Tuberculosis in Australia: bacteriologically confirmed cases and drug resistance, 2003

A report of the Australian Mycobacterium Reference Laboratory Network

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Abstract

The Australian Mycobacterium Reference Laboratory Network collected and analysed laboratory data on new cases of disease caused by *Mycobacterium tuberculosis* complex in the year 2003. A total of 784 cases were identified by bacteriology, representing an annual reporting rate of 3.9 cases of laboratory confirmed tuberculosis per 100,000 population. The most commonly encountered culture-positive specimens were sputum (n=351), lymph node (n=176) and from bronchoscopy (n=97). Smears containing acid fast bacilli were present in sputum (53.0%), bronchoscopy (32.0%) and lymph node (23.3%). Five children (female n=3, male n=2) under 10 years of age had bacteriologically confirmed tuberculosis. Eighty isolates of *M. tuberculosis* and one of *Mycobacterium africanum* (10.3%) were resistant to at least one of the standard anti-tuberculosis agents. Mono-resistance to isoniazid, ethambutol, rifampicin, and pyrazinamide was detected in 45, three, two, and one isolates respectively. Multidrug-resistance (MDRTB) defined as resistance to both isoniazid and rifampcin was observed in seven (0.9%) isolates. Of the seven MDRTB isolates, six were from the respiratory tract and four were from smear positive specimens. Of the 81 patients with drug resistant isolates, 78 (96.3%) were classified as having initial resistance; two had acquired resistance and no information was available for one isolate; five were Australian-born; and 76 (93.8%) had migrated from a total of 30 countries. *Commun Dis Intell* 2004;28:474–480.

Introduction

The annual incidence of tuberculosis (TB) diagnosed clinically in Australia has fallen from 55 cases per 100,000 population in the mid 1950s to a current level around 5 to 6 cases per 100,000 population. As part of the Western Pacific region of the World Health Organization, Australia enjoys one of the lowest rates of disease compared with the rest of the region which reported an overall notification rate of 47 per 100,000 population in year 2002. This rate has shown no significant variation since 1993.[3] The Western Pacific region contains several countries (China, Philippines, Viet Nam, Cambodia and Papua New Guinea) with a high burden of TB. Another regional neighbour, the Republic of Indonesia, has the third highest burden of TB in the world.[2]

There are two sources of TB-related data for Australia. Since 1991, the National Notifiable Diseases Surveillance System (NNDSS) has pro-vided statistics on cases of tuberculosis reported to public health authorities in Australia's states and territories. The second source, 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 will have a proportion of 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 2003.

Methods

The data are based on clinical specimens that were culture-positive for *Mycobacterium tuberculosis* complex (MTBC). Although the BCG strain of *Mycobacterium bovis* is a member of the MTBC, no information on this organism is included in the

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present report. Almost all isolates of MTBC were referred to one of the five laboratories comprising the AMRLN for specific 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, were included in the laboratory data as laboratories are generally unable to differentiate relapse cases from new cases.[3] Temporary visitors to Australia were included as were illegal aliens within correctional services facilities and asylum seekers located in detention centres or on temporary visas within Australia.

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: species of mycobacterium and results of drug susceptibility testing;

* nucleic acid amplification testing: results of testing; and

* if the isolate was drug resistant: 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 scheme 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 the year 2003 supplied by the Australian Bureau of Statistics.[4]
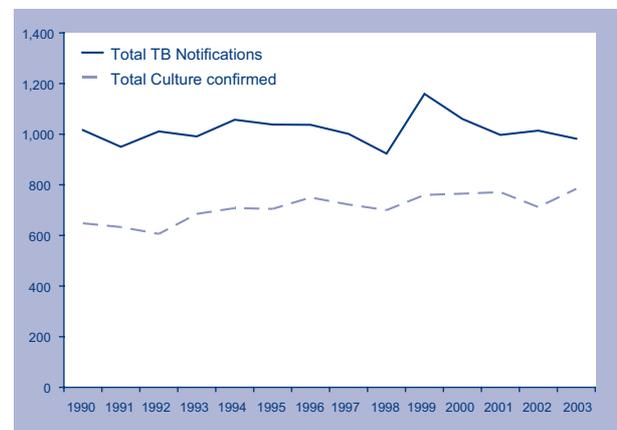
For each case, the nature of the first clinical specimen that yielded an isolate of MTBC was used to record the nominal site of disease. Culture-positive specimens collected at bronchoscopy or by gastric lavage were considered to indicate pulmonary disease. Cases with multi-site isolations, provided a sputum or bronchoscopy specimen was culture-positive, were listed as having pulmonary disease, the most important category for public health purposes. Cases for which there were multiple-site isolations were not categorised as having miliary or disseminated disease as differentiation is based on clinical findings that are generally not available to the reporting laboratories. Initial drug resistance was defined as the presence of drug resistant strains of *M. tuberculosis* and *M. africanum* in

cases of tuberculosis in which there was no known history of anti-tuberculosis treatment. Patients who had begun anti-TB treatment and had developed resistance to one or more of the drugs used during treatment were recorded as having acquired drug resistance.[5]

