Extensively resistant tuberculosis in the lands Down Under

Paul D R Johnson

As tuberculosis resistance increases linearly, the cost and complexity of managing these cases increases exponentially

New Zealand's first case of extensively drug-resistant tuberculosis (XDR-TB) is reported in this issue of the Journal.[1] Even though the patient did not have transmissible pulmonary TB, the case highlights the complexity of managing such patients and draws attention to the long delay between suspecting TB and confirming XDR-TB. Two cases of XDR-TB have been reported in Australia, one in 2004[2] and one in 2010,[3] but there have been many more cases overseas.[4] Still, only three cases in our two countries — should we care?

A quick revision of history can help us to understand why multidrug-resistant TB (MDR-TB), and now XDR-TB, are so important. Tens of thousands of Australians and New Zealanders died of TB during the 19th and early 20th centuries.[5] For generations, TB engendered the same dark fear that we now associate with cancer. One face in the crowd provides a poignant example. Archie Jackson, who in 1929 became the youngest cricketer to have scored a test century against England, was also one of the youngest to die — he was just 23 when he died from pulmonary tuberculosis in 1933.[6] The advent of safe and effective antibiotic therapy after World War II meant the end of the great fear, and TB seemed defeated. In fact, rates of TB were already falling before the age of antibiotics, partly due to improvements in nutrition and living conditions.[7] However, it would be folly to assume "game over, TB". TB notifications have stopped falling in Australia and New Zealand, although they remain very low by international standards (about seven new cases per 100 000 population per year).[8] In contrast, drug-resistant TB is out of control in several regions of the world. In Burma (Myanmar), the country of origin of the patient described in the case report from New Zealand, there were an estimated 4250 cases of MDR-TB in 2006 alone.[4] The reasons for the worldwide emergence of resistance include poverty, breakdown in public health systems following the fall of the Soviet Union,[4] the interaction of TB with AIDS in Africa, and a laissez-faire attitude to antibiotic control in some increasingly wealthy emerging nations.[9]

Because of the biphasic biology of TB, whereby frequent asymptomatic infection is followed unpredictably by active transmissible disease, there is no practical way of isolating Australia and New Zealand from TB drug resistance. Infection with *Mycobacterium tuberculosis* is initially acquired by breathing but the risk depends heavily on the local prevalence of active TB. If a person lives for many years in a high-risk country, infection is likely, but usually remains silent and can only be detected by performing a Mantoux test or interferon-gamma release assay. Neither test detects bacterial cells directly, so will not reveal the resistance profile of the infecting strain. The silent stowaways then travel with refugees, overseas students and migrants who come seeking sanctuary or opportunity. Screening by chest x-ray allows early detection in some, but it is not always appreciated that people with normal chest x-rays may also carry latent *M. tuberculosis*. For example, as described in this issue of the Journal by Trauer and Krause, of 146 refugees arriving in the Northern Territory who were found to have latent TB infection (LTBI), only 6% had chest x-rays showing abnormalities.[10] Those with LTBI were offered isoniazid preventive therapy in accordance with current guidelines, but this is unlikely to reduce future reactivation of antibiotic-resistant TB. Fortunately, most people with LTBI remain well, but a small group will develop active disease, often relatively soon after arrival. In Victoria, the median time between arrival in Australia and notification of TB was 2 years in a 10-year review of MDR-TB.[11] About half of new cases of TB in Australia and NZ have transmissible pulmonary disease, mostly caused by the same strain of TB that they breathed in years earlier, antibiotic susceptible or otherwise.[11] In this way, good public health practice at home can be undone by poor public health practice abroad.

Why does resistance matter? First, there is the cost. The World Health Organization has estimated that the cost of treating a patient with MDR-TB is about 100 times the cost of treating fully susceptible disease.[12] For the patient, there is a long and difficult 18–24-month treatment course. And then, there is the return of the age-old fear — although patients with XDR-TB can be treated too, resistance to the most effective second-line antibiotics increases the risk of treatment failure and death.[13,14]

So what is a rational response to this threat in low-risk countries such as Australia and New Zealand? Predicting where new cases of resistant TB will appear is very difficult. In Australia, there were only 153 cases of MDR-TB and one case of XDR-TB in the period 1995–2007.[2] There have been about 2700 more cases of TB

Definitions of tuberculosis-related terms

TB Tuberculosis — a clinically apparent disease caused by *Mycobacterium tuberculosis* that typically presents with one or more systemic symptoms (eg, night sweats, fever, loss of weight) and a local symptom indicating the site of active infection (eg, cough, headache, back pain, neck gland swelling).

