TUBERCULOSIS IN AUSTRALIA: BACTERIOLOGICALLY CONFIRMED CASES AND DRUG RESISTANCE, 2007

A report of the Australian Mycobacterium Reference Laboratory Network

Richard Lumb, Ivan Bastian, Robyn Carter, Peter Jelfs, Terillee Keehner, Aina Sievers

Abstract

The Australian Mycobacterium Reference Laboratory Network collects and analyses laboratory data on new cases of disease caused by the *Mycobacterium tuberculosis* complex. In 2007, a total of 872 cases were identified by bacteriology; an annual reporting rate of 4.1 cases per 100,000 population. Isolates were identified as *M. tuberculosis* (n = 867), *M. africanum* (n = 4) and *M. bovis* (n = 1). Fifteen children aged under 10 years had bacteriologically-confirmed tuberculosis. Results of *in vitro* drug susceptibility testing were available for 871 of 872 isolates for isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). A total of 98 (11.3%) isolates of *M. tuberculosis* were resistant to at least one of these anti-tuberculosis agents. Resistance to at least H and R (defined as multi-drug resistance, MDR) was detected in 24 (2.8%) isolates, all from overseas-born patients; 17 were from the respiratory tract (sputum n=16, endotracheal aspirate n=1). Thirteen patients with MDR-TB were from the Papua New Guinea–Torres Strait Islands zone. Of the 98 *M. tuberculosis* isolates resistant to at least one of the standard drugs, 54 (55.1%) were from new cases, 9 (9.2%) from previously treated cases, and no information was available on the remaining 35 cases. Seven were Australian-born, 90 were overseas- born, and the country of birth of 1 was unknown. Of the 90 overseas-born persons with drug resistant disease, 66 (73.3%) were from 5 countries: India (n=16); Papua New Guinea (n=15); the Philippines (n=12); Vietnam (n=12); and China (n=11). No XDR-TB was detected in 2007. *Commun Dis Intell* 2009;33(3):298–303.

Keywords: *Mycobacterium tuberculosis, Mycobacterium bovis*, laboratory diagnosis, drug resistance

Introduction

Australia continues to record one of the lowest notification rates (5–6 cases per 100,000 population) of tuberculosis (TB) in the world. Australian TB services continue to ensure that treatment success rates remain high, there are low rates of relapse, a complete absence of treatment failure cases and a low case fatality rate.[1,2] Drug resistant TB has emerged as a global problem that threatens TB control programs in many countries. Drug resistance is mainly associated with people born in high-burden TB countries within the Western Pacific and South East Asia regions.[3,4] Multidrug-resistant TB (MDR-TB) (resistance to at least isoniazid and rifampicin) has remained low in Australia, although the 2.4% reported in 2006 was the highest recorded figure since data collection began in 1986.[5]

There are 2 sources of TB-related data for Australia. Since 1991, the National Notifiable Diseases Surveillance System (NNDSS) has provided statistics on TB notifications reported to public health authorities in Australia's states and territories. The Australian Tuberculosis Reporting Scheme has been conducted by the Australian Mycobacterium Reference Laboratory Network (AMRLN) since 1986. Statistics compiled by the AMRLN relate to cases of bacteriologically-confirmed tuberculosis, whereas NNDSS data also include cases that are identified on the basis of clinical and epidemiological information, or on non-bacteriological laboratory investigations. This report describes the bacteriologically-confirmed TB diagnoses for the year 2007.

Methods

The data are based on clinical specimens that were culture-positive for *Mycobacterium tuberculosis* complex (MTBC). Although the bacille Calmette-Guérin strain of *Mycobacterium bovis* is a member of the MTBC, no information on this organism is included in the present report. Almost all isolates of MTBC were referred to one of the 5 laboratories comprising the AMRLN for species identification and drug susceptibility testing. Comparable methodologies are used in the reference laboratories. Relapse cases, as defined by the *National Strategic Plan for TB Control in Australia Beyond 2000* prepared by the National TB Advisory Committee,[6] were included in the laboratory data as laboratories are generally unable to differentiate relapse cases from new cases.

