Tuberculosis in Australia: bacteriologically confirmed cases and drug resistance, 1996

Report of the Australian Mycobacterium Reference Laboratory Network

David Dawson,[1] WHO Collaborating Centre in Tuberculosis Bacteriology, Queensland Health Pathology Services, Brisbane

Abstract

The Australian Mycobacterium Reference Laboratory Network collected and analysed laboratory data on new diagnoses of infection with *Mycobacterium tuberculosis* complex during 1996. A total of 750 cases were identified, representing an annual incidence of 4.1 cases of laboratory confirmed tuberculosis per 100,000 population. The incidence rate varied between States, reflecting differences in the distribution of persons belonging to 'high-risk' categories for tuberculosis. Incidence statistics were almost identical to those recorded by the Network in 1994 and 1995. The male:female ratio remained at around 1.2:1. As was the case in 1995, the median age group for males was 45-49 years and for females 35-39 years. The frequency of positive microscopy in pulmonary samples was stable at around 55%. Lymphatic disease accounted for 19% of the total cases in 1996 compared with 15% in the previous year, confirming that lymphadenitis is becoming more common in females with tuberculosis in Australia. Approximately 11% of isolates had *in vitro* resistance to at least one of the four standard anti-tuberculosis drugs, an increase from 8% in 1994-95. Fifteen isolates were multi-drug resistant, compared with a total of only 38 during the previous seven years. Thus, the 1996 data points to an increasing frequency of multi-drug resistant strains among isolates from Australian patients with tuberculosis. *Commun Dis Intell* 1998;22:183-187.

Introduction

Tuberculosis remains unchallenged as a major cause of human suffering in much of the world. The World Health Organization (WHO) has estimated that tuberculosis will cause the deaths of around 30 million people in this decade.[1] With the bulk of incident cases (and deaths) occurring in developing countries with minimal public health resources, there seems little possibility that the global picture will improve significantly in the short term. The impact of the spread of HIV into countries with high rates of tuberculosis infection, as well as the increasing prevalence of strains resistant to the most effective anti-tuberculosis drugs, has been well publicised.

The Australian population, primarily due to good management, but in part due to good fortune, has generally been spared many of the problems experienced elsewhere with tuberculosis. National data has shown the

1. Correspondence address: The Prince Charles Hospital, Chermside, Queensland 4032

Table 1. MTBC isolates in Australia, 1994-1996, by State or Territory and year

State	1996		1995	1994
	Number of isolates	Isolates per 100,000 population	Isolates per 100,000 population	Isolates per 100,000 population
New South Wales[1]	341	5.3	4.8	4.4
Victoria	214	4.7	4.1	4.8
Queensland	90	2.7	2.6	2.8
Western Australia	51	2.9	3.2	3.1
South Australia	28	1.9	2.2	2.8
Tasmania	3	0.6	0.4	2.1
Northern Territory	23	12.6	21.3	12.3
TOTAL	750	4.1	3.9	4.0

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

annual incidence rate to be stable at 5-6 cases per 100,000 population, among the lowest in the world.[2] As would be expected, Australians in the older age groups account for many cases, but there is evidence of persistent high rates of disease (and infection) in certain population subgroups such as indigenous Australians and persons born in high-prevalence countries. Only small numbers of multi-drug resistant strains have been encountered thus far, and only a small proportion of cases are related to HIV infection.

The Tuberculosis Working Party of the National Health and Medical Research Council (NHMRC) has recently developed draft guidelines for elimination of tuberculosis in Australia. These guidelines emphasise the importance of surveillance as a strategic tool.[3] In Australia, surveillance data for tuberculosis is available through two sources: the National Mycobacterial Surveillance System (NMSS, conducted by the Communicable Diseases Network Australia New Zealand) and the Australian Tuberculosis Reporting Scheme (supported by the Mycobacterium Reference Laboratory Network, MRLN). The NMSS is based on clinical notifications. Data from the reference laboratory network relates to cases confirmed by isolation of the *Mycobacterium tuberculosis* complex (MTBC). The laboratory network has published data for the period 1986 to 1995.[4,5,6,7] This report is based on data for 1996.

Methods

The Australian Tuberculosis Reporting Scheme is a joint project of the MRLN and the Department of Health and Family Services. Data for tuberculosis are based on isolates of MTBC (other than the BCG strain) from clinical samples. Due to the specialised nature of tuberculosis bacteriology, it can be assumed that the five laboratories that comprise the MRLN account for almost all, if not all, of the bacteriological diagnoses in Australia. Comparable bacteriological procedures are used in the reference laboratories. Relapse patients, that is, those previously diagnosed, treated and considered cured, were included in these data because laboratories cannot usually differentiate them from new cases. Temporary visitors to Australia are also included.

