
TUBERCULOSIS IN AUSTRALIA: BACTERIOLOGICALLY CONFIRMED CASES AND DRUG RESISTANCE, 2005

A report of the Australian Mycobacterium Reference Laboratory Network

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Abstract

The Australian Mycobacterium Reference Laboratory Network (AMRLN) collects and analyses laboratory data on new cases of disease caused by the *Mycobacterium tuberculosis* complex. In 2005, a total of 810 cases were identified by bacteriology; an annual reporting rate of 4.0 cases per 100,000 population. Isolates were identified as *M. tuberculosis* (n=806), *Mycobacterium africanum* (n=2) and *Mycobacterium bovis* (n=2). Fifteen children aged under 10 years had bacteriologically-confirmed tuberculosis. Results of *in vitro* drug susceptibility testing were available for all 810 isolates for isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). A total of 74 (9.1%) 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 12 (1.5%) isolates; nine were from the respiratory tract (sputum n=8, bronchoscopy n=1). Of the 74 *M. tuberculosis* isolates resistant to at least

one of the standard drugs, 67 (90.5%) were from new cases, 6 from previously treated cases, and no information was available on the remaining case. Eight were Australian-born, 65 were overseas-born, and the country of birth of one was unknown. Of the 65 overseas-born persons with drug resistant disease, 41 (63.1%) were from 4 countries; Vietnam (n=16), Papua New Guinea (n=10), the Philippines (n=9), and India (n=6). A retrospective review of AMRLN data on isolates collected between 2000 and 2005 found that none of 70 MDR-TB isolates met the new definition for extensively drug resistant TB (XDR-TB, i.e. MDR-TB with additional resistance to quinolones and second-line injectable agents). *Commun Dis Intell* 2007;31:80–86.

Keywords: *Mycobacterium tuberculosis*, *Mycobacterium bovis*, laboratory diagnosis, tuberculosis, drug resistance, nucleic acid amplification test

Introduction

Australia continues to record one of the lowest notification rates (5–6 cases per 100,000 population) of tuberculosis (TB) in the world.¹ New Zealand experienced a long-term decline in TB notification rates until the mid-1980s when annual rates stabilised at around 10 cases per 100,000 population.² In contrast, TB has a large impact on the health of our regional neighbours in the World Health Organization (WHO) Regions of South East Asia (SEAR) and the Western Pacific (WPR).^{3,4} The SEAR, comprising 11 countries with a combined population of over 1.5 billion, has one-third of all annual cases worldwide. In 2005, there were an estimated 5.7 million prevalent cases of TB in the SEAR (351 cases per 100,000 population), of which almost three million were new cases (incidence rate of 190 cases per 100,000 population). Five countries, namely Bangladesh; India; Indonesia; Myanmar; and Thailand, accounted for almost 95% of all new cases.³ The WPR includes 37 countries with a combined population of over 1.7 billion. In 2004, there were an estimated 3.8 million prevalent cases of TB (216 cases per 100,000 population), of which almost 2 million were new cases (111 cases per 100,000 population). Three countries (China, the Philippines and Vietnam) accounted for approximately 90% of all estimated cases in the region.⁴

There are two 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 includes 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 2005.

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 five 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,⁵ 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 aliens 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 2005 supplied by the Australian Bureau of Statistics.⁶

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 one month) and, in countries where adequate documentation is available, for whom there is no evidence of such a history. 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 one month or more or, in countries where adequate documentation is available, for whom there is evidence of such a history.⁷

The participating laboratories were also asked to review their laboratory records for 2000–2005 to identify MDR-TB isolates that fulfilled the current definition for extensively drug resistant TB (XDR-TB, i.e. MDR-TB with additional resistance to a quinolone and to at least one of the second-line injectable agents: kanamycin, amikacin, capreomycin).

Results

There were 810 bacteriologically-confirmed cases of tuberculosis in 2005, representing an annual rate of 4.0 cases per 100,000 population. State-specific reporting rates varied from 2.1 (Tasmania and Western Australia) to 11.9 (Northern Territory) cases per 100,000 population (Table 1).

Causative organism

Almost all isolates were identified as *M. tuberculosis* (n=806), the remaining isolates being *Mycobacterium africanum* (n=2) and *Mycobacterium bovis* (n=2).