Results

There were 784 bacteriologically confirmed cases of tuberculosis in 2003 (Figure 1), representing an annual rate of 3.9 per 100,000 population. State-specific reporting rates varied from 0.8 cases (Tasmania) to 10.1 cases per 100,000 population (Northern Territory) (Table 1).

Figure 1.   Comparison between tuberculosis notifications and laboratory data, Australia; 1990 to 2003

Causative organism

Almost all isolates were identified as *M. tuberculosis* (n=782), the remaining two isolates being a single *M. africanum* and a *M. bovis*.

Distribution by gender, age and site of disease

Complete information for gender and age were submitted for all patients, due to additional information provided by state and territory Tuberculosis Centres. Five children (female n=3 male n=2) under 10 years of age had bacteriologically confirmed tuberculosis (lymph node n=2, tracheal aspirate n=1, gastric aspirate n=1, biopsy n=1).

The relationship of tuberculosis to age and gender are shown in Figure 2. For males, there were two distinct age groups; a rise to 6.9 cases of tuberculosis per 100,000 population at 20–24 and 25–29 years, and in the elderly male where the rate rose from 5.6 at age grouping 65–69 to a peak of 17.1 per 100,000
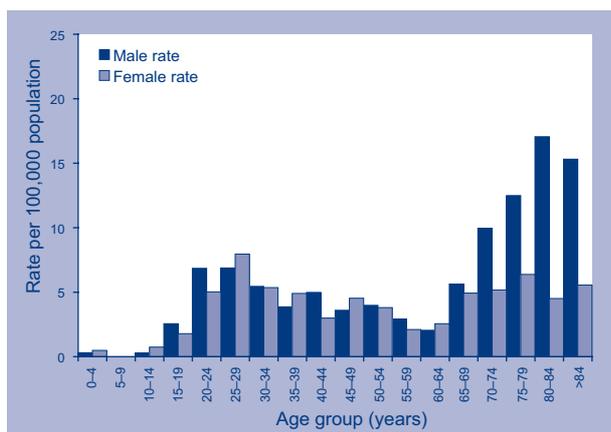
Table 1.　Bacteriologically confirmed cases of tuberculosis in Australia, 1994 and 2000 to 2003, cases and rate per 100,000 population by state or territory*

State or territory	2003		2002[16]		2001[15]		2000[14]		1994[10]	
	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate
New South Wales†	325	4.6	301	4.3	327	4.8	307	4.5	278	4.4
Victoria	254	5.2	208	4.3	222	4.6	231	4.8	217	4.8
Queensland	91	2.4	97	2.6	81	2.2	76	2.1	88	2.8
Western Australia	54	2.8	46	2.4	68	3.6	63	3.3	53	3.1
South Australia	36	2.4	26	1.7	38	2.5	41	2.7	41	2.8
Tasmania	4	0.8	8	1.7	12	2.8	2	0.4	10	2.1
Northern Territory	20	10.1	26	13.0	23	11.6	45	23.0	21	12.3
Total	784	3.9	712	3.6	771	4.0	765	4.0	708	4.0

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

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

population for the 80–84 age group. Females in the 25–29 year age group had a peak rate of 8.0 per 100,000 population but in contrast to males, the rate for tuberculosis in the elderly female was more modest rising only to 6.4 cases per 100,000 population. In part, these differences are due to the site of infection. Overall, the male:female ratio was 1.16:1, for sputum isolates, but the ratio was reversed for lymph node isolates (1:1.4). The median age group for patients with respiratory disease was 35–39 for females and 45–49 for males, and for lymph node cases, the median age group for both genders was 35–39 years.

Figure 2.　Laboratory confirmation of *Mycobacterium* tuberculosis complex disease, Australia 2003, by age and sex

The predominant specimen type was sputum, including three gastric aspirates (n=351, 44.7%); bronchoscopy (n=97, 12.4%), lymph node (n=176, 22.4%) and pleural (n=35, 4.5%) (Table 2).

