Tuberculosis in Australia: bacteriologically confirmed cases and drug resistance, 1994 and 1995

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 isolates of *Mycobacterium tuberculosis* reported during 1994 and 1995. The total number of confirmed isolates was 708 in 1994 and 705 in 1995. This represents an annual incidence of approximately 4 cases of laboratory confirmed tuberculosis per 100,000 population. These figures are similar to those reported in previous years and confirms that the incidence of tuberculosis in Australia remains stable. The incidence rate varied between States. Overall the male:female ratio fell, and there were signs of a downward shift in the median age. We were unable to assess the impact of HIV infection on the number of isolates reported. Positive microscopy was obtained in 55-60% of patients with pulmonary disease. Approximately 8% of isolates had *in vitro* resistance to at least one of the four standard anti-tuberculosis drugs. Over the two year period seven strains were found to be multi-drug resistant. Overall, the data from 1994 - 1995 gives no indication of a significant change in the drug susceptibility profiles of isolates from Australian patients with tuberculosis.

Introduction

Globally, tuberculosis (TB) remains an unconquered disease. The World Health Organization (WHO) estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis*, and that more than 4 million deaths occur each year[1]. In many developing countries, particularly Africa and Asia, co-infection with HIV and the emergence of drug-resistant strains pose major threats to national TB control programs[2,3]. The annual incidence of TB in Australia is low[4]. However the presence of population sub-groups with comparatively high rates of infection, and migration from neighbouring high incidence countries dictates that we maintain an effective national program.

Surveillance data for TB in Australia is available from two different sources. These are (i) the National Mycobacterial Surveillance System (conducted by the Communicable Diseases Network Australia New Zealand) and (ii) the Australian Tuberculosis Reporting Scheme

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Table 1. MTBC isolates in Australia, 1994 and 1995, by State or Territory

State	1994		1995	
	Isolates	Isolates per 100,000 population	Isolates	Isolates per 100,000 population
New South Wales[1]	278	4.4	305	4.8
Victoria	217	4.8	186	4.1
Queensland	88	2.8	86	2.6
Western Australia	53	3.1	56	3.2
South Australia	41	2.8	33	2.2
Tasmania	10	2.1	2	0
Northern Territory	21	12.3	37	21.3
Total	708	4.0	705	3.9

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

(part of the Mycobacterium Reference Laboratory Network).The National Mycobacterial Surveillance System is based on clinical notifications[4]. Data from the laboratory network relates to cases confirmed by isolation of the *M. tuberculosis* complex (MTBC). The laboratory network has previously published reports for 1986 to 1993 [5,6,7]. The data for 1994 and 1995 are presented in this report.

Methods

The Australian Tuberculosis Reporting Scheme is a joint project of the Mycobacterium Reference Laboratory Network and the Department of Health and Family Services. The data are based on isolates of MTBC from clinical specimens. Due to the specialised nature of TB bacteriology, it can be assumed that the five laboratories that comprise the Mycobacterium Reference Laboratory Network account for almost all, if not all, of the bacteriological diagnoses in Australia. Comparable bacteriological procedures were used in each of the reference laboratories. Relapse patients, that is, those previously diagnosed, treated and considered cured, were included in these data as laboratories cannot usually differentiate these 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 from contributing laboratories were submitted for each calendar year, 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.

The nature of the first clinical sample that yielded an isolate of MTBC was used to record the site of disease. Culture-positive specimens taken during the bronchoscopy, as well as

Figure 1. MTBC isolates, 1994 and 1995, by age group and sex

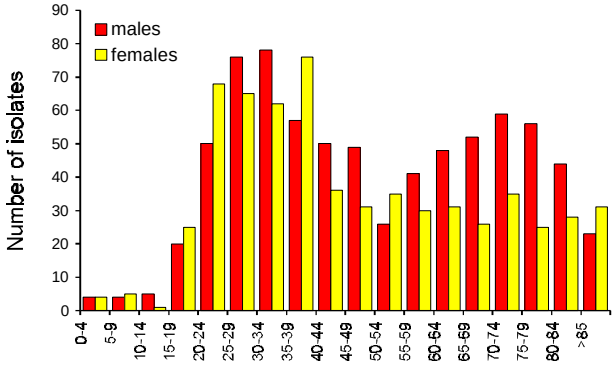

Figure 2. MTBC isolates, 1994 and 1995, by site of disease

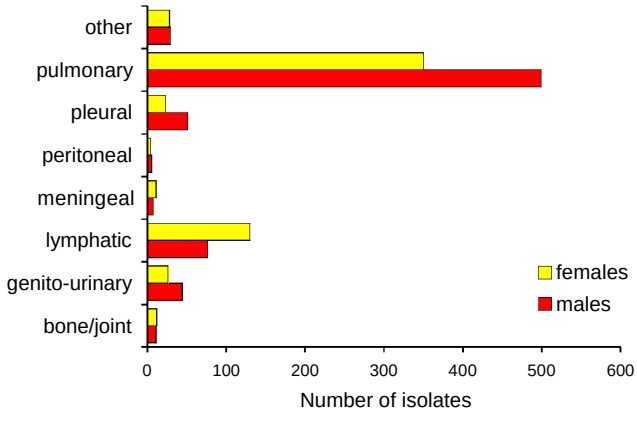

Table 2. Microscopy results for MTBC pulmonary isolates, 1994 and 1995, by State or Territory

