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Short communication

To BCG or not to BCG?
Preventing travel-associated tuberculosis in children

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ABSTRACT

With the rise in travel to countries with a high prevalence of tuberculosis (TB), the risk of travel-associated TB is of increasing concern. However, the use of Bacille Calmette–Guérin (BCG) vaccine for the prevention of travel-associated TB is a neglected area. We review and discuss national and international recommendations and guidelines for the prevention of travel-associated TB in children. Three children who developed travel-associated TB disease are described to illustrate that current recommendations, and in particular the use of pre-travel BCG immunisation, are inconsistent and controversial. The wide variation in recommendations reflects the paucity of data on the effectiveness of BCG immunisation and other preventive strategies in this setting. Until evidence-based guidelines can be produced, we believe that a low threshold for recommending BCG immunisation for travelling children is the safest strategy. A practical approach to deciding which children should be immunised with BCG prior to travel is presented.

1. Introduction

Global tourism is increasing rapidly: in the first 3 months of 2007 tourist arrivals rose by more than 6% worldwide [1]. South Asia, Southeast Asia and Northeast Asia are the destinations that have experienced the largest rise in international tourist arrivals, with increases between 9% and 12%. The high incidence and prevalence of tuberculosis (TB) in most of the countries in these regions has particular significance to travellers' health (Table 1, Fig. 1). The spread of multidrug-resistant (MDR) TB (exceeding 5% in some areas) and extensively drug resistant (XDR) TB (reported in over 40 countries) constitutes an additional threat to the growing number of travellers exposed to TB [2,3]. The risk of an individual traveller acquiring TB infection depends on several factors that include the local TB incidence, the duration of travel, the degree of contact with the local population and the susceptibility and age of the traveller. Younger children, especially those under 1 year of age, are at particular risk, as following TB infection, they are more likely to develop severe and disseminated forms of TB, including meningitis and miliary disease. We describe three children who developed TB disease following travel and review existing national and international recommendations for Bacille Calmette–Guérin (BCG) immunisation in travellers and the evidence underlying them.

2. Illustrative cases

2.1. Case 1

A 14-year-old girl, born in Australia, travelled to India for 6 weeks to visit friends and relatives (Table 2). She had visited India 2 years prior and had remained well in the interim. She had never been immunised with BCG and had never sought pre-travel medical advice. Eight months after returning from India she presented to her local hospital with a persistent cough, left-sided chest pain, night sweats and significant weight loss. A chest X-ray showed a left lower lobe opacity. She completed an empiric two-week course of oral amoxicillin/clavulanic acid and roxithromycin with no improvement. A repeat chest X-ray showed persistent left basal consolidation and an additional opacity in the left hilum. Sputum microscopy revealed acid-fast bacilli and culture was positive for *Mycobacterium tuberculosis*. A whole blood TB interferon gamma release assay (QuantiFERON-TB Gold) was positive. The patient was treated with isoniazid and rifampicin for 6 months, together with pyrazinamide and ethambutol for the first 2 months and she made an uneventful recovery.

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Table 1
Annual TB incidence in different regions and countries worldwide (based on WHO incidence data 2006 [23])