Table 2.　Site of specimens smear- and culture-positive for *Mycobacterium tuberculosis* complex, in the year 2003

	n*	Smear positive (%)†
Sputum	351	186 (53.0)
Bronchoscopy	97	31 (32.0)
Lymph node	176	41 (23.3)
Pleural	35	2 (5.7)
Genito-urinary	18	9 (50.0)
Bone/Joint	25	9 (36.0)
Peritoneal	24	2 (8.3)
Skin	11	ND†
CSF	6	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 small numbers.

Association with HIV

The AMRLN database recorded the HIV status for only 55 (7.0%) patients. Only two patients were identified as HIV seropositive; one had smear-positive respiratory disease and the other patient had genitourinary TB.

Microscopy

Results of microscopy were available for 751 of 784 (95.8%) of specimens; microscopy was not performed on seven specimens and no results were provided for the remaining 26 specimens. Smears were positive for 186 of 351 (53.0%) sputum and 31 of 97 (32.0%) bronchoscopy specimens respectively (Table 2). A total of 35 pleural specimens (8 biopsy and 27 fluids) were culture positive for *M. tuberculosis*, but only one of each specimen type was smear positive. Lymph node specimens were smear positive for only 41 of 176 (23.3%) cases.

Drug susceptibility testing

Results of *in vitro* drug susceptibility testing were available for all 784 isolates for isoniazid (H), rifampicin (R) and ethambutol (E) and for 783 isolates for pyrazinamide (Z). A total of 81 isolates (10.3%) of *M. tuberculosis* (n=80) and *M. africanum* (n=1) were resistant to at least one of the above anti-tuberculosis agents. Results of testing for streptomycin (S) were available for 222 of 784 (28.3%) of isolates with nine demonstrating S mono-resistance and another eight were resistant to S + H. Resistance to at least both H and R (defined as multidrug resistance) was detected in seven (0.9%). All of the MDR isolates were *M. tuberculosis* (Table 3). Of the 7 MDRTB isolates, six were from the respiratory tract (sputum n=4, bronchoscopy n=2); the remaining isolate was from a lymph node. Three of the MDRTB-positive sputum specimens were smear positive as was one of the bronchoscopy specimens and the single isolate from lymph node tissue. A single isolate of *M. bovis* from a smear-positive sputum was not included in the above results.

Mono-resistance to isoniazid, ethambutol, rifampicin, and pyrazinamide was detected in 45, three, two, and one isolates respectively. There were 75 isolates that demonstrated resistance to H at a concentration of 0.1 mg/L. Of these, 41 (54.7%) demonstrated resistance to H at the higher level of 0.4 mg/L. Thirty-seven of 81 (45.7%) specimens culture-positive for drug resistant *M. tuberculosis*, including 26 of 55 (47.3%) sputum or bronchoscopy specimens, were smear-positive for AFB. Six of the seven MDRTB isolates had high level isoniazid resistance.

Initial or acquired resistance, and country of origin

There were 80 *M. tuberculosis* and one *M. africanum* resistant to at least one of the standard drugs (H, R, E, Z). Of these, 78 of 81 (96.3%) were classified as having initial resistance, two had acquired resistance, and no data was available for one isolate on the presence or absence of previous treatment. The country of birth was known for all patients with drug resistant strains; five were Australian born, and 76 (93.8%) had migrated from a total of 30 countries.

Of the 76 migrants with drug-resistant disease, 49 (64.5%) had migrated from one of six countries; Viet Nam (n=18), India (n=8), Philippines (n=7), Indonesia (n=5), Sudan (n=5), and China (n=4).

Use of nucleic acid amplification tests

Nucleic acid amplification testing (NAAT) was performed on 201 of 784 (25.6%) specimens, all of which subsequently grew *M. tuberculosis* on culture. Of these, 123 specimens were of respiratory origin (sputum, n=90, bronchoscopy, n=26, tissue, n=4, aspirate, n=3), and 112 (91.1%) were NAAT positive. For smear positive respiratory specimens, 80 of 83 (96.4%) were NAAT positive whilst 26 of 32 (81.3%) of smear negative respiratory specimens were NAAT positive (Table 4A). Seven specimens did not record a smear result and one smear negative tissue specimen recorded an equivocal result.

