organization (WHO) estimates that there were 31,000 new TB cases among children in the European Region in 2014, of which only 32% were reported [1]. In many countries, the majority of TB cases are foreign-origin, and with the current migration in Europe this will affect epidemiology in low incidence TB countries [3,4]. Furthermore, with the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, treatment is becoming increasingly challenging, placing further emphasis on the importance of prevention [3].

Infant Bacille Calmette-Guérin (BCG) immunisation prevents severe and disseminated TB in children, and may also protect against latent TB infection [5,6]. The protective efficacy of BCG against drug-susceptible and MDR TB is likely similar and, therefore, BCG immunisation has been suggested as a preventative measure for individuals exposed to MDR-TB [7]. BCG is one of the most commonly used vaccines globally, with approximately 90% of children covered worldwide and over 120 million individuals vaccinated annually [8,9]. Vaccine coverage is however not uniform worldwide since many low TB incidence countries do not offer BCG at all or only for selected high-risk groups, while some high TB incidence countries including Papua New Guinea, Somalia and the Ukraine have coverage rates below 70% [10]. In high TB incidence countries, BCG immunisation is a cost-effective intervention and an essential part of TB control and prevention particularly in young children [5]. In addition, BCG immunisation is known to have a number of non-specific or heterologous effects, including reducing all-cause mortality in resource limited countries and influencing the immune response to other routine immunisations [11,12].

Currently, three BCG vaccine strains are in large-scale production (BCG Denmark, BCG Russia and BCG Japan) which are produced by five WHO prequalified vaccine manufacturers in Bulgaria, Denmark, India and Japan [13,14]. In Europe, BCG Denmark has been the most commonly used BCG vaccine strain in the last decade [15,16].

BCG supply and demand has been influenced by a decrease in manufacturers worldwide together with an increased global demand, likely as a result of rising birth rates and improved immunisation coverage. In 2014, the demand increased by more than 20 million doses, as a result of unmet demand carry-over from the previous year and incremental demand from some large countries in the Middle East and South East Asia, and it is estimated to increase further by an annual 10 million doses [8]. In addition to this, since 2013, a reduced production capacity of two manufacturers, the Statens Serum Institut (SSI) in Denmark and the Serum Institute of India, further affects annual global BCG availability [17]. Although some manufacturers were able to increase their production, the overall BCG availability fell by 6 million doses [8]. In fact, the United Nations Children's Emergency Fund (UNICEF) estimated that in 2014 the global BCG production fell short by over 20 million doses, and that in 2015 the unmet demand carry-over together with growing demand and continuing production shortage may result in a deficit of over 70 million doses [8].

This shortage is likely to affect BCG immunisation practices and coverage in Europe, as universal or selective immunisation is a part of TB prevention in at least 27 European countries [15]. We

therefore conducted a survey to determine current availability of BCG vaccine across Europe, and describe the implications on immunisation practices and policies.

2. Methods

We conducted a web-based survey among Paediatric Tuberculosis Network European Trials Group (ptbnet) members between May 2015 and October 2015. Ptbnet comprises clinicians, microbiologists, epidemiologists and researchers with a special interest in paediatric TB [18,19]. At the time of the survey, ptbnet had a total of 117 members in 25 European countries. Members were invited by e-mail to participate in the survey, which included 16 questions on the participant's demographics, use of BCG vaccine, BCG availability, and consequences of possible shortage. Answers were collected through Google Docs software (Google Inc., Mountain View, CA, US) and/or Word questionnaire (Microsoft Corporation, Redmond, WA, US). Participants were allowed to reply to all or only some of the questions. The full questionnaire and the response rates to each question are shown in the [supplementary data](#). Two reminders were sent: to all members in September 2015, and only to the designated ptbnet representative of member countries in October 2015. In instances where responses were unclear or conflicting, these were clarified through email until January 2016. The final data were collated into and analysed using Excel (Version 2011, Microsoft Corporation, Redmond, WA, US).

3. Results

Twenty individuals (20/117, 17%) from 13 European countries (13/25, 52%) participated ([Table 1](#)). Respondents were based in Austria, Belgium, Bulgaria, Croatia, Finland, Germany, Greece, Italy, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Respondents from eleven countries reported using BCG as part of their national immunisation programme (11/13, 85%). The most commonly reported vaccine strain used was BCG Denmark SSI 1331 (10/11, 91%). In addition, BCG Russia Bulbio Sofia was used, in Bulgaria (1/11, 9%), where it is manufactured. BCG was reported to be imported in most countries (10/11, 91%), with the exception of Bulgaria, where it was reported to be produced nationally (1/11, 9%). Respondents reported that BCG was distributed by government agencies or departments of health in most countries (5/7, 71%); in two countries, private companies were reported to be national distributors - Econophar (Kortenberg, Belgium) and Pro Farma AG (Baar, Switzerland). Data regarding the total number of doses imported in 2014 were only available from two countries and therefore not further analysed.

