Should medical students be routinely offered BCG vaccination?

Maryza Graham, Tanya M Howley, Robert J Pierce and Paul D Johnson

Young adults who initially have negative tuberculin skin test (TST) results but have subsequent positive TST results have a relatively high rate of early progression to clinical tuberculosis (TB),[1] and the estimated lifetime risk of developing pulmonary TB is highest after infection in early adulthood — around 15% for those infected at age 20 years.[2] In Box 1, we describe a medical student who may have developed symptomatic pulmonary tuberculosis during her intern year had her infection not been detected early by her university screening program. However, might TB have been prevented if she had received BCG vaccine at medical school?

BCG vaccination: current practice

Until recently, all medical students in Victoria were routinely screened with TSTs, and those with negative results were offered BCG vaccine. Melbourne University stopped this practice in 1996 and Monash University stopped it in 2000.

The 2003 *Australian immunisation handbook* makes no clear statement about BCG for health care workers, stating that "State and Territory guidelines should be consulted".[3] The 2002 Victorian Department of Human Services guidelines advise that BCG may be considered in health care workers who have a high risk of occupational exposure to TB, who are TST-negative, and who are likely to be exposed to active cases of multidrug-resistant TB (MDR-TB).[4]

ABSTRACT

- BCG vaccination is no longer routinely offered to all medical students in Victoria.

- Practices in Australia's 15 medical schools vary widely with respect to BCG vaccination and surveillance for tuberculosis (TB) infection during the medical course.

- Health care workers can be exposed to TB in Australian hospitals, but the risk is much higher if they undertake work in countries with a high prevalence of TB, such as during student electives.

- BCG vaccination is safe, cheap and protects 50% or more of recipients from active TB, including multidrug-resistant TB. Protection is long-lasting, requires only a single dose, and there is new evidence that BCG may prevent primary infections, not just active disease.

- Although BCG vaccination interferes with the interpretation of the tuberculin skin test (TST), newer tests (QuantiFERON-TB Gold, T-SPOT.*TB*) are unaffected by BCG vaccination.

- We propose a standard approach for all Australian medical students that includes screening with TST and QuantiFERON-TB Gold/T-SPOT.*TB* at course entry, and recommending BCG vaccination for students who test negative, provided they have not previously received BCG vaccine.

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In the absence of definitive national and state guidelines covering medical students, the Committee of Deans of Australian Medical Schools developed their own guidelines in 2003. The document states that BCG vaccination is not required in students with a negative TST result, but that this recommendation is not universally accepted and medical schools may choose to include this recommendation within their programs.[5]

Current practice in Australia's 15 medical schools varies widely (see Box 2). We contacted all Australian medical schools and found that all except one recommend a baseline TST early during the medical course, one also offers an "exit" TST to medical students before graduation, four schools recommend the BCG vaccine to all medical students with a negative TST result, and one offers the BCG vaccine, but the uptake rate is variable; the remaining medical schools do not routinely recommend BCG vaccine.

Risk of TB in Australian health care workers

Health care workers can be exposed to TB in Australian hospitals,[6,7] although the risk is clearly higher if they work overseas. For example, the risk of TB infection in long-term Dutch travellers to high-endemicity countries was 2.8 per 1000 person-months of travel (3.3% per year), after excluding health care workers. However, for health care workers who worked overseas in patient care, the rate was 9.8 per 1000 person-months of travel (12% per year).[8] In a low-incidence setting comparable with Australia (Germany), culture-positive isolates over a 6-year period were genotyped as well as

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1 Case record of a medical student who became infected with *Mycobacterium tuberculosis*

In 2004, a previously well 24-year-old medical student was referred to us by her university vaccination program. She had undergone a two-step tuberculin skin test (TST) at course entry (1998) and in September 2002; the results of both were negative. However, her end-of-course TST in November 2004 gave a positive (15 mm) result. She had never had a BCG vaccination, nor been exposed to any identified risk of tuberculosis (TB) before December 2002.

From December 2002 to February 2003 she undertook a 2-month elective at Maluti Adventist Hospital in rural Lesotho (an enclave of South Africa), where TB was common. She did not enter the hospital's TB ward, but frequently encountered patients with known or suspected TB in clinics and medical wards. After her elective, she travelled for 3 months in Africa, a month in Thailand, then 3 months in Nepal. She also spent 3 weeks in Borneo in mid 2004.