Data include temporary visitors to Australia, illegal immigrants, or persons detained in Australia in correctional services facilities, and asylum seekers. For each new bacteriologically-confirmed case, the following information was collected where available: demography: patient identifier, age, sex, HIV status

and state of residence; specimen: type, site of collection, date of collection and microscopy result; isolate: *Mycobacterium* species and results of drug susceptibility testing; nucleic acid amplification testing results; and for drug resistant isolates: patient country of origin, and history of previous TB treatment to determine whether resistance was initial or acquired. Data from contributing laboratories were submitted in standard format to the AMRLN coordinator for collation and analysis. Duplicate entries (indicated by identical patient identifier and date of birth) were deleted prior to analysis. Rates were calculated using mid-year estimates of the population for 2007 supplied by the Australian Bureau of Statistics.[7] For each case, the nature of the first clinical specimen that yielded an isolate of MTBC was used to record the nominal site of disease. Culture-positive specimens collected at bronchoscopy or by gastric lavage were counted as pulmonary disease. Patients with isolates recovered from multiple sites were counted as pulmonary disease (the most important category for public health purposes) if a sputum, bronchoscopy, or lung biopsy specimen was culture positive.

Drug resistance among new cases (proxy for primary resistance) was defined as the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, denied having received any prior anti-TB treatment (for more than 1 month) and, in countries where adequate documentation is available, for whom there is no evidence of such a history.[8] Drug resistance among previously treated cases (proxy for acquired resistance) is defined as the presence of resistant isolates of *M. tuberculosis* in cases who, in response to direct questioning, admit having been treated for 1 month or more or, in countries where adequate documentation is available, for whom there is evidence of such a history.[8]

Results

There were 872 bacteriologically-confirmed cases of tuberculosis in 2007, representing an annual rate of 4.1 cases per 100,000 population. State-specific reporting rates varied from 1.6 (Tasmania) to 15.4 (Northern Territory) cases per 100,000 population (Table 1).

Causative organism

Almost all isolates were identified as *M. tuberculosis* (n=867), the remaining isolates being *Mycobacterium africanum* (n=4) and *Mycobacterium bovis* (n=1).

Distribution by sex, age and site of disease

Complete information for sex and age was available for 863 (99.0%) patients. Of the 863 MTBC isolates, 402 (46.6%) were from females, 461 (53.4%) were from males, and sex was not recorded for 9 cases. The site of disease was dependent upon age and sex. The overall male:female ratio was 1.15:1. For respiratory isolates, the male:female ratio was 1.24:1. For TB lymphadenitis, the male:female ratio was 1:1.5. For males, there were 2 distinct peak age groups in bacteriologically-confirmed rates: a rise to 10.9 cases of TB per 100,000 population at 25–29 years and a second peak in elderly males aged 75 years or over (up to 12.2 cases of TB per 100,000 population). The age distribution of female cases was similar with 9.5 and 6.9 bacteriologically-confirmed TB cases per 100,000 population at the 25–29 and >84 year age groups, respectively. The median age group for patients with bacteriologically-confirmed disease was 35–39 years for both males and females. The predominant culture-positive specimen type was sputum (n=393, 45.1%); a further 132 (15.1%) were obtained from bronchoscopy, 10 were aspirates, 8 were from lung biopsies, and a single specimen of pus (Table 2). Fifty-two pleural specimens

Table 1: Bacteriologically confirmed cases of tuberculosis, Australia, 1997 and 2005 to 2007, cases and rate per 100,000 population, by state or territory

State or territory	2007		2006*		2005*		1997*	
	n	Rate	n	Rate	n	Rate	n	Rate
New South Wales†	343	5.0	342	4.8	346	4.9	329	5.0
Victoria	279	5.4	263	5.2	261	5.2	193	4.2
Queensland	118	2.8	120	3.0	91	2.3	74	2.2
Western Australia	45	2.1	93	4.5	42	2.1	51	2.8
South Australia	46	2.9	51	3.3	36	2.3	39	2.6
Tasmania	8	1.6	9	1.8	10	2.1	8	1.8
Northern Territory	33	15.4	27	12.9	24	11.9	28	15.0
Total	872	4.1	905	4.4	810	4.0	722	3.9

* Data from previous reports of the Australian Mycobacterium Reference Laboratory Network.