There were 78 specimens of non-respiratory origin (tissue, n=50, aspirate, n=14, fluid, n=13, swab, n=1) and only 47.4 per cent were NAAT positive. For smear positive non-respiratory specimens, 19 of 22

Table 3. Drug resistance patterns in MDR strains, Australia, 1993 to 2003

Resistance pattern (standard drugs)*	2003	2002[16]	2001[15]	2000[14]	1999[13]	1998[13]	1997[12]	1996[11]	1995[10]	1994[10]	1993[9]
H+R‡ only	4	8	8	3	2	2	6	10	3	2	7
H+R+E‡	2	1	1	1	1	1	1	1	1	0	
H+R+Z‡	1	1	3	3	1	2	5	4	1	0	
H+R+E+Z‡	0	2	0	1	0	1	0	0	0	0	1
Total (%)	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)	2 (0.3)	10† (1.5)

*   The streptomycin result was not considered for this table.

†   The multi-drug profiles for all 10 strains were not identified.

‡   H = Isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinamide.

Table 4A.   Results for nucleic acid amplification tests performed on respiratory specimens, Australia, 2003

NAAT result	Culture positive respiratory specimens	
	Smear positive	Smear negative
Positive	80	26
Negative	3	6
Total* (115)	83	32

*   Seven specimens did not record a smear result and one smear negative tissue specimen recorded an equivocal result.

Table 4B.   Results for nucleic acid amplification tests performed on non-respiratory specimens, Australia, 2003

NAAT result	Culture positive NON-respiratory specimens	
	Smear positive	Smear negative
Positive	19	18
Negative	3	33
Total* (73)	22	51

*   Four specimens did not record a smear result and one smear-positive spinal tissue specimen recorded the presence of NAAT inhibitors.

(86.4%) were NAAT positive and 18 of 51 (35.3%) of smear negative non-respiratory specimens were NAAT positive (Table 4B). Four specimens did not record a smear result and one smear-positive spinal tissue specimen recorded the presence of NAAT inhibitors.

Discussion

The finding of 784 cases of bacteriologically confirmed tuberculosis representing 3.9 cases per 100,000 population in 2003 is consistent with the results of previous AMRLN reports. Since the network began collecting data in 1986, the range for bacteriologically confirmed cases has remained between 3.5–4.1 per 100,000 population.[6–16]

For 2003, the NNDSS reported 982 notified cases of TB, a difference between the two datasets of 198 (25.3%).[17] The NNDSS has consistently recorded a higher number of notifications than the AMRLN data (range 22.7–44%). Possible reasons for the gap between the two data sources have been discussed previously.[14] Furthermore, the handling of multiple sites of disease differs also. The NNDSS database documents all sites of disease, whereas the AMRLN database lists only one site, and when multi-site disease is present, prioritises respiratory disease over non-respiratory sites. Although comparison of the unlinked databases is problematic, there were 483 and 236 notifications of respiratory and lymph node disease respectively in 2003.[17] The AMRLN dataset recorded 351 respiratory and 176 lymph node cases. If the two datasets are compared, then 74.7 per cent and 74.6 per cent of respiratory and lymph node notifications respectively were bacteriologically confirmed. Over the period, 2000–2003, the range of bacteriologically confirmed respiratory or lymph node disease was 70.5–88.5 per cent or 63.5–86 per cent respectively.[14–16, 18–20]

In 2003, almost all isolates were identified as *M. tuberculosis* (n=782), the remaining two isolates being a single *M. africanum* and an *M. bovis*. In the past decade, the absolute number of cases caused by *M. bovis* has fallen from a high of 10 and nine cases in 1996 and 1997 respectively down to four, two, one, zero, and one cases in the years 1999–2003. The number of cases caused by *M. africanum* has remained at a steady, low level between zero and seven cases per year over the past decade. Hence, a positive result by a rapid method that detects the presence of MTBC in a clinical specimen most likely indicates *M. tuberculosis* rather than any other member of the MTBC.[8–16]

A total of 81 isolates (10.3%) of *M. tuberculosis* (n=80) and *M. africanum* (n=1) were resistant to one at least one of H, R, E, or Z. This finding is consistent with previous reports provided by the AMRLN where drug resistance has remained between a high of 17.7 per cent in 1989 and a low of 7 per cent in 1994.[6–16] For 2003, mono-resistance to isoniazid, ethambutol, rifampicin, and pyrazinamide was detected in 45, three, two, and one isolates respectively. Again, this finding is consistent with previous data.

