

TUBERCULOSIS IN AUSTRALIA: BACTERIOLOGICALLY CONFIRMED CASES AND DRUG RESISTANCE, 2010

A report of the Australian Mycobacterium Reference Laboratory Network

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Abstract

The Australian Mycobacterium Reference Laboratory Network collects and analyses laboratory data on new cases of disease caused by the *Mycobacterium tuberculosis* complex. In 2010, a total of 1,051 cases were identified by bacteriology; an annual reporting rate of 4.7 cases per 100,000 population. Twelve children aged less than 10 years had bacteriologically-confirmed tuberculosis. Results of *in vitro* drug susceptibility testing were available for 1,050 isolates for isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and pyrazinamide (PYZ). A total of 126 (12%) isolates of *M. tuberculosis* were resistant to at least one of these anti-tuberculosis agents. Resistance to at least INH and RIF (defined as multi-drug resistance, MDR) was detected in 37 (3.5%) isolates, including three Australians with extensive travel in high burden TB countries; 33 were from the respiratory tract (sputum $n=28$, bronchoscopy $n=5$). Nineteen (65.5%) of the MDR-TB-positive sputum specimens were smear-positive, as were single samples from bronchoscopy and urine. Sixteen patients with MDR-TB were from the Torres Strait Protected Zone. If these Papua New Guinea nationals are excluded from the analysis, the underlying MDR-TB rate in Australian isolates was 2.0%. One case of extensively drug-resistant TB (defined as MDR-TB with additional resistance to a fluoroquinolone and an injectable agent) was detected in 2010.

Keywords: *Mycobacterium tuberculosis*, *Mycobacterium bovis*, laboratory diagnosis, tuberculosis, 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. For non-indigenous persons born in Australia, the notification rate is around 0.7 per 100,000 population.¹ In both 2008 and 2009, more than 85% of notified cases occurred in the overseas-born population. The current epidemiology of TB in Australia is largely a direct effect of the global TB situation with overseas-born persons contributing to a steadily increasing number

and proportion of notifications since 2002. In 2007 and 2008, treatment success was attained in 95% of cases, well above the national target of 90%.²

Nationals from Papua New Guinea who are able to access Australian health care facilities in the Torres Strait Protected Zone (TSPZ) continue to influence Australian laboratory data. In 2008 and 2009, there were 40 notifications of TB among this patient group reported to NNDSS. Drug susceptibility testing was performed for 30 patients in 2009. Eleven of the 30 patients had MDR-TB and a further three had mono-resistance to rifampicin.^{1,3}

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 have been 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 2010. This report should be considered in conjunction with the National TB Advisory Committee (NTAC) TB notification report.⁴

Methods

These data are based on clinical specimens that were culture-positive for *Mycobacterium tuberculosis* complex (MTBC). 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 NTAC,² were included in the laboratory data as laboratories are generally unable to differentiate relapse cases from new cases. Data include temporary visitors to Australia, asylum seekers and persons detained in Australia in correctional services facilities. 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 2010 supplied by the Australian Bureau of Statistics.⁵ 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 (a proxy for primary resistance) was defined as the presence of resistant isolates of *M. tuberculosis* in patients who, in response to direct questioning, report that they had not 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.⁶ Drug resistance among previously treated cases (a proxy for acquired resistance) is defined as the presence of resistant isolates of *M. tuberculosis* in cases who, in response to direct questioning, report 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.⁶ For 2009 onwards, the AMRLN has been requested by NTAC to provide laboratory data on bacteriologically confirmed isolation of *Mycobacterium bovis* (bacille Calmette Guérin) (BCG).

Results

There were 1,051 bacteriologically-confirmed cases of tuberculosis in 2010 (Figure 1), representing an annual rate of 4.7 cases per 100,000 population. State-specific reporting rates varied from 1.8 (Tasmania) to 10.0 (Northern Territory) cases per 100,000 population (Table 1).

