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# The imminent threat of multidrug-resistant tuberculosis in Singapore

*Cynthia Bin-Eng Chee*[1], MBBS, FRCP, *Kyi Win KhinMar*[1], MBBS, MMed, *Jeffery Cutter*[2], MMed, FAMS, *Yee Tang Wang*[1], MBBS, FRCP

Man has battled tuberculosis (TB) for centuries. The discovery of streptomycin in the 1940s and that of rifampicin in the 1960s, which heralded the era of short-course chemotherapy, had raised hope that this ancient enemy would at last be conquered. This optimism was short-lived, with the global emergence of multidrug-resistant (MDR)-TB (defined as resistant to at least rifampicin and isoniazid, the two key drugs in short-course chemotherapy) in the 1980s, followed by that of extensively drug-resistant (XDR)-TB (defined as MDR strains resistant to any fluoroquinolone and any second-line anti-TB injectable agent) in the early 21st century.[1] Drug-resistant TB is a man-made phenomenon created by weak TB control programmes, where the lack of laboratory capacity, prescription of inappropriate treatment regimens, interrupted or poor-quality drug supplies and treatment non-adherence have led to the generation and amplification of drug-resistance. The World Health Organization (WHO) estimated that 390,000–500,000 MDR-TB cases emerged globally in 2008, and that among all incident TB cases, 3.6% were estimated to have MDR-TB.[2] Only 7% of the estimated MDR-TB cases are actually reported, and far less (1%) receive treatment according to international guidelines.[2]

Treatment of MDR-TB and XDR-TB requires at least 20 months of highly toxic and costly medications.[3] The reported treatment success rate for MDR-TB is about 60% and that for XDR-TB about 30%.[2,4] The drug cost for a full course of treatment for an MDR-TB patient is ≥ 50 times higher than that for a drug-susceptible patient. In Singapore, this may range from S$5,000.00 for a patient who is resistant only to rifampicin and isoniazid to S$50,000.00 for an XDR-TB patient. Taking into account the cost of laboratory investigations, medical consultation, air-borne isolation and surgery, the cost to treat an XDR-TB patient (without guarantee of success) easily exceeds S$100,000.00.[5] It is clear that the economic and social cost of MDR-TB/XDR-TB is a burden that any country can ill-afford, particularly in the midst of the current global economic crisis.

TB is notifiable by Singapore law. Singapore is fortunate to have two mycobacteriology laboratories with the capacity to perform routine drug-susceptibility testing (DST) to first-line TB drugs (streptomycin, rifampicin, isoniazid and ethambutol) for all patients with positive TB isolates, and second-line DST to kanamycin, ethionamide and ofloxacin for patients with isolates that are resistant to isoniazid and/or rifampicin. Both laboratories are electronically linked to the Singapore TB Elimination Programme (STEP) Notification Registry, enabling the total capture and monitoring of the drug-resistance spectrum of all culture-positive TB patients in the country.

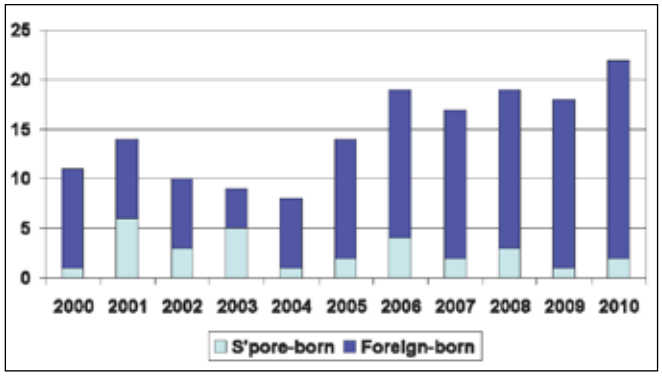


**Fig. 1** Graph shows the number of new and previously treated pulmonary MDR-TB cases by birth status (local or foreign-born) over the period 2000–2010.

There were 161 pulmonary MDR-TB cases (106 primary and 55 previously treated) reported to the STEP Registry from 2000 to 2010. Of these, 30 (19%) occurred among local-born patients. During this period, an additional 13 pulmonary TB cases that were initially drug-susceptible or isoniazid-resistant developed MDR-TB during their course of treatment (these cases are not included in the data presented in this paper). Among Singapore-born pulmonary TB cases, the incidence of MDR-TB among new and previously treated cases was 0.2% and 1.3%, respectively. Since 2004, the number of new and previously treated MDR-TB cases among the local-born has remained low (less than five cases per year) (Fig. 1). This is likely due to the use of Directly Observed Therapy (DOT) for the treatment of the majority of pulmonary TB cases in Singapore under STEP. As at October 2011, XDR-TB had yet to be reported in our local population. The vast majority (81%) of pulmonary MDR-TB cases diagnosed in Singapore have been among the foreign-born, with a doubling in the number of cases per year for the last five years compared to the first half of the decade (Fig. 1). This is not entirely surprising, as Singapore had liberalised its immigration policy in 2005. This, together with rapid economic growth, resulted in an influx of immigrants and their dependants, migrant workers and students from surrounding