Region	Annual TB incidence		
	40-100/100,000	> 100-500/100,000	> 500/100,000
Central Africa	–	Angola, Burundi, Central African Republic, Congo, Democratic Republic of Congo, Equatorial Guinea, Gabon, Rwanda, Sao Tome & Principe	Zambia
Southeast Africa	Eritrea	Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Somalia, Uganda, United Republic of Tanzania	Botswana, Djibouti, Lesotho, Namibia, South Africa, Swaziland, Zimbabwe
North Africa	Algeria, Benin, Morocco	Burkina Faso, Cameroon, Cape Verde, Chad, Cote d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sudan, Togo	Sierra Leone
Southeast Asia	Bhutan, China, Maldives, Republic of Korea, Sri Lanka	Bangladesh, DPR Korea, India, Mongolia, Nepal, Pakistan	–
Asia Pacific	Brunei Darussalam, Niue, Palau, Vanuatu	Cambodia, Federated States of Micronesia, Indonesia, Kiribati, Lao PDR, Malaysia, Myanmar, Nauru, Papua New Guinea, Philippines, Solomon Islands, Thailand, Tuvalu, Viet Nam	Timor-Leste
Middle East	Armenia, Azerbaijan, Bahrain, Georgia, Iraq, Qatar, Saudi Arabia, Turkmenistan, Yemen	Afghanistan, Kazakhstan, Kyrgyzstan, Russian Federation, Tajikistan, Uzbekistan	–
Central and South America	Belize, Brazil, Colombia, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Suriname, Venezuela	Bolivia, Ecuador, Guyana, Haiti, Peru	–
North America	–	–	–
East Europe	Belarus, Bosnia, Herzegovina, Latvia, Lithuania	Republic of Moldova, Romania, Ukraine	–
West Europe	–	–	–

2.2. Case 2

A 4-year-old boy, born in Australia, travelled on his first overseas visit to Pakistan for 4 months to visit friends and relatives (Table 2). He had not been immunised with BCG and his family did not seek pre-travel medical advice. One week after returning from Pakistan, the boy presented to his local hospital with fever, diarrhoea and cough. He was treated empirically for possible enteric fever with intravenous ceftriaxone and subsequently defervesced. However, a chest X-ray showed mediastinal enlargement and a tuberculin skin test (TST) showed 13 mm induration. He was treated with isoniazid and rifampicin for 6 months with pyrazinamide for the first 2 months. Despite good compliance, the patient represented with fever, malaise and lethargy 8 months after starting treatment. A repeat chest X-ray showed persistent mediastinal enlargement and cardiomegaly. Echocardiography revealed a pericardial effusion. The patient was referred to our hospital for the drainage of the pericardial effusion and biopsy of the pericardium and mediastinal lymph nodes. Acid-fast bacilli were not seen on microscopy of the pericardial fluid. Culture and PCR of the pericardial fluid and tissue also did not detect *M. tuberculosis.* Histology of the lymph node showed a granulomatous inflammation consistent with TB. No other bacterial or viral cause for his pericarditis was found. Treatment was changed to rifampicin, pyrazinamide, ethambutol and ciprofloxacin for presumed drug-resistant TB. After 12 months treatment with this regimen he made a complete recovery.

2.3. Case 3

A 9-year-old boy, born in Australia and non-BCG immunised, travelled on his first overseas visit to Vietnam for 4 weeks to visit friends and relatives (Table 2). Four years later he presented with cough, fever, night sweats and loss of 10% of his body weight. His grandmother had visited the family from Vietnam 2 months prior