Causative organism

Almost all isolates were identified as *M. tuberculosis* (n=1,045), the remaining isolates being *Mycobacterium africanum* (n=2), *M. bovis* (n=2), *Mycobacterium orygis* (formerly known as the "Oryx" bacillus; n=1) and a mixed *M. tuberculosis* complex/*Mycobacterium avium* isolation (n=1). In addition, a total of 18 *M. bovis* (BCG) were isolated from clinical samples.

Distribution by sex, age and site of disease

Complete information for gender and age was available for 1,047 patients. Of the 1,047 MTBC isolates, 457 (44%) were from females, 589 (56%) were from males, and sex was not recorded for 1 case. The site of disease was dependent upon age and sex. The overall male:female ratio was 1.3:1. For respiratory isolates, the male:female ratio was 1.4:1. For TB lymphadenitis, the female:male ratio was 1.4:1. For males, there were two distinct peaks in age-group specific rates of bacteriologically-confirmed TB; 14.1 cases of TB per 100,000 population at 25 to 29 years and a second peak in elderly males aged

Table 1: Bacteriologically confirmed cases of tuberculosis in Australia, 2000 and 2008 to 2010, and rate per 100,000 population by State or Territory

| State or territory | 2010 | | 2009* | | 2008* | | 2000* | |
|--------------------|------|------|-------|------|-------|------|-------|------|
| | n | Rate | n | Rate | n | Rate | n | Rate |
| New South Wales† | 370 | 4.9 | 409 | 5.5 | 327 | 4.5 | 307 | 4.5 |
| Victoria | 344 | 6.2 | 331 | 6.1 | 299 | 5.6 | 231 | 4.8 |
| Queensland | 166 | 3.7 | 153 | 3.4 | 111 | 2.6 | 76 | 2.1 |
| Western Australia | 87 | 3.8 | 87 | 3.9 | 72 | 3.3 | 63 | 3.3 |
| South Australia | 52 | 3.2 | 51 | 3.1 | 49 | 3.1 | 41 | 2.7 |
| Tasmania | 9 | 1.8 | 7 | 1.4 | 3 | 0.6 | 2 | 0.4 |
| Northern Territory | 23 | 10.0 | 24 | 10.9 | 25 | 11.4 | 45 | 23.0 |
| Total | 1051 | 4.7 | 1,062 | 4.9 | 886 | 4.1 | 765 | 4.0 |

* 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.

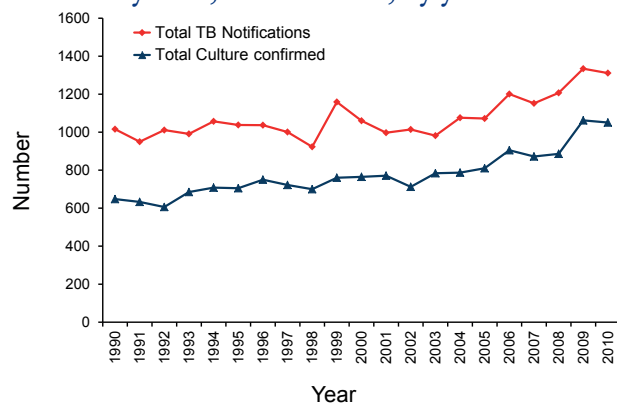
more than 75 years (greater than 9 cases of TB per 100,000 population). The age distribution of female cases was similar with 12.5 and 7.3 bacteriologically-confirmed TB cases per 100,000 population in the 25 to 29 and 80 to 84 year age groups, respectively. The median age for patients with bacteriologically-confirmed disease was 32 years for both males and females. The predominant culture-positive respiratory specimen was sputum (n=505), a further 137 specimens were obtained from bronchoscopy, 10 were aspirates, and 3 from lung biopsies. Fifty-five pleural specimens (44 fluid, 11 biopsy/tissue) were culture positive. The most commonly encountered extrapulmonary culture-positive specimen was lymph tissue (n=184) followed by pleural (n=55), bone/joint (n=32), genitourinary tract (n=24), and peritoneal (n=23) specimens.

