Editorial

The Dollars and Sense of Managing Drug-Resistant Tuberculosis in Singapore

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In the Mortality Bills, pneumonia is an easy second, to tuberculosis; indeed in many cities the death-rate is now higher and it has become, to use the phrase of Bunyan 'the captain of the men of death.'

— Sir William Osler[1]

The tremendous advances in the treatment of tuberculosis (TB) beginning with the advent of streptomycin, followed by a whole range of highly effective anti-tuberculosis therapies, many of which were studied in high quality randomised clinical trials conducted in Singapore[2] have largely removed TB from the public imagination as a feared and deadly contagious disease. However, in the 1990s, highly publicised nosocomial outbreaks of multidrug-resistant tuberculosis (MDR-TB) in New York City which led to mortality even among healthcare workers[3] brought TB back onto the radar screen. Tuberculosis (TB) was declared a global health emergency by the World Health Organisation in 1994, and it continues to kill 1.5 million people per year. It is estimated that one third of the world's population is infected with the causative organism, *Mycobacterium tuberculosis*.[4] Seventeen years after the global health emergency was declared, there are expected to be 9.8 million new cases worldwide in 2010, more than any other year in history.[5] In Singapore, the number of newly diagnosed TB cases rose in 2008 after a period of steady decline; although the incidence of TB in Singapore is higher than in developed countries, it is much lower than in the developing countries around us.[6]

More alarmingly, the greatest number of new and previously treated MDR-TB patients is in Asia, which has an estimated 62% of all MDR isolates, especially in India and China.[7] Closer to home, countries including Bangladesh, Myanmar, Vietnam, Philippines and Indonesia have also been designated high MDR-TB burden countries.[8] A variety of reasons including limited access to healthcare resources, lack of culture and susceptibility testing and inappropriate use of second-line drugs has led to the emergence of extensively drug-resistant tuberculosis (XDR-TB) which are refractory not only to isoniazid and rifampicin but also to at least one fluoroquinolone and at least one injectable second-line drug. XDR-TB have now been found in 58 countries, including Bangladesh, Philippines, and Indonesia.[8] This issue of Annals documents a case of XDR-TB managed in a Singapore hospital with all the complications associated with such a difficult to treat infection that eventually required surgery to control the underlying disease. This brings back memories for some older readers of the days when lobectomy and even "plombage" were routinely done for patients with tuberculosis because of the lack of effective anti-tuberculous chemotherapy.

As with other infectious diseases, resistance to TB drugs stems primarily from inadequate control of infection due to non-adherence by patients for economic or other reasons, incorrect drug prescribing by providers due to lack of susceptibility data or other reasons, poor quality drugs, or erratic supply of drugs. Treatment options are dwindling in the treatment of drug-resistant TB. The last drug approved for treating TB was rifampicin, and that was in 1963. The treatment of drug resistant tuberculosis includes agents to which the organism remains susceptible, which translates to a combination therapy of 5 to 10 drugs that should be continued for a minimum of 18 to 24 months. There are serious side effects of these MDR and XDR-TB drugs, such as the nephrotoxicity and ototoxicity of aminoglycosides, hepatotoxicity with ethionamide and psychosis with cycloserine. Compounding the challenging situation are drug-drug interactions, particularly with antiretrovirals and oral hypoglycaemic agents, as patients with HIV and diabetics are at higher risk of developing drug-resistant TB. Surgery is another option. As would be expected with a complex disease like this, approximately one third of MDR-TB patients experience treatment failure, and this can reach 50% in XDR-TB.[9] It is also well recognised that patients with drug-resistant tuberculosis have a higher mortality rate which can reach up to 83% in HIV-TB coinfected patients.[10] Even in Singapore with our small size and well developed public health programmes, drug resistance is associated with a higher mortality as well as certain socioeconomic factors including ethnicity and residence in a long-term care facility.[11] There are a few notable exceptions to the bleak picture for patients with drug-resistant TB — successful

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programmes for treatment of MDR-TB have acknowledged the importance of socioeconomic factors including the alleviation of poverty and reduction of income inequality.[12] The financial costs of treatment of MDR-TB are enormous as highlighted in this case report. The cost of drugs alone for treating the average MDR-TB patient is 50 to 200 times higher than for treating a drug-susceptible TB patient, and the overall costs for care have been found to be 10 times higher or more.[13] A programme that does not take into account these financial realities is doomed to fail.