[1]TB Control Unit, Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore, [2]Ministry of Health, Singapore
**Correspondence**: Dr Cynthia BE Chee, Senior Consultant, TB Control Unit, Department of Respiratory and Critical Care Medicine, 144 Moulmein Road, Singapore 308089. cynthia_chee@ttsh.com.sg

**Table I. Number and incidence of primary and previously treated pulmonary MDR-TB cases by country of birth in 2000–2010.**

| Country of birth | No. of cases | | | | |
|---|---|---|---|---|---|
| | New culture-positive pTB | New MDR-TB (%) | Previously treated culture-positive pTB | Previously treated MDR-TB (%) | Total MDR-TB (%) |
| Indonesia | 1,438 | 30* (2.2) | 84 | 28** (33.3) | 58 (3.8) |
| Myanmar | 311 | 25 (8.0) | 28 | 5 (17.9) | 30 (8.8) |
| China | 798 | 18¶ (2.3) | 130 | 3 (2.3) | 21 (2.2) |
| Philippines | 420 | 6 (1.4) | 9 | 1 (11.1) | 7 (1.6) |
| Vietnam | 68 | 3† (4.4) | 2 | 1 (50.0) | 4 (5.7) |
| India | 427 | 3 (0.7) | 6 | 1 (16.7) | 4 (0.9) |
| Bangladesh | 136 | 1 (0.7) | 3 | 1 (33.3) | 2 (1.4) |
| Malaysia | 980 | 3 (0.3) | 76 | 1 (1.3) | 4 (0.4) |
| Singapore | 8,050 | 16 (0.2) | 1,110 | 14 (1.3) | 30 (0.3) |

XDR-TB: *n = 2, **n = 2, ¶n = 1, †n = 1
pTB: pulmonary tuberculosis; MDR-TB: multidrug resistant tuberculosis; XDR: exclusively drug-resistant tuberculosis

high TB-incidence countries. Singapore's position as a medical hub has also attracted medical tourists seeking medical consultation and treatment for MDR-TB/XDR-TB, or for chronic respiratory symptoms, which in some cases, have turned out to be pulmonary MDR-TB/XDR-TB.

Among notified cases of pulmonary TB in Singapore between 2000 and 2010, the highest number of MDR-TB cases (new and previously treated) originated from Indonesia (n = 58), followed by Myanmar (n = 30) and China (n = 21) (Table I). The highest proportion of new (i.e. primary) pulmonary MDR-TB occurred among cases from Myanmar (8%), followed by Vietnam (4.4%), China (2.3%) and Indonesia (2.2%). Among previously treated cases, the highest proportion occurred among those from Vietnam (50%), followed by Indonesia (33%), Bangladesh (33%), Myanmar (18%) and India (17%). Although 50% of MDR-TB cases among the foreign-born were short-term social visitors (medical tourists mainly from Indonesia), a fair proportion were work permit holders/applicants (18%) and newly inducted citizens/permanent residents (PRs) (14%) (Fig. 2). To date, there have been six XDR-TB cases diagnosed in Singapore; four from Indonesia, one from Vietnam and one from China. Four cases were reported as primary XDR-TB and two as previously treated cases. Of concern, we have observed that the majority of primary MDR-TB cases from Myanmar and China have had high-grade drug-resistance (i.e. resistance to all first-line drugs, including pyrazinamide) (data not shown).

Has transmission of MDR-TB occurred within Singapore? To answer this question, DNA fingerprinting of isolates needs to be performed. In the past, primary MDR-TB cases among the Singapore-born have occurred mostly among those with a history of frequent travel to, or long-term residence in high MDR-TB prevalence countries. However, a teenager who did not travel out of the country and who had no known exposure to any person with MDR-TB was diagnosed with high-grade MDR-TB in 2011. This is a worrisome signal that MDR-TB transmission has likely occurred within the country.

Tremendous effort and resources are required to diagnose and treat MDR-TB/XDR-TB, as well as to prevent its spread.