Specific national BCG immunization policies that were reported included selective newborn immunization (5/11, 45%), selective immunisation at a later age (3/11, 27%), or both (1/11, 9%), and universal newborn immunisation (2/11, 18%). BCG immunisations were reported to take place in maternity hospitals (3/11, 27%), community health centre in primary care (3/11, 27%), primary school (1/11, 9%), or all of these/multiple places (4/11, 36%).

A current BCG shortage was reported by respondents from eight countries (8/11, 73%). In addition, a respondent from Croatia reported a recent shortage that lasted less than a month; the respondent stated that unmet carry-over immunisations took place when the shortage had resolved. All affected countries were using BCG Denmark. Responses concerning the onset of the shortage varied and were sometimes conflicting; most respondents reported that the shortage had started at some point from 2013 onwards.

Changes in BCG immunisation practices or policies were reported by respondents from seven countries (7/8, 86%) ([Table 2](#)). Members from Belgium and Italy reported a discontinuation of

immunisations as a result of BCG being entirely unavailable; in Greece, BCG was reported to be given whenever available. In Spain, BCG was reported to be available only in certain regions of the country and, due to the shortage, given only to selected high-risk individuals. Members from Finland, Sweden and the United Kingdom reported cohorting vaccinees on specific days to use as many doses from multi-dose vials as possible. One respondent from the United Kingdom also reported that due to the shortage BCG was only given to selected high-risk individuals. Switching manufacturer and BCG strain were reported to be under consideration in Belgium and Finland. A respondent from Sweden reported that national data about the BCG shortage was being collected. Out of the eight countries in which a BCG shortage was reported, five reported that national BCG stockpiling was not taking place (5/8, 63%), two reported that stockpiling was done (2/8, 25%), and one did not respond to this question. Public national information about the BCG shortage was reported to be available in five countries (5/8, 63%), and unavailable in three countries (3/8, 38%).

Shortage of BCG for bladder cancer treatment was reported by respondents from two countries (2/11, 18%) and nine respondents had no personal knowledge on this matter.

4. Discussion

Our results show that the ongoing global BCG vaccine shortage has significant consequences on immunisation practice in Europe. The survey identified BCG shortages in eight European countries, all of which were using BCG Denmark produced by SSI. A survey conducted in 2013 showed that 24 out of 31 countries in the European region were using BCG Denmark, and that at least 3 out of the 18 high priority countries in the fight against TB, as defined by the European Centre for Disease Prevention and Control (ECDC), were using BCG Denmark [3,15]. Therefore, it is likely that the limited supply of BCG Denmark affects also further countries not captured in our survey. Among the countries captured in our survey, only Bulgaria is classified as a high priority country in the fight against TB [3]. Bulgaria uses a nationally produced BCG vaccine, and no shortage was reported from this country.

Our results also highlight that in many European countries ongoing BCG shortages have resulted in changes in immunisation practices and policies. One approach is optimising the use of multidose BCG vaccine vials by centralising and cohorting BCG immunisations to reduce vaccine loss, and there is some data to support that this may be effective. Unpublished data from Finland suggest that centralising immunisations and giving BCG only on specific dates using multidose vials resulted in halved vaccine consumption (personal communication from Pertti Sormunen, Director of Pharmaceutical Wholesale, National Institute for Health and Welfare, Finland, April 19, 2016). However, a report from Australia where a similar approach was used, estimated vaccine wastage to be around 75% [20].

Table 1
Demographic details of participants and summary of BCG use and shortage.

	n	%
Participants working at	20	100
Paediatric hospital	16	80
General hospital	3	15
Outpatient Tb specialised clinic	1	5
Countries	13	100
Not routinely using BCG (Austria, Germany)	2	10
No current shortage (Bulgaria, Slovenia, Croatia*)	3	15
Current shortage (Belgium, Finland, Greece, Italy, Spain, Sweden, Switzerland, United Kingdom)	8	75

* Reported a recent shortage prior to the survey being conducted.

Table 2
Details of BCG shortage and reported consequences for immunisation practice and policy.

Reported current BCG shortage	Country	TB incidence/100,000 in 2014 [1]	BCG coverage in 2014 [10]	BCG strain used	BCG immunisation policy [§]		BCG shortage consequences		Other (reported in comment section)			BCG stockpiling		
					Universal newborn	Selective newborn	Selective at older-age	No BCG given	BCG given only to selected high-risk individuals	Cohorting vaccinees	Considering manufacturer and strain change	Available only in some regions	Used whenever available	NS Yes,
No	Bulgaria	27	97%	R	x									x
	Croatia*	12	98%	D	x									x
	Slovenia	7.7	NS	D		x								x
Yes	Belgium	9	NS	D			x			x				
	Finland	5.6	NS	D		x			x					
	Greece	4.8	NS	D			x							x
	Italy	6	NS	D										x
	Spain	12	NS	D										x
	Sweden	7.5	26%	D										x
	Switzerland	6.3	NS	D										x
	UK	12 [†]	NS	D										x

NS – not specified.
UK – United Kingdom.