† Data from the Australian Capital Territory are included with those from New South Wales.

(36 fluid, 16 biopsy/tissue) were culture positive. The most commonly encountered extrapulmonary culture-positive specimen was lymph tissue (n=175, 20.0%) followed by pleural (n=52, 6.0%), peritoneal (n=28, 3.2%), bone/joint (n=26, 3.0%), and genitourinary tract (n=13, 1.5%).

Fifteen children aged under 10 years (male n=9, female n=6) had bacteriologically-confirmed tuberculosis (sputum n=4, gastric aspirate n=3, lymph node n=3, oropharyngeal aspirate n=2, and one each from pleural, cerebrospinal fluid, and pus).

Association with HIV

The AMRLN database recorded the HIV status of only 48 (5.5%) patients. No patient was identified as HIV-seropositive.

Table 2: Site of specimens smear– and culture-positive for Mycobacterium tuberculosis complex, 2007

	n*	Smear positive (%)*
Sputum	393	211 (54.8)
Bronchoscopy	128	46 (35.9)
Lymph node	175	33 (18.9)
Pleural	52	2 (3.8)†
Genito-urinary	13	‡
Bone/joint	26	‡
Peritoneal	28	‡
Skin	0	‡
Cerebrospinal fluid	7	‡

* Based on specimens that reported a microscopy result and excludes (i) microscopy not performed or (ii) result unknown.

† One pleural biopsy and 1 pleural fluid was smear positive.

‡ Percentage of specimens smear positive not calculated due to the small number of cases.

Microscopy

Of the 872 bacteriologically-confirmed cases in 2007, the results of microscopy were available for 851 (97.6%); microscopy was not performed on 5 specimens and no result was provided for the remaining 16 specimens. Smears were positive in 211 of 393 (53.7%) sputum and 46 of 128 (35.9%) bronchoscopy specimens respectively (Table 2). Of 52 pleural specimens (16 biopsy and 36 fluids) that were culture-positive for *M. tuberculosis*, only 1 biopsy and 1 fluid was smear-positive. Lymph node specimens were smear-positive in only 33 of 175 (18.9%) cases.

Drug susceptibility testing

Results of *in vitro* drug susceptibility testing were available for 871 of 872 isolates for isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). A total of 98 (11.3%) isolates of *M. tuberculosis* were resistant to at least one of these anti-tuberculosis agents. Resistance to at least H and R (defined as MDR) was detected in 24 (2.8%) isolates (Table 3). All of the MDR isolates were *M. tuberculosis*. Of the 24 MDR-TB isolates, 18 were from the respiratory tract (sputum n=17, endotracheal aspirate n=1), lymph node (n=5) and a single isolate from pleural tissue. Eleven of the MDR-TB-positive sputum specimens were smear-positive, as were single samples from lymph node and pleural tissue.

None of the MDR-TB cases were extensively drug resistant resistant-TB (XDR-TB). The revised definition of XDR-TB is an isolate that has resistance to at least isoniazid and rifampicin (MDR-TB) plus additional resistance to a fluoroquinolone and an injectable (kanamycin, amikacin, capreomycin).[8] In 2007, one of the 24 MDR-TB isolates also had resistance to ofloxacin, and another MDR-TB isolate had resistance to amikacin.

Table 3: Drug resistance patterns in multi-drug resistant strains, Australia, 1995 to 2007

Resistance pattern (standard drugs)*	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996	1995
H+R only	16	16	5	7	4	8	8	3	2	2	6	10	3
H+R+E	2	1	3	2	2	1	1	1	1	1	1	1	1
H+R+Z	5	0	1	1	1	1	3	3	1	2	5	4	1
H+R+E+Z	1	5	3	2	0	2	0	1	0	1	2	0	0
XDR-TB	0	0	0	1	0	0	0	0	0	0	0	0	0
Total	24	22	12	12†	7	12	12	8	4	6	14	15	5
(%)	(2.8)	(2.4)	(1.5)	(1.5)	(0.9)	(1.7)	(1.6)	(1.0)	(0.5)	(0.9)	(1.9)	(2.0)	(0.7)

* The streptomycin result was not considered for this table.