Distribution by gender, age and site of disease

Complete information for gender and age was available for 806 (99.5%) patients. Of the 810 MTBC isolates, 379 (47.0%) were from females, 427 (53.0%) were from males, and gender was unknown for 4 cases. Fifteen children aged under 10 years (male n=8, female n=7) had bacteriologically-confirmed tuberculosis (gastric aspirate n=8, lymph node n=3, pleural n=2, sputum n=1, nasopharyngeal aspirate n=1).

The site of disease was dependent upon age and gender. The overall male:female ratio was 1.1:1. For respiratory isolates, the male:female percentage was 1.5:1. For TB lymphadenitis, the female:male percentage was 2.1:1. For males, there were two distinct

peak age groups in bacteriologically-confirmed rates: a rise to 8.0 cases of TB per 100,000 population at 20–24 years and a second peak in elderly males aged more than 75 years (>9.9 cases of TB per 100,000 population). The age distribution of female cases was similar with 7.5 and 11.3 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 30–34 years for males and 35–39 years for females.

The predominant culture-positive specimen type was sputum (n=354, 43.7%); a further 103 (12.7%) were obtained from bronchoscopy, and 5 were from lung biopsies (Table 2). Forty-seven pleural specimens (29 fluid, 18 biopsy/tissue) were culture-positive. Of these 47 pleural specimens, only a single biopsy was smear-positive. The most commonly encountered extrapulmonary culture-positive specimen was lymph tissue (n=173, 21.4%) followed by pleural (n=47, 5.8%), peritoneal (n=24, 3.0%), bone/joint (n=24, 3.0%), and genitourinary tract (n=19, 2.3%).

Association with HIV

The AMRLN database recorded the HIV status of only 42 (5.2%) patients. No patient was identified as HIV-seropositive.

Microscopy

Results of microscopy were available for 790 of 810 (97.5%) of specimens; microscopy was not performed on 19 specimens and no result was provided for the remaining one specimen. Smears were positive in 189 of 354 (54.3%) sputum and 35 of 103 (34.3%) bronchoscopy specimens respectively (Table 2). Of 47 pleural specimens (18 biopsy and 29 fluids) that

Table 1. Bacteriologically-confirmed cases of tuberculosis in Australia, 1995 and 2003 to 2005, cases and rate per 100,000 population, by state or territory

State or territory	2005		2004*		2003*		1995*	
	n	Rate	n	Rate	n	Rate	n	Rate
New South Wales†	346	4.9	308	4.4	325	4.6	305	4.8
Northern Territory	24	11.9	21	10.5	20	10.1	37	21.3
Queensland	91	2.3	88	2.3	91	2.4	86	2.6
South Australia	36	2.3	43	2.8	36	2.4	33	2.2
Tasmania	10	2.1	8	1.7	4	0.8	2	0
Victoria	261	5.2	262	5.3	254	5.2	186	4.1
Western Australia	42	2.1	57	2.9	54	2.8	56	3.2
Total	810	4.0	787	3.9	784	3.9	705	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.

were culture-positive for *M. tuberculosis*, only one biopsy was smear-positive. Lymph node specimens were smear-positive in only 29 of 173 (17.3%) cases.

Table 2. Site of specimens smear- and culture-positive for *Mycobacterium tuberculosis* complex, Australia, 2005

	n	Smear positive (%) [*]
Sputum	354	189 (54.3)
Bronchoscopy	103	35 (34.3)
Lymph node	173	29 (17.3)
Pleural	47	1 (2.2)
Genitourinary	19	ND [†]
Bone/joint	24	ND [†]
Peritoneal	24	ND [†]
Skin	9	ND [†]
Cerebrospinal fluid	4	ND [†]

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

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

Drug susceptibility testing

Results of *in vitro* drug susceptibility testing were available for all 810 isolates for isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z). A total of 74 (9.1%) isolates of *M. tuberculosis* were resistant to at least one of these anti-tuberculosis agents. Results of testing for streptomycin (S) were available for 200 of 810 (24.7%) isolates with 35 demonstrating resistance to at least S; 9 had mono-resistance, 14 were resistant to S and H, 10 MDR-TB strains were also S-resistant, and there was a single S/R resistance, and a single S/H/Z resistance. Resistance to at least H and R (defined as MDR) was detected in 12 (1.5%) isolates. All of the MDR isolates were *M. tuberculosis* (Table 3). Of the 12 MDR-TB isolates, 10 were from

the respiratory tract (sputum n=8, bronchoscopy n=1, nasopharyngeal aspirate n=1) and 1 each from a knee synovium biopsy and a lymph node. Four of the MDR-TB-positive sputum specimens were smear-positive, as were samples from lymph node, nasopharyngeal neck abscess and bronchoscopy specimens.