R – BCG-Russia Bulbio Sofia.

D – BCG-Denmark SSI 133.

* Reported a recent shortage prior to the survey being conducted.
† Incidence in United Kingdom of Great Britain and Northern Ireland (the).

§ As reported by participants of the survey.

Another option to address the ongoing shortage is changing the BCG vaccine manufacturer. In our survey, authorities in two countries (Belgium and Finland) were reported to be considering an alternative manufacturer. As of April 2016, two countries captured in the survey (Finland and Sweden) have changed the manufacturer and are now using BCG-Japan (personal communication from Pertti Sormunen, Director of Pharmaceutical Wholesale, National Institute for Health and Welfare, Finland, April 19, 2016) [21]. Furthermore, other countries, including France and Australia, have temporarily replaced BCG Denmark with BCG Brazil manufactured by Biomed Lublin in Poland [22,23]. This decision is somewhat surprising as there is limited information on safety and protective efficacy of this BCG vaccine strain as it accounts for only a very small proportion of BCG vaccine strains used globally [24]. BCG Poland is a descendant of BCG Brazil (frequently called BCG Moreau or BCG Rio de Janeiro) which has been used in Poland exclusively since 1955 and has been shown to be genetically different to its parent strain [24]. Recent update from Public Health England reports that the shortage is on-going [25]. Considering the ongoing BCG Denmark vaccine delivery delays, it appears likely that further countries in Europe and globally will change to another BCG manufacturer, resulting in a change of the BCG vaccine strain used in their national immunisation programmes.

Importantly, changes in the BCG vaccine strains may have significant consequences. Different BCG vaccine strains have been shown to influence the immune response and protection against TB [9,14,26]. Recent evidence from a study comparing the genomes and transcriptomes of several BCG vaccine strains showed an increase in expression of ribosomal proteins in some strains which may be responsible for increased immunogenicity and better protection against TB [27]. However, it currently remains unclear which BCG vaccine strain offers the best protective efficacy, and consequently any change might affect protection on a population level. In addition, previous reports have shown that changes in the BCG vaccine strain can be associated with an increased incidence of BCG-associated adverse events (AEs). For instance, in 2002 Finland changed from BCG Glaxo to BCG Denmark, as the production of the former was discontinued. In the subsequent two years the incidence of BCG-associated AEs increased considerably, which, in combination with a decreasing TB incidence, ultimately led to discontinuation of universal BCG immunisation in Finland in 2006 [28,29]. Similarly, a change from BCG Connaught to BCG Denmark in Australia in 2012 led to, when administered doses were taken into account, an estimated increased incidence of BCG-induced abscesses and lymphadenitis [20]. AEs related to immunisations cause concern in both healthcare professionals and the general public, potentially impacting the general attitude on immunisations and thereby influencing coverage rates. Thus, monitoring protective efficacy and AEs after a BCG vaccine strain change is of utmost importance.

The key limitations of this survey are the relatively small number of participants, and the fact that we were unable to obtain data from several European countries. In addition, the majority of participants were based in specialised paediatric institutions, and the data may therefore not be representative of the situation in regional hospitals or at the private practice level. As the ptbnet is mainly a European network we were unable to collect data on BCG vaccine shortage outside Europe, where the impact is likely to be considerably greater. However, a report from the WHO Child TB Subgroup meeting in December 2015 stated that critical BCG vaccine shortages were affecting many countries worldwide [17].

It appears obvious that the problems related to the ongoing BCG vaccine shortages cannot be solved by changing the vaccine manufacturer, as this approach simply shifts the demand to another manufacturer. It is therefore important that supranational health

organisations, such as UNICEF, WHO and ECDC, engage with vaccine manufacturers to jointly devise mechanisms that ensure a stable BCG vaccine supply that meets global demand. Notably, in December 2015 UNICEF reported having increased orders with three manufacturers amounting to an additional 38.3 million BCG doses in 2015, which still left an estimated deficit of 16.5 million doses that year [30]. To our knowledge there is currently no specific national or global assessment of the impact of this deficit on childhood TB, and such an assessment should be conducted by either WHO or UNICEF based on TB notification rates in the next few years. In addition, the communication between manufacturers, national public health agencies and end users of the BCG vaccine requires improvements so that the immunisation services can adapt timely in the event of future shortages.

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Competing interests

None declared.

Ethical approval

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tube.2016.08.005>.

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