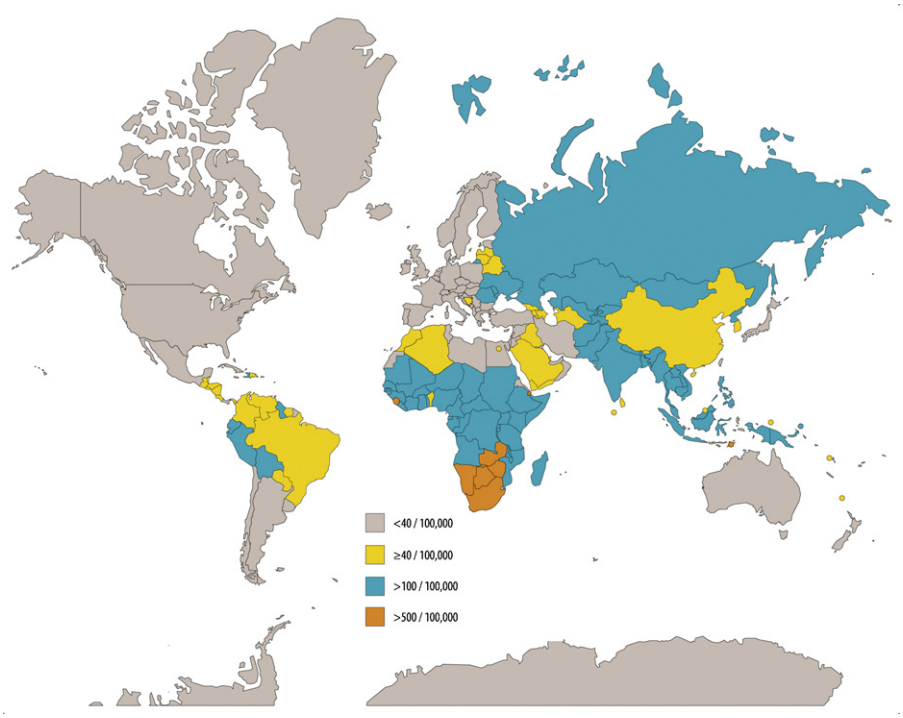

Fig. 1. Annual TB incidence in different regions and countries worldwide (based on WHO incidence data 2006 [23]).

to the onset of his symptoms. Although she had a persistent cough, TB was said to have been excluded as a cause when investigated whilst in Australia. The patient did not improve following treatment with 7 days of clarithromycin. A chest X-ray showed an opacity in the left upper lobe with possible cavitation. A TST showed 22 mm induration. Acid-fast bacilli were found on sputum microscopy and subsequent sputum culture was positive for *M. tuberculosis*. He was treated with isoniazid and rifampicin, with pyrazinamide and ethambutol for the initial 2 months and made a full recovery.

3. Discussion

Travel-associated TB, other than acquired during air travel, has been reported infrequently although perceived as relatively common. The three children reported here were most likely infected during travel overseas as the TB prevalence in Australia is low and none of them had a known TB exposure prior to departure. Pulmonary TB was excluded in any household contacts by routine contact tracing by the local TB control program. In addition, with the exception of case 3, they were not exposed to visitors or relatives from high TB prevalence countries, an important risk factor for acquisition of childhood TB [4].

Pre-travel recommendations and guidelines for the prevention of travel-associated TB are variable and include: avoidance of TB exposure, BCG immunisation, TST before and after travel, and preventive treatment with isoniazid [5–7]. BCG immunisation is most effective for the prevention of severe forms of TB in children under 5 years of age [8] The protective efficacy of BCG for TB meningitis has been estimated at 75–87% [9] and for miliary TB at 70–80% [8]. These forms of disseminated TB are most commonly seen in children under 2 years of age. Although BCG

Table 2
Summary of the three illustrative cases

	Case 1	Case 2	Case 3
Age (years)	14	4	9
Sex	female	male	male
Pre-travel medical advice	no	no	unknown
BCG status	Non-immunised	Non-immunised	Non-immunised
Country visited	India	Pakistan	Vietnam
Length of stay (weeks)	6	14	4
Interval between travel and symptoms (months)	8	1	72
Symptoms	Cough, chest pain, night sweats, weight loss	Fever, cough, lethargy	Fever, cough, night sweats, weight loss
Tuberculin skin test (mm)	Not done	13	22
Interferon gamma release assay (QuantiFERON-TB)	Positive	Not done	Not done
Form of TB	Pulmonary	Pulmonary and extrapulmonary (Percarditis)	Pulmonary
Diagnosis confirmed with	Sputum smear and culture	Histology of mediastinal lymph nodes, mediastinal wound swab	Sputum smear and culture
Duration of treatment (months)	6	12	9
Outcome	Full recovery	Full recovery	Full recovery

Table 3
Recommendations for pre-travel BCG immunisation from selected countries worldwide and from travel and infectious diseases reference books and from internet resources