Six 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.⁸ MDR-TB was also isolated from patients born in Vietnam (n=2) and Australia (n=2), with a single case each from India and the Sudan. Of the two Australian-born MDR-TB cases, one had travelled extensively in South East Asia. There was no additional information on the second case.

Mono-resistance to isoniazid (H) was detected in 42 isolates. One isolate was resistant to rifampicin (R) alone and another isolate was resistant to pyrazinamide (Z) alone. No ethambutol mono-resistance was observed. Seventy-one isolates demonstrated resistance to H at a concentration of 0.1 mg/L. Of these, 49 (69.0%) demonstrated resistance to H at the higher level of 0.4 mg/L. Among MDR-TB strains, 10/12 (83.3%) demonstrated H resistance at the higher concentration (0.4 mg/L). Twenty-seven of 74 (36.5%) specimens culture-positive for drug resistant strains, including 21 of 51 (41.2%) sputum or bronchoscopy specimens, were smear-positive for acid-fast bacilli. The two *M. bovis* isolates, which are inherently resistant to pyrazinamide, were not included in the above results.

AMRLN isolate susceptibility results between 2000 and 2005 were reviewed for isolates that might meet the definition of 'extensive drug resistance (XDR-TB)'. None of the 70 MDR-TB strains met the case definition for XDR-TB. Several MDR-TB isolates were also resistant to fluoroquinolones, including a patient from South Africa, but none of these isolates was also resistant to the second-line injectable agents.

Table 3. Drug resistance patterns in multi-drug resistant strains, Australia, 1995 to 2005

Resistance pattern (standard drugs) [*]	2005	2004	2003	2002	2001	2000	1999	1998	1997	1996	1995
H+R only	5	7	4	8	8	3	2	2	6	10	3
H+R+E	3	2	2	1	1	1	1	1	1	1	1
H+R+Z	1	1	1	1	3	3	1	2	5	4	1
H+R+E+Z	3	2	0	2	0	1	0	1	2	0	0
Total (%)	12 (1.5)	12 (1.5)	7 (0.9)	12 (1.7)	12 (1.6)	8 (1.0)	4 (0.5)	6 (0.9)	14 (1.9)	15 (2.0)	5 (0.7)

* The streptomycin result was not considered for this table.

† H = isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinamide

New or previously treated cases, and country of birth

Of the 74 *M. tuberculosis* isolates resistant to at least one of the standard drugs (H,R,E,Z) 67 (90.5%) were from new cases, 6 were from previously treated cases, and treatment information was not available for the remaining case. The country of birth was known for 73 (98.6%) cases; 8 were born in Australia and 65 were overseas-born. Of the 65 overseas-born cases with drug resistant disease, 41 (63.1%) were from four countries: Vietnam (n=16), Papua New Guinea (n=10), the Philippines (n=9), and India (n=6). The remaining 24 came from 14 other countries.

Discussion

In 2005, there were 810 cases of bacteriologically-confirmed tuberculosis representing 4.0 cases per 100,000 population, a similar rate to that found in 2004 and consistent with the results dating back to 1986.⁹⁻²¹ *Mycobacterium tuberculosis* was the predominant species reported with only two isolates each of *M. bovis* and *M. africanum* identified in 2005.

The level of drug resistance in *M. tuberculosis* isolates remains at a relatively constant level; excluding resistance to streptomycin, only 9.1% (74 of 810) of strains had resistance to one or more anti-tuberculosis drugs. Most cases with drug-resistant strains occurred in the overseas-born as observed in previous years.^{9-18,22,23} The rates of resistance in these cases who most likely acquired their infections outside Australia, reflect the prevalence of drug resistant TB in their countries of birth. These findings reflect the performance of the TB program from their country of origin rather than the clinical management of these patients in Australia. Therefore, national drug resistance data has limited usefulness as a measure of performance of Australia's TB control program.