State of Residence	1994[1]			1995[2]		
	Positive	Negative	Unknown	Positive	Negative	Unknown
New South Wales	3	1	162	13	16	150
Victoria	59	55	5	61	42	0
Queensland	32	26	0	41	25	1
Western Australia	19	15	0	25	14	1
South Australia	13	1	13	9	11	1
Tasmania	0	0	6	0	0	1
Northern Territory	5	9	1	18	11	0
Total	131	107	187	167	120	154

1 A total of 425 cases of pulmonary disease were recorded in 1994

2 A total of 444 cases of pulmonary disease were recorded in 1995

gastric washings, were taken to identify cases of pulmonary disease. In most cases of multi-site disease, sputum yields 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 presented. Similarly, it is not always possible to categorise cases of miliary and disseminated disease from data available to laboratories.

Results

Total reports

In 1994 and 1995 there were 708 and 705 laboratory isolates of MTBC respectively. These figures represent an annual incidence of approximately 4.0 cases of laboratory confirmed tuberculosis per 100,000 population. The rate varied markedly between States and Territories (Table 1).

The overall male:female ratio was 1.3:1 in 1994 and 1.2:1 in 1995. In both years the median age group for males was 45-49 years. For females it was 40-44 years in 1994 and 35-39 years in 1995 (Figure 1). There was a low rate of reporting for children less than 10 years of age. Of the seven isolates from this age group in 1994 and 10 in 1995, the majority were pulmonary infections. Laboratories identified only one case of meningeal disease in a young child.

Five diagnoses in 1994 and one in 1995 were associated with HIV infection.

Site of disease

Pulmonary sites accounted for approximately 60% of all cases diagnosed (Figure 2), with lymphatic disease in approximately 15% of all cases. During the period reviewed, 22.3% of females with tuberculosis presented with lymphatic disease.

Smear-positivity in pulmonary disease

Microscopy results were available for the majority of cases of pulmonary disease in all States except for New South Wales. Future reports from the Australian Tuberculosis Reporting Scheme are expected to include more complete data for New South Wales. Positive microscopy was obtained for 55-60% of patients for whom a result was available (Table 2).

Causative organism

The majority of TB-related isolates during 1994 and 1995 were *M. tuberculosis*. In both of the years studied, four isolates from adults were identified as *M. bovis*.

In vitro drug susceptibility

The standard drugs for the treatment of TB are isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z). In 1994, 658 of 707 isolates (93%) tested were fully susceptible to each drug in the E+H+R+Z drug regimen. Six hundred and thirty nine of 705 isolates (91%) tested in 1995 were fully sensitive (Table 3). In 1994, 47 strains (6.6%) were resistant to only one of these compounds, whereas the corresponding figure for 1995 was 60 (8.5%). Resistance to H alone was recorded for 5-6% of isolates. Resistance to R alone was found in two isolates in 1994 and three in 1995. Ten isolates identified as *M. tuberculosis* were found to be resistant to Z alone. All but one of these was reported from the New South Wales reference laboratory. Multi-resistant profiles (Table 4) indicate that two patients diagnosed in 1994, and five patients in 1995, were infected with strains resistant to both H and R. Such strains are referred to as being multi-drug-resistant (MDR). One case of MDR-TB was diagnosed from bronchial washings which were microscopy-positive. Isolates from all but one of the six patients known to be HIV positive were found to be fully-susceptible.

Discussion

The number of isolates reported for 1994 and 1995 are similar to those recorded for 1993[7]. It can be concluded that the incidence of laboratory confirmed TB in Australia is stable. The same conclusion was reached in the most recent analysis of clinical notifications[4]. It is expected that case totals from clinical

Table 3. MTBC isolate drug resistance, 1994 and 1995, by drug

	1994			1995		
Drug	Total isolates	Resistant	% resistant[1]	Total isolates	Resistant	% resistant[1]
Isoniazid (H)	707	43	6.1	705	53	7.5
Rifampicin (R)	707	4	0.6	705	8	1.1
Ethambutol (E)	707	0	0.0	705	2	0.3
Pyrazinamide[2](Z)	429	4	0.9	648	13	2.0
Streptomycin (S)	359	43	12.0	191	12	6.3

1 Percentage of strains tested which were resistant to drug alone or in combination with others

2 All strains of *M bovis* are resistant to pyrazinamide.

notifications will exceed those from laboratory sources. In 1994, 960 cases were recorded by the National Mycobacterial Surveillance System, indicating that only around 75 per cent of reported clinical cases were supported by definitive laboratory diagnoses.