For each new laboratory diagnosis the following information was collected:

- demographic: patient identifier, age, gender, HIV status and State of residence
- specimen: type, site of collection, date of collection and microscopy result, and
- isolate: species of *Mycobacterium* and results of drug susceptibility tests.

Data for 1996 from contributing laboratories were submitted to the scheme co-ordinator, collated and analysed. Duplicate entries (as indicated by identical patient identifier and age) were deleted before analysis. Incidence rates were calculated using the mid-year estimates of the population supplied by the Australian Bureau of Statistics (ABS).

The nature of the first clinical sample that yielded an isolate of MTBC was used to record the site of disease for individual cases. Culture-positive specimens collected at bronchoscopy, as well as gastric washings, were taken to identify cases of pulmonary disease. In most cases of multi-site disease, sputum is the first positive sample. These cases were therefore included among those listed as having pulmonary disease, the most significant category for public health purposes. Although many patients were known to have isolates from more than one body site, such data are of doubtful value for the laboratory-based report and were not collated. Similarly, it is not always possible to accurately categorise cases of miliary and disseminated disease from data available to laboratories.

Results

Total reports and distribution by State

A total of 750 cases were recorded in 1996. This figure represents an annual incidence of 4.1 cases of laboratory confirmed tuberculosis per 100,000 population. The distribution of cases by State of residence is shown in Table 1 (in which data from 1994 and 1995 are included for comparison). State specific incidence rates varied from

Figure 1. MTBC isolates by age group and sex, Australia, 1996

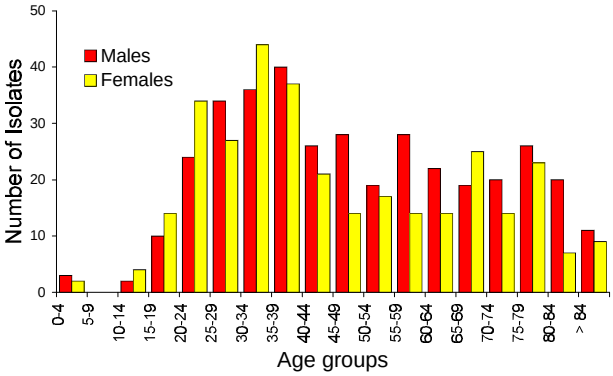
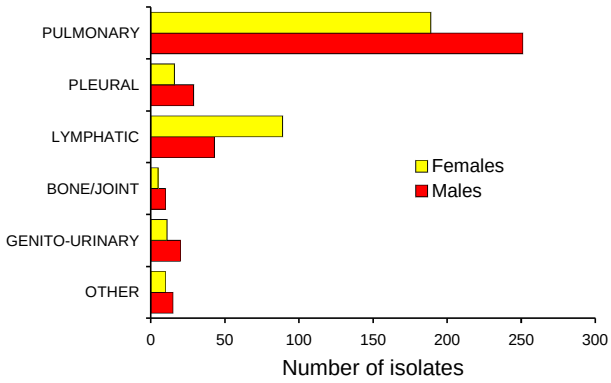


Figure 2. MTBC isolates by site and sex, Australia, 1996



less than 1 (Tasmania) to around 12 per 100,000 (Northern Territory).

Causative organism

The large majority (740) of the 750 cases were due to *Mycobacterium tuberculosis*. The remaining ten were caused by *M. bovis*, typically in males over 60 years of age.

Distribution by gender, age and site of disease

Full information for gender, age and site of disease was submitted for 688 of the 750 cases recorded. Figure 1 shows the distribution of 688 cases by age group and gender. The overall male:female ratio was 1.2:1, although this ratio was reversed in the younger age groups. For all cases, the median age group was 40-44 years. The median age group for males was 45-49 years whereas that for females was 35-39 years. Age and gender specific rates varied from nearly zero in children younger than 15 years to almost 19 per 100,000 per year in males over 80 years of age (data not shown). Only five cases were recorded in children younger than ten years, one of which was a 3 year old child with tuberculous meningitis.