† Excludes the 1 extensively drug-resistant strain (XDR-TB), which was included in the multi-drug resistant strains.

H = isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinimide.

Thirteen patients with MDR-TB were from the Papua New Guinea (PNG) – Torres Strait Islands (TSI) cross-border region who access health services in outer TSI and are eligible to receive treatment in Australia. MDR-TB was also isolated from patients born in India (n=4), China (n=3), and Vietnam (n=2), with a single case each from Timor Leste and Sierra Leone. The impact of MDR-TB arising from the PNG-TSI zone is demonstrated in the Figure. In the past 3 years (2005–07), the impact of MDR-TB cases from the PNG-TSI zone has lifted the proportion of MDR-TB cases above the 0.5%–2.0% range.

Mono-resistance to isoniazid (H) was detected in 52 isolates, with some mono-resistance to rifampicin (n=3) and to ethambutol (n=3) There was no mono-resistance to pyrazinamide (Z). Ninety-two isolates demonstrated resistance to H at a concentration of 0.1 mg/L. Of these, 44 (47.8%) demonstrated resistance to H at the higher level of 0.4 mg/L. Among MDR-TB strains, 13/24 (54.2%) demonstrated H resistance at the higher concentration (0.4 mg/L). Forty-one of 98 (41.8%) specimens culture-positive for drug resistant strains, including 30 of 56 (53.6%) sputum or bronchoscopy specimens, were smear-positive for acid-fast bacilli. The single *M. bovis* isolate, which is inherently Z-resistant, was not included in the above results.

Results of testing for streptomycin (S) were available for 259 of 871 (29.7%) isolates with 36 demonstrating resistance to at least S; 7 had mono-resistance, 11 were resistant to S and H, and 18 MDR-TB strains were also S-resistant.

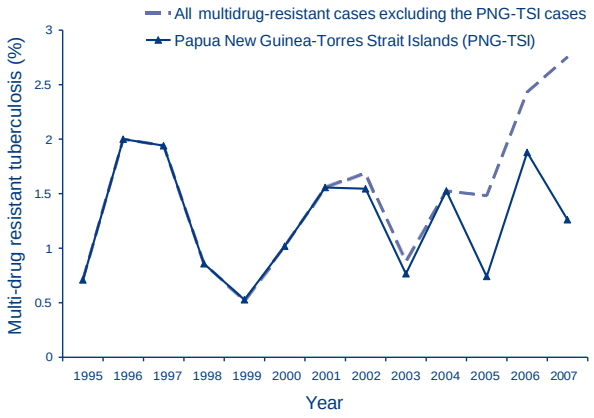
New or previously treated cases, and country of birth

Of the 98 *M. tuberculosis* isolates resistant to at least one of the standard drugs, 54 (55.1%) were from new cases, 9 (9.2%) from previously treated cases, and no information was available on the remaining 35 cases. Seven were Australian-born, 90 were overseas-born, and the country of birth of one was unknown. The 90 overseas-born persons with drug resistant disease were from 21 countries; 66 (73.3%) were from 5 countries; India (n=16), Papua New Guinea (n=15), the Philippines (n=12), Vietnam (n=12), and China (n=11).

Discussion

In 2007, there were 872 cases of bacteriologically-confirmed tuberculosis representing 4.1 cases per 100,000 population, a similar rate to that found in 2006 and consistent with the results dating back to 1986.[5,9] *M. tuberculosis* was the predominant species reported with only 4 isolates of *M. africanum* and 1 strain of *M. bovis* identified in 2007 respectively.

Figure: Percentage of multi-drug resistant tuberculosis in Australia: the impact of cases from the Papua New Guinea–Torres Strait Island zone



For 2007, the NNDSS reported 1,183 notifications, a difference between the 2 datasets of 311 (26.3%) cases.[1] The NNDSS has consistently recorded a higher number of notifications, typically in the range of 20%–30%, than the AMRLN dataset.