Overall, these findings parallel those presented in previous laboratory reports[6,7], and are in general agreement with those from clinical notifications. Differences in rates between States is probably due to varying distributions of persons in high risk categories, including migrants from South East Asian communities and Aboriginal Australians. Differences in rates within States for the two periods under review must be interpreted with caution, particularly for the less populous States, and no conclusion should be drawn.

The male:female ratios for 1994 and 1995 were lower than those recorded by this scheme in previous years[5]. Earlier reports identified the significant skew to males in older age-groups, and the variation of the male:female ratio with site-of-disease. For example, in cases of lymphatic disease, the male:female ratio has been found to be around 1:2, whereas for pleural disease it is greater than 3:1. Increasing numbers of females, particularly in the middle age-groups, with lymphatic disease, and from South East Asian countries, are probably contributing to this change.

In both years the median age group for males was 45 - 49 years. For females it was 40 - 44 years in 1994 and 35 - 39 years in 1995. The corresponding ages for the period 1989-1992 were 50 - 54 years (male) and 40 - 44 years (female) [6]. This apparent shift towards the younger age groups, if true, is probably attributable to the increasing proportion of migrants from South East Asian countries, who are generally younger than the Australian population as a whole. A downward shift in age group distribution could also be explained by increasing numbers of TB linked to HIV infection; this however has not been determined. There are, in Australia at present, relatively small numbers of such cases[4].

As expected, the site of disease reported by this scheme is similar to reports based on clinical notifications[4]. The frequent occurrence of lymph node infections in females is, again, a striking feature. During the period reviewed, 22% of females with tuberculosis presented with lymphatic disease. The corresponding figure in 1989-1992 was 18%[6], while in 1986-1988, it was 14%[5]. The most likely explanation for this change is that the number of females from South East Asia in the middle age groups is increasing. The proportion of females with pulmonary disease fell from 67% in 1986-1988 to just below 60% in 1994-1995.

Information regarding HIV status is not always available to laboratories; therefore the number of isolates reported in association with HIV infection must be viewed as an underestimate of the true number. Notification data show that in 1995 there were at least six cases of TB in patients with HIV[4].

When interpreting the microscopy results it must be noted that around one-quarter of all pulmonary diagnoses were made from bronchoscopy collections, rather than from sputum. Positive microscopy in a bronchoscopy collection should not be taken as proof that a patient was infectious. Given that the sputum microscopy result is a major criterion for contact-tracing, physicians should where practicable, arrange sputum testing prior to bronchoscopy being carried out.

Patients with 'smear-positive' pulmonary tuberculosis are regarded as more likely to transmit infection than others. A positive acid-fast microscopy result in a case of suspected tuberculosis is a valuable finding, providing a basis for prompt intervention, and initiation of case-finding activities. In order to provide information on this, in 1994 the laboratory database was expanded to include microscopy results.

Differentiation of the subspecies within the MTBC can be useful in contact-tracing, and for identifying occupationally-acquired disease due to *M. bovis*. In almost every case of TB diagnosed in the Australian laboratories, appropriate tests are performed in order to differentiate *M. tuberculosis*, *M. bovis* and *M. africanum*. Isolates of BCG strain are not included in the laboratory database. In keeping with earlier reports, the majority of isolates were *M. tuberculosis*.

Although rarely used in Australia, streptomycin (S) is frequently listed as a 'first-line' drug for the treatment of TB[8]. Since susceptibility testing for S is no longer carried out in the reference laboratories in New South Wales and Victoria (the States with the highest numbers of patients from countries where resistance to S is most prevalent), the data shown for S in Table 3 may not reflect the situation across Australia as a whole. In 1993, 20% of 443 isolates tested were resistant to S[7]. Clinicians should note

Table 4. MTBC isolate drug resistance, 1994 and 1995, by drug combination

Multi-resistance pattern[1]	Number of Isolates	
	1994	1995
H + R + E + S[2]	0	1
H + R + Z[2]	0	1
H + R + S[2]	0	2
H + R[2]	2	1
H + E	0	1
H + S	4	6

1 H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin

2 Strains resistant to H and R in combination are considered 'multi-drug-resistant'

that resistance to H is frequently associated with resistance to S.

The finding that 10 isolates of *M. tuberculosis* were resistant to Z alone may suggest that resistance to Z in *M. tuberculosis* might be more common than is generally appreciated; alternatively these results could reflect the technical difficulty in performing susceptibility tests for Z.

The drug susceptibility tests for the period reviewed show no notable changes in the prevalence of drug-resistant strains in the Australian population. During the five years, 1989 - 1993, 31 isolates were found to be resistant to H+R[6,7]. The current data show that the prevalence of such strains among cases of active TB in Australia is not increasing. It must be stressed however, that around one in every 15 patients is infected with a strain resistant to either H or R, or to H+R. For therapy to be optimally effective, such patients should be promptly identified and treated on an individual basis by experienced clinical personnel. Routine drug susceptibility tests, carried out in competent laboratories and with due regard to rapid testing and reporting mechanisms, are indispensable components of Australia's tuberculosis program.

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