The strategy to control drug-resistant tuberculosis is one that incorporates advancing diagnostic services for rapid drug-susceptibility testing, developing new drugs, implementing high quality Directly Observed Therapy Short-Course (DOTS), increasing disease surveillance together with improving infection control. The availability of point-of care diagnostic tests is critical in determining the appropriate therapy and decreasing transmission of a disease of which treatment is fraught with difficulties. Tests currently endorsed by WHO include molecular line-probe assays (e.g. Hain Genotype MTBDRplus), nitrate reductase assay, colorimetric redox indicator assay and Microscopic-Observation Drug-Susceptibility Assay (MODS). In the drug development pipeline, there are 4 drugs in Phase 2, including ATP synthase inhibitor TMC-207 and cell wall and multitarget inhibitors PA-824 and OPC-67683.[14] Immunotherapy such as new vaccines and vitamin D may serve as adjunctive treatment for prevention and active disease, together with shortening the course of treatment. DOTS has improved treatment outcomes and reduced TB and MDR-TB incidence in many countries. This framework of DOTS, promulgated by WHO, and the pilot MDR TB management projects (DOTS-Plus projects) became the basis for programme based management of MDR TB, which have been successful in many settings. Here in Singapore,[6] only about half of our TB patients are on DOTS raising the risk for emergence of drug resistance locally. In the Singapore context, however, as Cutter and Wang pointed out, the greater risk is in importation of MDR- and XDR-TB as also illustrated by this case report. From 2000 to 2006, there were 48 cases of MDR TB in non-residents compared with 27 cases in Singapore residents. The non-resident MDR TB cases were predominantly in short-term social vistors from Indonesia, Burma and China.[15]

Urban settings and a sharp rise in HIV fuelled the outbreak of MDR-TB in New York in the 1990s. Infection control practices in both community and healthcare facilities are keys in disrupting the cycle of transmission of drug-resistant tuberculosis. Infection control measures in healthcare settings involve administrative measures primarily, which identify and isolate patients likely to have TB, followed by engineering controls. Improvements in ventilation alone would be among the most effective measures. Opening windows and doors maximises natural ventilation and has been reported to be more efficacious than costly, mechanical ventilation systems.[16] While much attention is paid to personal protective equipment, administrative controls that reduce the entry of infectious patients into crowded outpatient clinics or multi-bedded wards can potentially be far more effective in controlling nosocomial tuberculosis transmission.

Medical tourism has meant that patients with infectious diseases can leave their home communities in search for cure, sometimes to escape the stigma and discrimination that are associated with diseases such as tuberculosis and HIV. Thailand, Malaysia and Singapore market themselves as major destinations for medical tourism. Singapore public hospitals have websites which are designed to attract foreign patients.[17-19] These patients are brought to our public hospitals to enjoy "market-subsidised" healthcare at rates lower than what they would pay at private hospitals and while they may provide ID trainees with a range of conditions that they would not otherwise see in Singapore, the risk of introduction of exotic diseases is not small. International travel was blamed for the global spread of SARS and the rapid spread of the 2009 Influenza A (H1N1) epidemic. More recently, medical tourism was thought to be responsible for the global spread of New Delhi metallo beta-lactamase-1 (NDM-1), which conveys carbapenem resistance in bacteria, rendering them untreatable by most conventional antibiotics. It is unsurprising that the first case of XDR-TB in Singapore was imported, but it is greatly worrying that the patient was highly infectious (AFB 4+) when she travelled and presented here. The WHO recommends that people who have drug-resistant TB avoid traveling on any commercial flights or public transportation, and the physician has the responsibility to convey this critical information to the patient.[20] It is probable that lapses occurred in this case. It is highly likely that such lapses will occur again unless strict action is taken by the regulators from both the Ministry of Health and those promoting medical tourism. The Ministry of Health has taken proactive steps to prevent the travel of individuals with active tuberculosis both into and out of Singapore in line with WHO's recommendations. The commercial forces promoting medical tourism in our country need to be regulated at a national level to curb the transmission of potentially lethal infectious diseases within our borders, lest we pay the price. It is simply not worth it.