The level of drug resistance in *M. tuberculosis* isolates remains at a relatively constant level; excluding resistance to streptomycin, 11.3% of strains had resistance to one or more anti-tuberculosis drugs. This finding is at the high end of the range 7.4%–11.0% for resistance to one or more anti-tuberculosis drugs for the years 2000–2006. Most cases with drug-resistant strains occurred in the overseas-born as observed in previous years.

There is increasing concern regarding the rise in the proportion of bacteriologically confirmed cases with MDR-TB. During the years 1995 to 2005, the level of MDR-TB has averaged 1.3% and stayed within a range of 0.5%–2.0%. However, in the past 2 years, the proportion of MDR-TB isolates has risen from 1.5% in 2005 to 2.4% and 2.8% for years 2006 and 2007 respectively.[5,9] A substantial contributor has been from the movement of persons across the PNG–TSI zone with TB being diagnosed and then managed within Australia's borders.[10] When the 13 MDR-TB cases from PNG–TSI region are excluded and the MDR-TB percentages adjusted, the MDR-TB rates fall to 0.7% (2005), 1.9% (2006), and 1.3% (2007) respectively.[5,9] These revised figures lie within the long-standing range of 0.5%–2.0% for the bacteriologically confirmed cases of MDR-TB in Australia.

Although the population movement in the PNG–TSI zone is relatively small, the financial and epidemiological implications for the Queensland TB services and for the Commonwealth are substantial. The implications for the PNG government are equally

obvious. The emergence of MDR-TB, in apparently increasing numbers, bodes ill for PNG and highlights critical weaknesses in their TB control program. The World Health Organization (WHO) estimates that more than 900 MDR-TB cases occurred in PNG in 2006, including 563 among new TB cases and 352 cases among retreatment cases.[3] At present, the MDR-TB strains from PNG–TSI patients remain susceptible to second-line TB drugs and no XDR-TB has been identified, yet.

The WHO estimated that 489,139 new cases of MDR-TB emerged in 2006, and that the global proportion of MDR-TB among all cases was 4.8%. China and India account for almost 50% of the global burden with the Russia Federation contributing a further 7%.[8] Where there is MDR-TB, XDR-TB will also be lurking because XDR-TB is promoted by the same deficiencies in TB control programs and suboptimal care. Some 41 countries have already reported XDR-TB within their borders[11]and there are countries yet to formally report the presence of XDR-TB within their borders. Drug-resistant TB has emerged independently in all countries treating TB, and the emergence of MDR-TB is merely the stepwise accumulation of mutations for drug resistance to anti-TB drugs in a single TB organism that then amplifies and spreads. XDR-TB is a logical extension whereby MDR-TB has acquired mutations for resistance to fluoroquinolones (FQ) and injectable agents, the 2 most effective second-line drug groups for the management of MDR-TB.[12]

Many low-income countries, such as PNG, do not have ready access to laboratory culture and drug susceptibility testing facilities. Australian laboratories can provide sentinel data for these countries through the testing of their ex-patriate migrants and refugees who develop TB after arrival in Australia. India, PNG, the Philippines, Vietnam, and China accounted for nearly three-quarters of the drug-resistant cases occurring in Australia in 2007. Our experience mirrors a WHO report on TB in the Western Pacific region which estimated that China, Vietnam and the Philippines account for almost 98% of the MDR-TB cases in the region in 2006 (i.e. 82,087 new and 70,601 retreatment cases).[3]