Figure 2 shows the distribution of 688 cases by site of disease and gender. Pulmonary disease accounted for 64% of the total cases (male:female ratio 1.3:1). Disease of lymph nodes was identified in 19% of the total cases (male:female ratio 0.5:1). For females between 20 and 40 years, lymphatic disease was almost as common as was pulmonary disease. Figure 3 shows the distribution of cases with lymphatic disease by age and gender.

Association with HIV

The laboratories recorded six isolates from persons known to be HIV positive. Three were from Queensland, two were from Western Australia, and one was from Victoria. All but one isolate came from pulmonary material.

Smear-positivity in pulmonary disease

A total of 466 cases were detected from samples of pulmonary origin. The specimen types that provided these diagnoses were: sputum (371), bronchoscopy samples (72), other (23). Results of microscopy were available for 418 samples (90%) of pulmonary origin; 53% were positive. For sputum alone, 56% were smear-positive, compared with 38% for bronchoscopy collections. The pulmonary samples from five patients with HIV were smear-positive.

In vitro drug susceptibility

Results were available for each of the 750 isolates. All but two were tested against each of the four drugs recommended for standard treatment of tuberculosis in Australia, that is, isoniazid (H), rifampicin (R), ethambutol

Table 2. *In vitro* resistance of isolates to the standard anti-tuberculosis drugs, Australia, 1994-1996

	1996			1995	1994
	Isolates tested	Number resistant	% resistant[1]	% resistant[1]	% resistant[1]
Isoniazid (H)	750	73	9.7	7.5	6.1
Rifampicin (R)	750	16	2.1	1.1	0.6
Ethambutol (E)	750	2	0.3	0.3	0.0
Pyrazinamide[2] (Z)	748	18	2.3	2.0	0.9

1. Percentage of strains tested which were resistant to drug alone or in combination with others
2. All strains of *M. bovis* are naturally resistant to pyrazinamide

Table 3. Drug resistance patterns in MDR strains, Australia, 1994-1996

Resistance pattern (standard drugs)	Number of isolates		
	1996	1995	1994
H + R only	10	3	2
H + R + E	1	1	0
H + R + Z	4	1	0

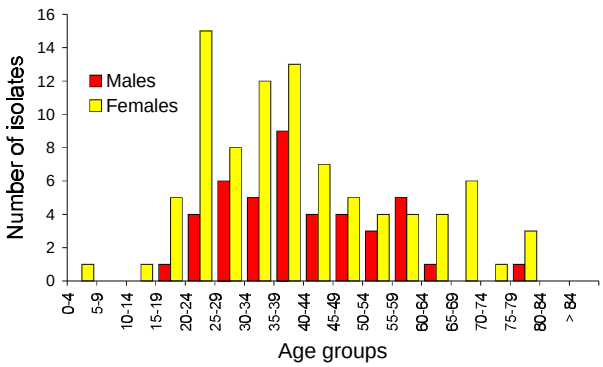
H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide

(E) and pyrazinamide (Z).[8] Only 192 were tested against streptomycin (S), a drug used occasionally in non-standard regimens. A total of 83 isolates (11.1% of the total) were resistant to at least one of the standard compounds. The frequency of resistance to H, R, E and Z, alone or in combination, is shown in Table 2. Included in Table 2 are results for 10 isolates of *M. bovis* which are naturally resistant to Z. Our data for S, although incomplete, show that at least 10% of isolates are resistant to S, alone or in combination. Resistance to H and/or R was recorded in 74 isolates (9.9% of total). Fifty-eight isolates were resistant to H alone, one was resistant to R alone, and 15 (2% of total) were resistant to both H and R in combination (Table 3). Isolates in the latter group are referred to as multi-drug resistant (MDR). Thirteen MDR isolates came from pulmonary specimens, of which five were smear-positive. All of the MDR isolates were *M. tuberculosis*. All five isolates known to be associated with HIV were fully susceptible to the standard regimen.

Discussion

The data for 1996 show that the incidence of laboratory confirmed tuberculosis in Australia continues to hover around 4 cases per 100,000 per year. This apparently stable situation reflects the findings of the analysis of clinical notifications for the same year.[9] The laboratory network recorded 750 cases, whereas the NMSS received information on 1,038 cases. This means that around 70-75% of Australian notified tuberculosis cases are at present supported by definitive bacteriological confirmation.

Figure 3. MTBC isolates from lymph nodes by age group and sex, 1996



The data in Table 1 show differences in annual tuberculosis incidence rates between States and Territories, ranging from close to zero in Tasmania to more than 12 per 100,000 in Northern Territory. The rates are almost identical to those in our previous report[7]. The consistent variations in rates between States are almost certainly due to peculiarities in the national distribution of high-risk categories, rather than local differences in the risk of acquiring tuberculous infection.