MDR-TB Multidrug-resistant tuberculosis — TB caused by *M. tuberculosis* that is resistant to at least rifampicin and isoniazid, the most active first-line antibiotics.

XDR-TB Extensively drug-resistant tuberculosis — MDR-TB that is also resistant to any fluoroquinolone, and to at least one of three injectable second-line anti-TB drugs (capreomycin, kanamicin, or amikacin).

LTBI Latent TB infection — an individual is infected but has no symptoms or signs of active disease.

TB reactivation A person with LTBI develops active TB. The lifelong risk is thought to be about 5%, but is much higher in patients with HIV or who are medically immunosuppressed.

Primary resistance Resistance in *M. tuberculosis* obtained from a patient with no history of treatment.

Secondary resistance The development of resistance during treatment of drug-susceptible TB due to incorrect prescribing and/or poor patient compliance.

Secondary case [of TB] A person who is infected by someone with active pulmonary TB before this initial diagnosis is made and the patient is isolated. ◆

diagnosed since then,[15] with an expected MDR-TB rate of about 2.5%.[2] If you are a manager thinking that maybe you could put your TB funds to work elsewhere, think again. Resistant TB in a low-prevalence country is an example of a low-probability, high-impact event — a "black swan", to borrow a concept recently popularised by the economist Nassim Taleb.[16] A black swan is something too improbable to worry about, but then it happens and everything changes. For Europeans, swans had been axiomatically white for millennia. In 1697, a black swan was observed during the exploration of what is now Western Australia, and an axiom collapsed because of a single exception. Moreover, according to Taleb, such events are immediately rationalised and considered to have been obvious in retrospect.[16] Consider the impact of a delayed diagnosis of pulmonary XDR-TB if the patient were an overseas-trained nurse or doctor working in a paediatric hospital. There is no proven postexposure prophylaxis; there is a risk of treatment failure and drug toxicity that would further distress already anxious parents; and the cost of successfully treating even one secondary case of XDR-TB has been estimated at US$600 000 in a Californian case series.[17] Something like this will happen — we just don't know when.

Here are some suggestions for how we can try to out-swim the black swan. First, we must sustain and extend our existing overseas programs that support our neighbours in their struggle to control TB. This is not philanthropy, it is just common sense. One example involves clinics that have been providing treatment for MDR-TB to Papua New Guinea nationals who cross the Torres Strait to receive it. A recent decision taken on cost grounds by the Queensland and Commonwealth governments to close these clinics is unlikely to save Australia any money in the long run.[18] Our next line of defence is the primary care clinician. Rapid diagnosis of pulmonary TB minimises secondary transmission, whatever the resistance pattern of the isolate. Then we need to strengthen our local TB public health services and recognise that as TB resistance increases linearly, the cost and complexity of managing these cases increases exponentially. Finally, we need to keep up to date with new technology. The latest molecular methods are now able to directly detect the presence of *M. tuberculosis* and rifampicin resistance simultaneously in primary specimens, including in some that are smear-negative (ie, acid-fast bacilli present but too few to be seen by microscopy).[19] This is an important advance because rifampicin resistance is a marker for MDR and XDR-TB and the result could be available within just a few hours. Molecular diagnostics are not yet perfect — we will need to retain culture-based methods for a while yet — but they are now becoming widely available and progressively cheaper. We should embrace these new technologies and make molecular screening of primary specimens standard practice, even though the upfront costs will seem high initially. We need to be organised and up to date if we want to stay ahead of TB.

Author details

Paul D R Johnson, MB BS, PhD, FRACP(Infectious Diseases), Deputy Director and Associate Professor of Medicine

Infectious Diseases Department, Austin Health and University of Melbourne, Melbourne, VIC.

Correspondence: Paul.Johnson@austin.org.au

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