Another worrying international phenomenon of which Australian healthcare professionals must be aware is 'pre-XDR-TB' (MDR-TB with resistance to either a fluoroquinolone or second-line injectable agent but not both).[13] Two such isolates were recognised in Australia in 2007: 1 MDR-TB strain resistant to ofloxacin, and another MDR-TB isolate was resistant to amikacin. Pre-XDR-TB is more commonly encountered than XDR-TB. An increasing incidence of FQ-resistant MDR-TB is occurring globally and represents a dangerous threat to TB control programs. For example, an Indian study from a tertiary care hospital and a referral centre in Mumbai for non-responding TB cases, determined that the proportion of *M. tuberculosis* isolates with FQ-resistance had risen from 2.6% in 1996 to 35.2% in 2004. Unfortunately, the proportion of MDR-TB with FQ-resistance was not documented although the proportion of isolates being MDR-TB had risen from 26.5% to 56.5% in the years 1996–2004 respectively.[14] High rates of quinolone resistance and pre-XDRTB have also been reported from the Philippines and China, and among foreign-born persons and recent migrants in California.[13,15,16] The increasing rates of quinolone resistance have been attributed to their wide use as first-line agents for community-acquired infections or in ineffective regimens for failed TB treatment in these countries.[17] Banerjee et al reported that the cost of inpatient treatment for a single XDR-TB case was US$600,000 in California.[13]

Fortunately, in Australia, access to FQs is restricted and fluoroquinolone use in TB cases is undertaken in a limited manner and with the benefit of drug susceptibilities performed by quality assured laboratories. In fact, all bacteriologically confirmed MDR-TB isolates and any rifampicin-resistant or multi-resistant strain of *M. tuberculosis* in Australia has second-line DST performed including against an FQ and an injectable agent. All 5 Australian Mycobacterium Reference Laboratories use the BACTEC MGIT 960 automated broth culture system for primary culture and DST for first-and second-line drugs. Recently-published WHO guidelines for second-line DST have highlighted that critical concentrations for kanamycin, cycloserine, *P*-aminosalicylic acid, thioacetazone, clarithromycin and clofazamine have not been determined for the MGIT 960 system, though, another recent study has suggested a breakpoint for kanamycin testing in a broth-based system.[18,19] Clinicians must desist from requesting laboratories to perform DST on the other second-line antibiotics listed above because the results are likely to be invalid.

The last AMRLN report mentioned that the NNDSS and AMRLN databases would be combined and a single report would describe the findings for 2007.[5] However, computing issues have confounded the roll-out of a standardised database and have lead to significant delays in several jurisdictions. A unified report will hopefully occur next year.

In conclusion, Australia remains the 'lucky country' in terms of TB incidence and level of drug resistance. The increasing number of MDR-TB cases from the PNG-TSI region has resulted in a rise in the proportion of isolates that are MDR-TB. After accounting for the influx of MDR-TB cases from PNG, the level of MDR-TB has remained stable within the 0.5%–2.0% band over the last decade. Although no XDR-TB was detected in 2007, and only 1 case has

been reported in the period 1986–2007, it is only a matter of time before further cases are identified. Importantly, 2 pre-XDR-TB isolates were identified in 2007. The AMRLN continues to be a vital part of the national TB control effort.

Acknowledgements

The Australian Mycobacterium Reference Laboratory Network comprises the Mycobacterium Reference Laboratories at the following facilities:

Microbiology and Infectious Diseases, SA Pathology

Queensland Health Pathology Services, Herston Hospitals Complex, Herston, Queensland

Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria

PathWest Laboratory Medicine WA – QEIIMC, Hospital Avenue, Nedlands, Western Australia

Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales

Additional information and support from Ms Amanda Christensen, Dr Ral Antic, Dr Vicki Krause, Ms Lynne Brown, Dr Anastasios Konstantinos, and Dr Justin Waring is gratefully acknowledged.

Author details

Richard Lumb[1,2]
Ivan Bastian[1,2]
Robyn Carter[2]
Peter Jelfs[2]
Terillee Keehner[2]
Aina Sievers[2]

1. Microbiology and Infectious Diseases, SA Pathology, Adelaide, South Australia
2. Australian Mycobacterium Reference Laboratory Network

Corresponding author: Mr Richard Lumb, Mycobacterium Reference Laboratory and WHO Supranational TB Reference Laboratory, Microbiology and Infectious Diseases, SA Pathology, PO Box 14, Rundle Mall, ADELAIDE SA 5000. Telephone: +61 8 8222 3579. Facsimile: +61 8 8222 3543. Email: richard.lumb@imvs.sa.gov.au