Despite the absence of symptoms, a chest x-ray showed faint opacity in the right upper zone, and her QuantiFERON-TB Gold blood test result was positive. Computed tomography of her chest showed multiple nodules (up to 10 mm) in the right upper lobe apical segment. Bronchoscopy showed a normal endobronchial tree. Smears of the bronchial brushings/washings and biopsy were negative for acid-fast bacilli, and histological tests showed no diagnostic features or evidence of granulomatous inflammation. Standard therapy for TB (isoniazid, rifampicin, ethambutol and pyrazinamide) was given.

Seven weeks after the bronchoscopy, fully sensitive *Mycobacterium tuberculosis* was cultured from bronchial washings. Typing of the isolate showed a unique pattern, suggesting acquisition outside Victoria. Her treatment course was uneventful. ◆

2 Examples of tuberculosis screening and vaccination policies at Australian Universities

University and jurisdiction	Policy	Website/source
Australian National University (Australian Capital Territory)	"Students undertaking placements in health facilities . . . must consider having . . . Mantoux testing." "Prophylactic BCG vaccination is not routinely recommended."	http://medicalschool.anu.edu.au/admission/admission.asp (accessed December 2005) *Infectious diseases policy*
The University of Queensland (Queensland)	"Qld Health (Division of Specialised Health Services) currently recommends that health care workers have a baseline Mantoux (skin) test and chest radiograph followed by BCG vaccination if the Mantoux test is negative."*	http://www.uq.edu.au/hupp/index.html?policy=2.30.15 (accessed December 2005) *Handbook of university policies and procedures*, Policy 2.30.15: Immunisation
The University of Melbourne (Victoria)	"The Healthcare Students Immunisation Program offers . . . tuberculosis screening by two-step tuberculin (Mantoux) skin testing in first year. Further screening may be offered during the clinical years of the course. BCG vaccine is *not* recommended."	http://www.medicine.unimelb.edu.au/current/policies.html (accessed December 2005) *Infectious diseases and immunisation policy*

*Similar policies exist for medical students at Bond University and Griffith University in Queensland. ◆

contact-traced. Epidemiological analysis showed that recent transmission was strongly associated with health care work.[9]

One strategy for preventing tuberculosis in health care workers who plan to work in a high-risk situation is serial TSTs, with post-exposure prophylaxis for those whose TST results convert from negative to positive. Prophylaxis with isoniazid carries the risk of side effects. The most serious of these is hepatitis; the risk of developing hepatitis increases dramatically with age, but is about 0.3% in those aged 20–34 years.[10] Furthermore, TST *ideally* involves a two-step protocol before departing for a TB-endemic area (to detect the booster phenomena), and retesting at 2–3 months after returning. This would involve six visits to health care providers experienced in giving and interpreting the TST for one period of overseas work. Several studies have shown that compliance with this recommendation is poor, even for only one pre-travel and one post-travel TST (four visits). For travellers, compliance rates of around 61% have been reported, with 33% of the compliant travellers requiring extra phonecalls.[8,11] Among physicians, adherence rates for TSTs vary from 30% to 72% in North American studies.[12]

MDR-TB is defined as resistance to both isoniazid and rifampicin, and is uncommon in Australia (1%–2% of bacteriologically confirmed isolates over the decade to 2003).[13] Rates in south-east Asia range from 2%–7%, and are higher in some provinces of China.[14] The proportion of MDR-TB cases in Lesotho, South Africa (where the medical student whose case we describe worked), was less than 2% in 1994, but, because of the high incidence of TB, this translated to an estimated 105 new cases of MDR-TB that year.[15] BCG vaccine can protect against MDR-TB (as well as sensitive TB), but TST screening with post-exposure prophylaxis cannot.