Resistance to isoniazid and rifampicin, defined as MDR-TB, remained at a constant low level in 2005 (Table 3). Australia's MDR-TB rate (1.5%) is lower than recent published estimates of MDR-TB globally (2.7%), and in the SEAR (2.2%) and WPR (4.2%) regions.²⁴

The number of TB patients born in Papua New Guinea and diagnosed in Queensland, has increased in recent years. In the period 1993-1997, patients from PNG represented only 7 (8.0%) of 87 notified TB cases from Far North Queensland, but in the period 1998-2002, 44 (47.8%) of 92 notified TB cases were from PNG, including three MDR-TB cases.⁸ In 2005, the Queensland Mycobacterium Reference Laboratory identified 6 patients with MDR-TB from the PNG-TSI cross-border region who accessed health services in outer TSI (Anastasios

Konstantinos, Director, TB Services, Queensland, personal communication). This influx of TB patients from PNG-TSI represents a significant burden for the Queensland health services.

MDR-TB is recognised as a threat to global TB control. Management of MDR-TB cases is intensive, expensive, prolonged, and associated with a greater likelihood of treatment failure.²⁵ Unfortunately, a small percentage of MDR-TB strains have additional resistance to second-line drugs (SLD). Such strains are termed extensively drug-resistant. Until recently, XDR-TB was defined as a strain which was resistant to isoniazid and rifampicin, and at least three of the six main classes of SLD's (aminoglycosides, polypeptides, fluoroquinolones, thiomides, cycloserine, and para-amino salicylic acid).²⁶ A survey of a supranational network of TB laboratories determined that 17,690 TB isolates evaluated between 2000-2004 were tested for first-line drugs and at least three of the six SLD classes.²⁷ Overall, 20% were MDR-TB and 2% were XDR-TB. In addition, previously identified MDR-TB 'hot-spots' (Armenia, Azerbaijan, Czech Republic, Latvia, Republic of Georgia, Russia, South Korea) had higher levels of XDR-TB. South Korea provided data for 11,939 isolates of which 1,298 (11%) were MDR-TB, and of these, 200 (15%) were XDR-TB. The remaining supranational laboratories provided data from 5,751 isolates, of which 2,222 (38.6%) were MDR-TB, but of these, only 147 (6.6%) were XDR-TB. Although the data is likely biased as supranational laboratories are more likely to receive isolates from retreatment cases, treatment failures or other complex cases, it does provide clear evidence that XDR-TB has a global distribution. Areas identified as 'hot spots' for MDR-TB have higher levels of XDR-TB than non-'hot spot' areas.²⁸ Furthermore, it is likely that XDR-TB is associated with an even worse prognosis than for MDR-TB. XDR-TB gained international notoriety following an outbreak in an HIV hospital/outpatient setting in Kwazulu-Natal, South Africa. Of the 53 patients identified with XDR-TB, 52 had died within an average of 25 days of diagnosis.²⁷

The WHO Global Task Force on XDR-TB met in October 2006 and developed a revised laboratory case definition: 'XDR-TB is TB showing resistance to at least isoniazid and rifampicin; which is the definition of MDR-TB, in addition to any fluoroquinolone, and to at least one of the following 3 injectable drugs used in anti-TB treatment: capreomycin, kanamycin, and amikacin'.²² There are three rationales for the revised definition: (i) protocols for drug susceptibility testing of fluoroquinolones and injectable anti-TB agents are established and there is good inter-laboratory agreement; there is less agreement for the other SLD's, and none whatsoever for cycloserine, (ii) the fluoroquinolones and

injectable agents are the most potent SLD's, and form the cornerstones of most MDR-TB treatment regimens, and (iii) are often the only SLD's available in developing countries.²²

No XDR-TB strains were identified in Australia between 2000–2005. The widespread use and the documented rapid development of fluoroquinolone resistance²⁹ has prompted the AMRLN to institute routine fluoroquinolone susceptibility testing of all isolates from the beginning of 2006.

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- Institute of Medical and Veterinary Science, Adelaide, South Australia.
- Queensland Health Pathology Services, Herston Hospitals Complex, Herston, Queensland.
- Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria.
- PathWest Laboratory Medicine WA – QEIIIMC, Hospital Avenue, Nedlands, Western Australia
- Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales.

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