References

1. Barry C, Konstantinos A and the National Tuberculosis Advisory Committee. Tuberculosis notifications in Australia, 2007. *Commun Dis Intell* 2009;33(3):304–315.
2. Roche P, Krause V, Konstantinos A, Bastian I, et al. Tuberculosis notifications in Australia, 2006. *Commun Dis Intell* 2008;32(1):1–11.
3. World Health Organization. Tuberculosis control in the western pacific region. 2008 report. Available from: http://stoptb.wpro.who.int
4. World Health Organization. Tuberculosis in the south-east asian region. 2008 report. SEA-TB-302. Available from: http://stoptb.wpro.who.int
5. Lumb R, Bastian I, Gilpin C, Jelfs P, Keehner T, Sievers A. Tuberculosis in Australia: bacteriologically confirmed cases and drug resistance, 2006 A report of the Australian Mycobacterium Reference Laboratory Network. *Commun Dis Intell* 2008;32(1):12–17.
6. Communicable Diseases Network Australia. National Strategic Plan for TB Control in Australia Beyond 2000/ Commonwealth Department of Health and Ageing, Canberra, July 2002.
7. Australian Bureau of Statistics. Population by age and sex, regions of Australia. Canberra: Australian Bureau of Statistics; 2007. Report No: 3235.0.
8. World Health Organization. Anti-tuberculosis drug resistance in the world; fourth global report. QHO/HTM/TB/2008.394. Available from: www.who.int/tb
9. Lumb R, Bastian I, Gilpin C, Jelfs P, Keehner T, Sievers A. Tuberculosis in Australia: bacteriologically confirmed cases and drug resistance, 2005 A report of the Australian Mycobacterium Reference Laboratory Network. *Commun Dis Intell* 2007;31(1):80–86.
10. Gilpin CM, Simpson G, Vincent S, O'Brien TP, Knight TA, Globan M, et al. Evidence of primary transmission of multidrug-resistant tuberculosis in the western province of Papua New Guinea. *Med J Aust* 2008;188(3):148–152.
11. World Health Organization. XDR-TB. The facts. November 2007. Available from: www.who.int/tb
12. National Tuberculosis Advisory Committee. Multi-drug resistant tuberculosis. Information paper. *Commun Dis Intell* 2007;31(4):406–409.
13. Banerjee R, Allen J, Westenhouse J, Oh P, Desmond E, Nitta A, et al. Extensively drug-resistant tuberculosis in California, 1993–2006. *Clin Infect Dis* 2008;47(4):450–457.
14. Agrawal D, Udwadia ZF, Rodriguez C, Mehta A. Increasing incidence of fluoroquinolone-resistant *Mycobacterium tuberculosis* in Mumbai, India. *Int J TB Lung Dis* 2009;13(1):79–83.
15. Grimaldo ER, Tupasi TE, Rivera AB, Quelapio MID, Cardano RC, Derilo JO, et al. Increased resistance to ciprofloxacin and ofloxacin in multidrug-resistant *Mycobacterium tuberculosis* isolates from patients seen at a tertiary hospital in the Philippines. *Int J TB Lung Dis* 2001;5(6):546–550.
16. Sun Z, Chao Y, Zhang X, Zhang J, Li Y, Qiu Y, et al. Characterization of extensively drug-resistant *Mycobacterium tuberculosis* clinical isolates in China. *J Clin Microbiol* 2008;46(12):4075–4077.
17. Ginsberg AS, Hooper N, Parrish N, Dooley KE, Dorman SE, Booth J, et al. Fluoroquinolone resistance in patients with newly diagnosed tuberculosis. *Clin Infect Dis* 2003;37(11):1448–1452.
18. World Health Organization. Policy guidance on drug susceptibility testing of second-line anti-tuberculosis drugs WHO/HTM/TB/2008.392
19. Martin A, von Groll A, Fissette K, Palomino JC, Varaine F, Portaels F. Rapid detection of *Mycobacterium tuberculosis* resistance to second-line drugs by use of the manual mycobacterium growth indicator tube system. *J Clin Microbiol* 2008;46(12):3952–3956.