The level of acquired resistance in Australia remains low with only 2/81 (2.5%) cases with a drug resistant strain being described as such. Interestingly, both cases were MDRTB, one from Papua New Guinea and the other from India. Most cases with drug resistant strains (93.8%) occurred in the overseas born and reflects previous data.[14–16] These findings reflect more upon the performance of the TB program from their country of origin rather than the clinical management of these patients in Australia. Therefore, as a measure of performance of Australia's TB control program, the national drug resistance data has limited usefulness.

Results of NAAT were evaluated with smear result and whether the sample was from respiratory or non-respiratory sites. Consistent with previous reports, 96.4 per cent of smear- and culture- positive respiratory specimens were NAAT-positive.[21–23] Importantly, 3/83 (3.6%) of smear positive respira-

tory specimens that subsequently grew MTBC were NAAT negative and only 35.3 per cent of smear-negative culture positive non-respiratory specimens were NAAT-positive. Inhibitors of amplification enzymes may be present in any specimen, especially those of non-respiratory origin. Clinicians must recognise the limited sensitivity of NAAT particularly on non-respiratory samples and laboratorians must remember that NAAT should have an internal amplification inhibitor control to validate a negative result.[23,24] NAAT should be considered a supplemental test that does not replace microscopy or culture. Culture also remains the priority because an MTBC isolate is required for specific identification to species level, drug susceptibility testing and genotyping.

The decision to perform NAAT on a specimen needs to consider several factors, including whether a sufficient amount of specimen has been set aside for microscopy and culture, the degree of clinical suspicion for TB, and the specimen type.[21,24] Public health considerations can also influence the decision to perform NAAT. For respiratory smear-positive with no risk factors for TB, the differential diagnosis also includes disease caused by environmental mycobacteria. A negative NAAT result in this setting supports the diagnosis of NTM disease for which the drug treatment is different, and the public health actions of isolation and contact tracing may be unnecessary. Smear-negative patients may also be suitable candidates for NAAT when the clinical suspicion of TB is moderate to high and multiple sputum specimens are smear negative NAAT may clarify the diagnosis without resorting to further, more-invasive investigations such as bronchoscopy. In contrast, smear negative respiratory specimens from patients with a low probability of TB are not suitable candidates for NAAT due to the test's low sensitivity for the diagnosis of smear negative pulmonary TB.[21,22,23]

For the first time, sufficient data was available to evaluate results of NAAT on non-respiratory specimens. As expected, the correlation for smear positive, non-respiratory specimens that were MTBC culture positive and NAAT positive was lower at 86.4 per cent, most likely due to the presence of inhibitors. For smear negative, non-respiratory specimens that were MTBC culture positive, only 18/51 (35.3%) were NAAT positive. The level of sensitivity for NAAT lies somewhere between that of culture (~10-100 colony forming units per mL) and microscopy (~10,000 acid fast bacilli per mL) and the majority of false-negative results are due to low concentrations of MTBC.[25] Non-respiratory specimens generally have a far lower smear-positivity rate than respiratory specimens (e.g. Table 2). Specimens from non-respiratory sites such as tissue samples or fluids from usually sterile

sites (e.g. cerebrospinal, meningeal, pleural, ascitic, pericardial) tend to be paucibacilliary and also have a higher proportion of specimens containing amplification inhibitors. There are circumstances, most notably when meningeal TB is suspected, that requests for NAAT are received. Only when sufficient specimen has been processed for microscopy and culture should NAAT be considered.[25,26]

There is no place for using NAAT for checking the response to treatment. NAAT does not differentiate nucleic acid from viable and non-viable MTBC and furthermore, MTBC nucleic acid may remain *in situ* for an extended period of time. The Centers for Disease Control and Prevention also recommended that NAAT should not be used on specimens from patients who have received greater than seven days of specific anti–TB treatment or have been on treatment within the previous two months.[24]

In summary, the 2003 AMRLN database on positive TB cultures shows a steady rate of laboratory-proven TB disease in Australia. The prevalence of drug-resistant disease also remains unchanged. Most patients with drug-resistant TB were migrants hence the rate of drug-resistant disease in Australia is an unreliable performance indicator for our national TB control program. Finally, the AMRLN database has provided further evidence on the performance characteristics of NAAT. These findings confirm that NAAT should not be performed automatically on every TB specimen or TB suspect. Furthermore, as with all mycobacterial investigations, the decision to perform NAAT and the result interpretation requires close liaison between the clinician and laboratory staff.

Acknowledgements

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