Source	Pre-travel BCG immunisation	Age limit	Definition of risk country	Duration of travel
National immunisation guidelines				
Australia [24]	Recommended	<5 years	>100/100,000 TB incidence	>3 months
Canada [25]	"To be considered"	Not specified	"High"	"Extended"
France [26]	Recommended	Not specified	"High prevalence"	"Prolonged"
Germany [27]	Not recommended	–	–	–
Ireland [28]	Recommended	Not specified	"High incidence"	>1 month
New Zealand [29]	Recommended	Neonatal	All but 25 named countries[a]	>3 months during first 5 years of life
Sweden [30]	Recommended for "travel involving close contact with local population"	Not specified	"High prevalence"	Not specified
Switzerland [31]	Not recommended	–	–	–
United Kingdom [15]	Recommended for "those who are going to live and work with local people"	<35 years	>40/100,000 TB incidence	>3 months
United States of America [32]	Not recommended	–	–	–
Travel and infectious diseases reference books				
Fast Facts – Travel Medicine [33]	"Should be considered"	Not specified	Asia, Africa, Central and South America	"Long-term"
International travel health guide [34]	"May be appropriate for prolonged and close contact with local populations"	"Chiefly children"	"Remote areas of developing countries" and "high incidences of TB"	Not specified
Manual of childhood infections [35]	"Must be given"	"Children"	"Low-income countries"	>1 month
Red book [36]	"Generally not recommended"	–	–	–
Textbook of Travel Medicine and Health [37]	"Children of immigrants should be BCG vaccinated when visiting their parent's native country"	Not specified	Not specified	Not specified
Travel Medicine [38]	"Might be administered"	<5 years	"TB endemic areas"	>6 months
WHO [39]	No recommendation but states "BCG is of limited use for travellers"	Not specified	Not specified	Not specified
Independent internet resources (non-peer-reviewed)				
Fit for travel (UK) [40]	No information	–	–	–
Shoreland's Travel Health Online (USA) [41]	"Should be considered"	"Young children"	"Highly endemic areas"	>1 year
Travel Health (UK) [42]	"For advice make an appointment with family doctor or travel clinic"	Not specified	"High risk"	Not specified

[a] Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Holland, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, New Zealand, Norway, Slovakia, Sweden, Switzerland, UK, US.

is most commonly given at birth or in the first year of life, studies show BCG is also protective when administered at a later age. In a large study in the United Kingdom, TST-negative adolescents were immunised with BCG at 14–15 years of age [10]. Significant protection (a 78% reduction in incidence) against all forms of TB was found for up to 15 years [10]. Moreover, BCG might even induce better protection when given at an older age. One study in aboriginal Canadians showed better protection against all forms of TB when BCG was administered to children over the age of 6 months (49% protective efficacy) compared to under the age of 6 months (33% protective efficacy) [11]. Similarly, a study in Columbia found the highest protective efficacy (47%) against all forms of TB in children immunised at between 1–3 years of age [12]. A recent meta-analysis including adult and paediatric data showed that BCG reduces the risk of pulmonary TB by at least 50% [13].

For travelling children the most commonly recommended strategy for the prevention of travel-associated TB is BCG immunisation. National and international immunisation guidelines and travel medicine resources vary in their recommendations with significant differences in the age of the child, the duration of travel and in the definition of a high TB incidence country for which such recommendations apply (Table 3). This remarkable variability reflects the lack of evidence and absence of studies on the potential preventive efficacy of pre-travel BCG immunisation. National guidelines also appear to be influenced by each country's internal policy for BCG immunisation: for example both the USA and Germany do not recommend BCG for 'at risk' populations in general and neither country includes BCG in their travel recommendations.

None of the children in this report had obtained pre-travel medical advice. However, depending on which guidelines had been used, none, one or all of these children would have been given BCG immunisation that might have prevented their disease. For example, in Australia BCG immunisation would have been recommended for only one of the children under current immunisation guidelines [14], whereas in the UK all three children would have been recommended BCG [15].