BCG vaccination: revisiting current practice

Given the risks of TB infection, why is BCG vaccine no longer routinely offered to medical students? Arguments include concerns about its efficacy, safety and potential to interfere with interpretation of the TST.[16-19]

Efficacy

It has long been held that BCG vaccination does not prevent TB infection and any benefit is restricted to preventing active TB. However, a recent study challenges this, with a reported 40% protection against infection in children with household TB contact.[20]

3 Managing risk of exposure to tuberculosis: proposed standard approach for all Australian medical students

At course entry
- Screen all medical students with tuberculin skin testing and QuantiFERON-TB Gold/T-SPOT.*TB* blood testing
  - Offer BCG vaccination to those who test negative, provided they have not previously received BCG vaccine
  - Chest x-ray and follow up of any students who test positive

At end of course
- Screen all students again with QuantiFERON-TB Gold/ T-SPOT.*TB* blood testing
  - Chest x-ray and follow-up of any students who test positive ◆

In adults, the reported efficacy of BCG vaccines varies greatly (range, 0–80%), but a meta-analysis found that, overall, the vaccine reduced the risk of tuberculosis by 50%.[16] The wide variation in vaccine efficacy has been attributed to differences in vaccine strains, prevalence of protective local atypical mycobacteria, variation in BCG vaccine protection against different forms of tuberculosis, and host factors such as genetics, age at vaccination and nutritional status. This meta-analysis found that geographic latitude and study validity explained 66% of the between-study variation in the trials, and that BCG vaccine efficacy increased with increasing distance from the equator in 13 of the 14 prospective trials included. Genetically identical BCG preparations yielded different results in different populations, and age at vaccination was not a significant predictor of BCG vaccine efficacy.[16,17]

A more recent report, based on 60 years of follow-up of Native Americans who had received either BCG vaccine or placebo, found that the efficacy of BCG vaccine persisted for 50–60 years, with no statistically significant waning over time.[21] Median age at vaccination was 7.6 years. This study also found an adjusted vaccine efficacy of 55%.

A review of studies of BCG vaccine efficacy in health care workers also found that it was effective in reducing the incidence of tuberculosis, although quantitation of the protective efficacy was limited by the methodological weaknesses of individual studies. These studies were performed in countries with relatively low incidences of tuberculosis (North America, Norway), comparable with that in Australia.[22]

Safety

Worldwide, one hundred million doses of BCG vaccine are given annually, and serious or long-term complications are rare.[18] A prospective study of 5.5 million vaccinees in six European countries found that local reactions occurred at a rate of 0.01–17.2 per 1000 infants, with lower rates for older children and adults.[23] These complications usually resolve without intervention, although keloid formation has been reported in almost 5% of BCG vaccinations.[24-26] In immunocompetent people, non-cutaneous complications are rare. For example, for those vaccinated between the ages of 1 and 20 years, the incidence of lymphadenitis or non-fatal disseminated disease was estimated to be 0.36 per million vaccinations. The incidence of fatal disseminated lesions was 0.06–0.72 per million vaccinations, and deaths occurred primarily among immunocompromised people.[23]

Interference with tuberculin skin testing

BCG vaccination interferes with the interpretation of TST results, and guidelines attempting to overcome this vary widely.[19] However, new tests have recently been developed that aim to solve the problems of poor TST specificity. Identification of genes in *Mycobcterium tuberculosis* that are absent from BCG vaccine and most non-tuberculous mycobacteria has allowed the development of blood tests (Quanti-FERON-TB Gold, T-SPOT.*TB*) that detect interferon-gamma response to TB-specific antigens. These newer tests are unaffected by BCG vaccination status.[27-29] They are entering routine clinical practice in Australia and elsewhere,[30] although they require further evaluation. Their availability means that avoidance of BCG vaccnation solely because it may interfere with TST interpretation can no longer be justified.

BCG vaccination: recommended practice

Australia has one of the lowest rates of TB in the world, but exposure to TB remains an occupational hazard for Australian health care workers.[6] We acknowledge that BCG vaccination is not perfect, but it is cheap and safe, provides reasonable long-lasting protection — including from MDR-TB — and only one dose is required. Until more definitive data become available, we propose a standard approach for all Australian medical schools that incorporates offering BCG vaccination to all students who test negative to tuberculin skin and TB blood testing (see Box 3).

Competing interests

None identified.

Author details

Maryza Graham, MB BS, Infectious Diseases Registrar[1]
Tanya M Howley, MB BS, Resident Medical Officer[2]
Robert J Pierce, MD, FRACP, FCCP, Director, Department of Respiratory Medicine[1]
Paul D Johnson, PhD, FRACP, Deputy Director, Department of Infectious Diseases,[1] and Associate Professor of Medicine[3]

1 Department of Infectious Diseases, Austin Health, Melbourne, VIC.

2 Ballarat Health Services, Ballarat, VIC.

3 University of Melbourne, Melbourne, VIC.

Correspondence: maryza.graham@mh.org.au

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