REFERENCES

1. Osler W. Medicine in the Nineteenth Century. London: H K Lewis, 1904.
2. Controlled trial of intermittent regimens of rifampicin plus isoniazid for pulmonary tuberculosis in Singapore: Singapore Tuberculosis Service/ British Medical Research Council. Lancet 1975;306:1105-9.
3. Weltman AC, DiFerdinando GT Jr, Washko R, Lipsky WM. A death associated with therapy for nosocomially acquired multidrug-resistant tuberculosis. Chest 1996;110:279-81.
4. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282:677-86.
5. Dye C, Williams BG. The population dynamics and control of tuberculosis. Science 2010;328:856-61.
6. Cutter J, Wang YT. Tuberculosis - an under-appreciated disease. Ann Acad Med Singapore 2010;39:261-2.
7. Wright A, Zignol M, Van Deun A, Falzon D, Gerdes SR, Feldman K, et al. Epidemiology of antituberculosis drug resistance 2002-07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Lancet 2009;373:1861-73.
8. Global Tuberculosis Control 2010. World Health Organisation, 2010. Available at: http://www.who.int/tb/publications/global_report/2010/gtbr10_main.pdf. Accessed 16 February 2011.
9. Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 2008;359:563-74.
10. Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. Am J Respir Crit Care Med 2010;181:80-6.
11. Low S, Ang LW, Cutter J, James L, Chee CB, Wang YT, et al. Mortality among tuberculosis patients on treatment in Singapore. Int J Tuberc Lung Dis 2009;13:328-34.
12. Keshavjee S, Gelmanova IY, Pasechnikov AD, Mishustin SP, Andreev YG, Yedilbayev A, et al. Treating multidrug-resistant tuberculosis in Tomsk, Russia: developing programs that address the linkage between poverty and disease. Ann N Y Acad Sci 2008;1136:1-11.
13. Multidrug and extensively drug-resistant TB (M/XDR-TB) 2010 World Health Organisation, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf. Accessed 16 February 2011.
14. Koul A, Arnoult E, Lounis N, Guillemont J, Andries K. The challenge of new drug discovery for tuberculosis. Nature 2011;469:483-90.
15. Multidrug-resistant pulmonary tuberculosis in Singapore, 2000-2006. In: Epidemiological News Bulletin: Ministry of Health, Singapore, 2007.
16. Escombe AR, Oeser CC, Gilman RH, Navincopa M, Ticona E, Pan W, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med 2007;4:e68.
17. International patients guide at Tan Tock Seng Hospital. Available at: http://www.ttsh.com.sg/IPLC/ Accessed 16 February 2011.
18. Patients Services at Singapore General Hospital. Available at: http://www.sgh.com.sg/Patient-Services/Overseas_Referral/Pages/overseas-referral-overview.aspx Accessed 16 February 2011.
19. International Patient Liaison Centre at National University Hospital Available at: http://www.nuh.com.sg/iplc/patients-and-visitors/singapore.html Accessed 16 February 2011.
20. Tuberculosis and Air Travel. World Health Organisation, 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547505_eng.pdf. Accessed 16 February 2011.