The three cases described here were chosen to illustrate that travel-associated TB can occur in children of all ages and can follow

Table 4
Suggested strategy to guide individualised pre-travel BIG immunisation recommendations in children. This guideline is not intended to be interpreted rigidly but rather to illustrate how the age of the child, the TB incidence in the country visited and the duration of travel should influence the decision to recommend BCG immunisation

TB incidence in country visited	Duration of travel	Age of child		
		<1 year	1–5 years	>5 years
High (>100/100,000)	>4 weeks[a]	BCG	BCG	Consider BCG
	<4 weeks	BCG	Consider BCG	No BCG
Intermediate (40 – 100/100,000)	>4 weeks[a]	BCG	Consider BCG	No BCG
	<4 weeks	Consider BCG	No BCG	No BCG

[a] Or if further travel planned such that cumulative duration of travel is >4 weeks.

even a short duration of TB exposure. It is very difficult to quantify the risk of travel-associated TB disease in children for two reasons. Firstly, although TB is a notifiable disease in Australia and other developed countries, information about travel history is not routinely collected and, secondly, accurate denominator data on the number of outbound travelling children and their duration and destination of travel is not available. For similar reasons it is not possible to determine the protective efficacy of BCG immunisation for travel-associated TB. However, of note, none of the patients in this report had obtained pre-travel medical advice or had been immunised with BCG.

Although no study has been able to calculate the risk of TB disease associated with travel, previous studies have quantified the risk of latent TB infection measured by TST conversion. In TST-negative adults the incidence of a positive TST after return from prolonged travel to high TB incidence countries was 0.35% (95% confidence interval (CI) 0.2–0.62%) per month of travel [16]. In a multi-centre study in California, children under 6 years of age who had travelled were five times more likely to have a positive TST than their peers who did not travel [4]. A case-control study in TST-positive children living in New York also found foreign travel to be associated with the acquisition of latent TB infection [17]. Unfortunately none of these studies has investigated the effect of BCG status on the risk of TST-conversion after travel. It is therefore unknown whether BCG immunisation prevents latent TB infection in travelling children. However, a study in children exposed to household contacts with sputum smear-positive pulmonary TB suggests that BCG immunisation protects against latent TB infection in this setting [18].

In the absence of information on the efficacy of BCG immunisation for the prevention of travel-associated TB, potential benefit versus risk needs to be carefully considered. There are several advantages to the BCG immunisation strategy. Compared to pre- and post-travel TST, only one rather than four visits is needed and it is not subject to the difficulty of interpretation in the context of potential boosting with repeated TST [19]. Other advantages of BCG immunisation is that it is only required once and it is likely to be equally effective against MDR- and XDR-TB. Further, the target population is likely to be repeatedly exposed on return visits to high TB incidence countries in the future. The majority of children attending travel clinics are TST-negative and can therefore be safely immunised with BCG. Children who have already been immunised with BCG, for example those from countries that routinely immunise with this vaccine [20,21] do not need an additional dose of BCG because repeat BCG immunisation has not been shown to improve or prolong protection (reviewed in [22]). The potential disadvantages of pre-travel BCG immunisation are rare adverse effects (BCG injection site abscess, regional BCG lymphadenitis and, in the immunocompromised, possible disseminated BCG infection) and the difficulty of TST interpretation post BCG immunisation.

Until evidence-based guidelines can be produced, we believe that the safest strategy for travelling children, particularly those under 5 years of age, is to maintain a low threshold for recommending BCG immunisation. Factors to consider are the child's age, the incidence of TB in the country to be visited and the duration of travel. Our current practice, summarised in Table 4, is to provide individualised advice based on these three key factors. In particular, we recommend BCG immunisation for children under 1 year of age (because of the high risk of developing severe or disseminated disease in this age group) and for children who are likely to have repeated visits during childhood to countries with intermediate or high incidence of TB.

In the absence of data on the risk of TB in travelling children this suggested strategy, in common with other guidelines for BCG immunisation in this context, remains arbitrary and highlights the urgent need for studies in children to create evidence-based guidelines for prevention of travel-associated TB.

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