Multidrug-resistant tuberculosis in Australia and our region

MDR-TB threatens TB control programs in Australia's region and will not diminish without concerted efforts

Tuberculosis (TB) is one of the world's great killers, but Australia has been relatively protected because of its strong public health system. Of 1300 cases reported in Australia each year, almost 90% occur in the overseas born, although Indigenous Australians are also disproportionately affected. Most cases arise in the large immigrant communities from India, Vietnam, the Philippines, China and Nepal, but high rates are also reported from Papua New Guinea (PNG), Ethiopia, Somalia and Myanmar. These cases occur primarily in permanent residents and students, rather than in refugees or those on humanitarian visas.[1]

Many countries are now reporting significant rates of drug-resistant tuberculosis, with at least 480 000 cases worldwide now attributable to multidrug-resistant TB (MDR-TB; defined as resistance to the two most effective first-line agents, isoniazid and rifampicin).[2] However, countries with the highest rates of drug resistance often have the poorest quality data, largely due to the lack of resistance testing. Globally, MDR-TB was estimated to constitute 3.3% of new and 20% of retreatment cases in 2014. Although the deployment of molecular diagnostics to detect resistance is progressing, only a quarter of these cases were correctly identified. For example, in PNG, MDR-TB rates are similar to those described globally, but a nationwide drug-resistance survey has not been undertaken and other data sources suggest that the rates could be underestimates.[3] Extensively drug-resistant TB (XDR-TB; resistant to isoniazid, rifampicin and the most effective second-line agents, quinolones and injectables) has also been sporadically reported in Australia from PNG.[4] For Australian clinicians, for whom diagnostics are widely available, the rise of MDR-TB makes definitive strain identification through culture even more important.

Traditional second-line agents to treat the handful of MDR-TB cases in Australia are generally available, but prolonged courses of toxic and expensive drug combinations are required. The agents used to treat MDR-TB depend on the remaining susceptibilities, but ototoxicity (aminoglycosides), nausea (p-aminosalicylic acid) and neuropsychiatric reactions (cycloserine) are among many common side effects. It is therefore unsurprising that globally, treatment outcomes are poor, with only about half of identified patients completing the 2-year treatment course, such that only around 10% of all incident cases complete treatment worldwide.[2] Meta-analyses demonstrate that the chance of treatment success diminishes as the number of drugs to which a strain is resistant increases.[5] Alarmingly, there are now data on outcomes for patients with "beyond XDR"-TB, with treatment success rates comparable to the pre-antibiotic era natural history of TB.[6]

There is a resurgence of interest in new treatments for TB, with the first new drugs in 40 years now proceeding through development, including bedaquiline, delamanid and pretomanid. As important as individual agents is the development of new regimens that can be deployed programmatically, such as the 9-month Bangladesh regimen (comprising gatifloxacin, clofazimine, ethambutol and pyrazinamide, with prothionamide, kanamycin and high-dose isoniazid added for the intensive phase).[7] There is also interest in off-label use of existing antibiotics with anti-TB activity, such as linezolid and meropenem–clavulanate, and new strategies to minimise toxicity, such as therapeutic drug monitoring. However, even if new regimens become established, significant barriers exist to providing treatment for MDR-TB in the countries that need them most. MDR-TB is both a cause and symptom of poor communicable disease control programs, with MDR-TB regimens costing around tenfold that of drug-susceptible cases.[8]

"The ambitious post-2015 targets for TB control ... present an opportunity for Australian leadership"

MDR-TB is not a problem that will just go away. Policy makers may prefer to treat the problem they can address — focusing on improving programs for drug-susceptible TB to prevent resistance amplification. However, modelling has consistently demonstrated that cases of MDR-TB predominantly arise from community transmission rather than from resistance amplification in previously susceptible strains,[9] such that only targeted control programs will achieve reduction in the disease burden attributable to MDR-TB.[10]

As global TB rates slowly decline, the contribution of late reactivation of latent infection to incidence is likely to increase. While this makes treatment for latent MDR-TB a key consideration, evidence for effective treatments remains scarce and clinical trials are ongoing.

The ambitious post-2015 targets for TB control, which replace the relatively modest Millennium Development Goals, present an opportunity for Australian leadership. In our setting, with most TB imported and the emergence of MDR-TB so dependent on the strength of health

James M Trauer
MPH, FRACP, FAFPHM[1]

Allen C Cheng
MPH, PhD, FRACP[1,2]

1 Monash University.
2 Alfred Health, Melbourne, VIC.

allen.cheng@med.monash.edu.au

doi: 10.5694/mja16.00012

systems, Australia has a critical role to play in supporting developing countries of our region to improve TB control programs and their health systems generally. A vision for an expanded international response, coordinated with global partners, governments, multinational organisations, affected individuals and communities is provided by the United States National Action Plan for Combating MDR-TB.[11] Given that 57% of MDR-TB cases occur in the Asia–Pacific region,[2] a similar response to improve clinical diagnostics and management in our region would help keep MDR-TB from our shores.

Acknowledgements: Allen Cheng is supported by a National Health and Medical Research Council Career Development Fellowship.

Competing interests: No relevant disclosures.

Provenance: Commissioned; externally peer reviewed. ■

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