Cases of active disease are distributed unevenly between sexes and across age groups. The data presented in Figure 1 are very similar to that from previous reports and are in keeping with what would be expected from the demographic features in Australia at present. The overall male:female ratio was around 1.2:1, the same as in 1995. Further, the median age groups for males and females are static at 45-49 years and 35-39 years respectively. When age specific rates are considered, our data generally agree with the notion that the risk of developing tuberculosis increases with age. It should be noted however, that all persons above 20 years have rates of at least 4 per 100,000 per year, while males in older age groups have disease rates up to five times this figure. The extremely low rates of bacteriologically confirmed disease in children under 15 years are comforting statistics because they indicate that young persons in the general Australian population are exposed to a low risk of tuberculous infection.

Our data suggest that gender and age are influential factors for determining the site of disease (Figures 2 and 3). In particular, lymphatic disease seems more likely to occur in females than in males. In 1996, 28% of females with tuberculosis had disease in lymph nodes; this statistic has shown a sustained increase from 14% in 1986-1988.[4] It is the author's impression that the majority of females with tuberculous lymphadenitis in Australia are of Asian ethnicity. The limited information available to laboratories does not allow us to determine whether lymphadenitis is common in females from other ethnic groups. A recent bulletin from WHO reports that tuberculosis is the single leading cause of deaths among women of reproductive age.[10]

Acid-fast microscopy continues to serve as a useful diagnostic tool. Data, for the first time, include microscopy results for the large majority of specimens from pulmonary sites. More than half (56%) of the diagnostic sputum samples were found positive by smear microscopy. In addition to providing an immediate rational basis for

chemotherapy, early detection of smear-positive cases will allow interventions that reduce the transmission of infection. Contact tracing can also begin when a positive sputum-smear report is delivered. Seventy-two cases were diagnosed from bronchoscopy samples, of which only 38% were smear-positive. While the degree of infectious risk from patients diagnosed by bronchoscopy is open to debate, it is reasonable to request that pre-bronchoscopy sputum should be submitted for patients undergoing bronchoscopy for suspected tuberculosis so that sputum-smear status will always be known.

The reference laboratories were informed of only six cases associated with HIV infection; no cases were reported from New South Wales. Published data suggests that at least 5-10 cases of HIV-tuberculosis occur annually in Australia.[11] We believe our data for HIV-tuberculosis should be regarded as an underestimate of the true figure.

Collation of surveillance data for *in vitro* drug resistance is an important activity of the reference laboratory network. We have shown that a total of 83 isolates (11.1%) in 1996 demonstrated *in vitro* resistance to at least one of the standard anti-tuberculosis drugs, H, R, E and Z. Because the response of resistant strains to standard short-course chemotherapy cannot be assured, chemotherapy in such cases must be managed by experienced physicians. Most importantly, 74 isolates were resistant to one or both of H and R, the key anti-tuberculosis compounds. As shown in Table 2, around one in ten of all MTBC strains encountered in Australia is resistant to H. Corresponding figures for 1994 and 1995 were only 6.1% and 7.5% respectively. Resistance to R was almost always accompanied by resistance to H, and we found a total of 15 strains (2%) were in this category (MDR). This figure is a significant increase from previous years in which less than 1% of isolates were MDR.

Ten cases of tuberculosis were due to *M. bovis* in 1996, whereas only four cases were recorded in both 1994 and 1995. Although bovine tuberculosis has been eradicated from the national cattle herd, we must, for the foreseeable future, expect that occasional cases of disease due to *M. bovis* will be detected in the population. Because the natural resistance of *M. bovis* to Z requires that the standard short-course regimen be adjusted, laboratories must continue to employ protocols that differentiate *M. bovis* from *M. tuberculosis*.