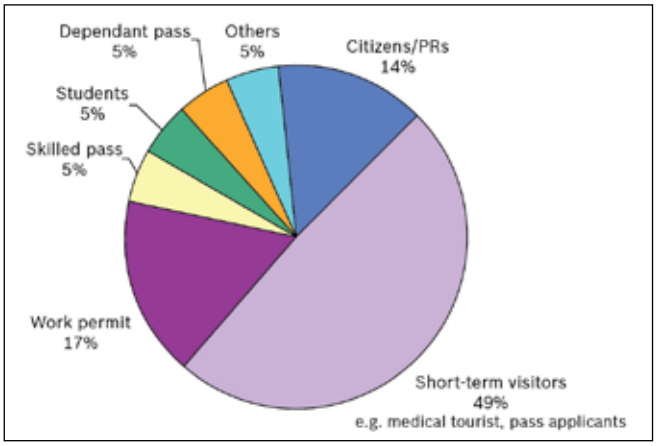


**Fig. 2** Pie chart shows the distribution of foreign-born pulmonary MDR-TB cases by immigration status.

These activities, while essential, must not divert attention or drain resources away from the management of drug-susceptible cases. It is vital to prevent the emergence of rifampicin and isoniazid resistance in the first place through successful treatment of drug-susceptible cases under DOT. In the era of XDR-TB, it is also just as vital to prevent the development of resistance to fluoroquinolones, which are key second-line drugs in MDR-TB treatment regimens. Moxifloxacin also has the potential to be included in future first-line TB regimens to shorten the duration of chemotherapy.[6] In intermediate/high TB burden settings, the liberal and injudicious use of fluoroquinolones for respiratory tract infections or acute exacerbations of chronic obstructive pulmonary disease may result in inadvertent monotherapy of persons with undiagnosed TB. This would not only lead to the emergence of fluoroquinolone-resistant strains,[7] but would also mask or delay TB diagnosis, resulting in increased morbidity and prolonged duration of infectiousness. National policies and guidelines to prevent the misuse of fluoroquinolones in TB endemic countries are urgently needed.[8]

In today's highly interconnected and globalised world, it will be only a matter of time before the MDR-TB rate increases and XDR-TB emerges in the local-born population. History has shown that new diagnostic tools and drugs, although desperately needed, have not been able to defeat this ancient scourge of man. Even

more vital are strong public health and TB control measures (which may be against the personal interests of individual patients and physicians) to safeguard the use and prevent the misuse of existing tools and drugs. The prevention of MDR-TB/XDR-TB is much more palatable than its cure. We must spare no effort in this task, before it is too late.

**ABSTRACT** The global emergence of multidrug-resistant (MDR) tuberculosis (TB) and extensively drug-resistant (XDR)-TB threatens to derail the efforts of TB control programmes worldwide. From 2000 to 2010, 161 pulmonary MDR-TB cases (including six XDR-TB cases) were reported in Singapore, and of these, 80% occurred among the foreign-born, with an increasing trend seen after 2004. Among new pulmonary TB cases, the highest incidence of MDR-TB occurred among patients from Myanmar (8%), followed by Vietnam (4.4%) and China (2.3%), while among those previously treated, the highest incidence was found in patients from Vietnam (50%), followed by Indonesia (33%) and Bangladesh (33%). Although the proportion of Singapore-born pulmonary TB cases with MDR-TB has remained comparatively low (0.2% and 1.3% in new and previously treated cases, respectively), there is no room for complacency. Top priority must be accorded toward the proper treatment of drug-susceptible TB cases under strict programme conditions so as to prevent the development of MDR-TB in the first place.

*Keywords: extensively drug-resistant-TB, foreign-born, multidrug-resistant-TB, Singapore, TB programme*
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## ENDNOTE

Since the acceptance of this article for publication, MDR-TB transmission has been documented from a foreign-born source case to two local-born Singaporeans.

## REFERENCES

1. Gandhi NR, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet 2010; 375:1830-43.
2. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. In: Geneva, World Health Organization, 2010 [online]. Available at: whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf. Accessed March 28, 2012.
3. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update. In: Geneva, World Health Organization, 2011 [online]. Available at: whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf. Accessed March 28, 2012.
4. Kim DH, Kim HJ, Park SK, et al. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. Am J Respir Crit Care Med 2008; 178:1075-82.
5. Phua CK, Chee CB, Chua AP, et al. Managing a case of extensively drug-resistant (XDR) pulmonary tuberculosis in Singapore. Ann Acad Med Singapore 2011; 40:132-5.
6. Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. Lancet 2009; 373:1183-9.
7. Devasia RA, Blackman A, Gebretsadik T, et al. Fluoroquinolone resistance in Mycobacterium tuberculosis: the effect of duration and timing of fluoroquinolone exposure. Am J Respir Crit Care Med 2009; 180:365-70.
8. Chiang CY. State of the Art series on drug-resistant tuberculosis: it's time to protect fluoroquinolones. Int J Tuberc Lung Dis 2009; 13:1319. Comment on: Int J Tuberc Lung Dis 2009; 13:1320-30.