The WHO and International Union Against Tuberculosis and Lung Disease have initiated a Global Project on Anti-tuberculosis Drug Resistance Surveillance.[12] A primary objective of the project is to collect accurate data on drug resistance in order to evaluate the efficacy of local control programs. The project requires that patients be stratified on the basis of previous treatment for tuberculosis to allow *in vitro* drug resistance to be categorised as either *primary* resistance (where the patient is known not to have received chemotherapy) or *acquired* resistance (where the patient is known to have received chemotherapy). Although Australian data for 1995 was included in the first project report,[13] it was not possible to differentiate resistance categories; the resistance was therefore listed as *combined* (denoting that treatment history is unknown). Drug resistance surveillance in Australia would be more productive if laboratory data were able to be linked to information in the NMSS database. The latter includes ethnicity data, but not details of previous treatment for tuberculosis. While concerns for privacy issues, and the difficulty in collecting accurate information on treatment are acknowledged, it must be stated that, without better information from clinical sources, the laboratory data on drug resistance will continue to be under-utilised. Some individual States already match drug resistance data with patient ethnicity, treatment history and other factors, but there is an unquestionable need for a uniform national approach.

Within the limitations of laboratory data, this report shows only minor changes in the epidemiology of tuberculosis in Australia. The overall rate is stable at around 4 cases per 100,000 per year and the distribution of cases by age and gender is in keeping with results from previous years. A noteworthy finding is that lymph node infections in females are accounting for an increasing proportion of total cases. There is also the apparent upward trend in the prevalence of strains resistant to H and/or R in persons with smear-positive pulmonary disease. This fact alone dictates that Australia's control program must at least be maintained, if not strengthened. More than ever, Australia needs modern and efficient diagnostic laboratories working with medical personnel skilled in the management of 'problem cases' of tuberculosis.

Acknowledgements

The Mycobacterium Reference Laboratory Network comprises:

- Queensland Diagnostic and Reference Laboratory for Mycobacterial Diseases, The Prince Charles Hospital, Chermside, Queensland
- Mycobacterium Reference Laboratory, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales
- Mycobacterium Reference Laboratory, Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria
- Mycobacterium Reference Laboratory, Institute of Medical and Veterinary Sciences, Adelaide, South Australia
- Mycobacterium Reference Laboratory, Centre for Pathology and Medical Research, The Queen Elizabeth II Medical Centre, Nedlands, Western Australia

The willing assistance of William Chew, Dr Lyn Gilbert, Frank Haverkort, Regina Lasaitis, Richard Lumb, Graeme Oliver, Tina Parr and Aina Sievers is acknowledged with thanks. The author is grateful for clinical advice provided by Dr Anil Patel and Dr Tasos Konstantinos.

References

1. Raviglione MC, Snider DE, Kochi A. Global epidemiology of tuberculosis: Morbidity and mortality of a worldwide epidemic. *JAMA* 1995;272:220-226.
2. Oliver G, Harvey B. Tuberculosis notifications in Australia, 1995. *Commun Dis Intell* 1997;21:261-269.
3. Tuberculosis Working Party of the National Health and Medical Research Council. Towards Elimination of Tuberculosis II (Final Draft). May 1998.
4. Dawson D, Anargyros P, Blacklock Z *et al*. Tuberculosis in Australia: An analysis of cases identified in reference laboratories in 1986-88. *Pathology* 1991;23:130-134.
5. Dawson DJ, Cheah DF, Chew WK, Haverkort FC, Lumb R, Sievers AS. Tuberculosis in Australia, 1989-1992: Bacteriologically confirmed cases and drug resistance. *Med J Aust* 1995; 162:287-290.

6. Curran M, Dawson D. Tuberculosis in Australia: Bacteriologically confirmed cases and drug resistance, 1993. *Commun Dis Intell* 1995; 19:343-345.
7. Dawson D. Tuberculosis in Australia: Bacteriologically confirmed cases and drug resistance, 1994 and 1995. *Commun Dis Intell* 1997; 21:245-249.
8. Patel A, Streeton J. Tuberculosis in Australia and New Zealand into the 1990's. 1990. Australian Government Publishing Service, Canberra.
9. Gilroy N, Oliver G and Harvey B. Tuberculosis notifications in Australia, 1996. *Commun Dis Intell* 22;9:173-183.
10. World Health Organization. TB is the single biggest killer of young women. Global Tuberculosis Programme, Geneva 1998. (Press release)
11. HIV/AIDS and related diseases in Australia: Annual Surveillance Report 1997. National Centre in HIV Epidemiology and Clinical Research, Sydney.
12. Cohn DL, Bustreo F, Raviglione MC. Drug resistant tuberculosis: review of the worldwide situation and the WHO/IUATLD Global Surveillance Project. *Clin Infect Dis* 1997; 24: S121-30.
13. Anti-tuberculosis drug resistance in the world. The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. WHO/TB/97.229. WHO Global Tuberculosis Prorgamme, Geneva. 1997.