Six children aged under 10 years (male n=2, female n=4) had bacteriologically-confirmed tuberculosis (sputum n=3, gastric aspirate n=2, bronchoscopy n=1). None of the specimens were smear positive and all were fully susceptible to first line anti-TB drugs. An additional 6 children (males n=5) from TSPZ were bacteriologically confirmed for TB (an isolate each from lymph node, brain tissue, leg aspirate, urine, sputum, gastric aspirate). Of these, 4/6 specimens were smear positive including sputum and brain tissue. Drug resistance was prevalent amongst cases in children from the TSPZ, including MDR (n=2) and resistance to streptomycin and isoniazid (n=2).

Association with HIV

The AMRLN database recorded the HIV status of only 91 (8.6%) patients. One patient was identified as being HIV-seropositive.

Figure 1: Tuberculosis notifications and laboratory data, 1990 to 2010, by year



Microscopy

Microscopy was available for 1,010 of the bacteriologically-confirmed cases in 2010. Microscopy was not performed on 33 specimens and no result was provided for the remaining 8 specimens. The majority of samples without a microscopy performed were from extrapulmonary sites. Smears were positive in 267 of 505 (52.9%) sputum and 37 of 137 (27.0%) bronchoscopy specimens respectively (Table 2). Of 55 pleural specimens (11 biopsy and 44 fluids) that were culture-positive for *M. tuberculosis* and reported a microscopy result, 4 fluids and 1 biopsy were smear-positive. Lymph node specimens were smear-positive in only 38 of 184 (20.6%) of cases.

Drug susceptibility testing

Results of *in vitro* drug susceptibility testing were available for all but one isolate (1,050/1,051) for isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and pyrazinamide (PYZ). A total of 126 (12.0%) *M. tuberculosis* isolates were resistant to at least one of these. Resistance to at least INH and RIF (defined as MDR-TB) was detected in 37 (3.5%) isolates. All of the MDR-TB isolates were *M. tuberculosis* (Table 3). Of the 37 MDR-TB isolates, 33 were from the respiratory tract (sputum n=28, bronchoscopy n=5). Isolates of MDR-TB were obtained from the following non-respiratory sites: lymph node (n=2), a thigh aspirate and a urine specimen.

Sixteen patients with MDR-TB were from the TSPZ, and these patients access health services in the outer TSPZ. MDR-TB was also isolated from patients born in the Philippines (n=4), India (n=3), China (n=2), Vietnam (n=3), Myanmar (n=2) with a single case each from Ethiopia, Papua New Guinea, South Korea, and unknown. Three Australians were identified with MDR-TB, all had a history of extensive travel in high-burden countries including the Philippines and South Africa. In the past three years (2005-07), the impact of MDR-TB cases from the TSPZ have lifted the proportion of MDR-TB cases above the 0.5 – 2.0% range (Figure 2).

In 2010, 3.5% of all isolates were MDR-TB, but only 2.0% when the Papua New Guinea TSPZ isolates were excluded. When the TSPZ isolates were excluded, 21 MDR-TB cases were documented from patients living in Australia. Of these, 14 were sputum, 5 were bronchoscopy specimens, and two were from lymph nodes. Ten of the sputum specimens were smear positive, as was a single bronchial washing.

The revised definition of extensively drug resistant-resistant-TB (XDR-TB) is an isolate that has resistance to at least INH and RIF (MDR-TB) plus

Table 2: Site of specimens smear- and culture-positive for *Mycobacterium tuberculosis* complex, 2010

| | N* | Smear positive | % |
|----------------|-----|----------------|------|
| Sputum | 505 | 267 | 52.9 |
| Bronchoscopy | 137 | 37 | 27.0 |
| Lymph node | 184 | 38 | 20.6 |
| Pleural | 55 | 5 [#] | 9.1 |
| Genito-urinary | 24 | † | |
| Bone/Joint | 32 | † | |
| Peritoneal | 23 | † | |
| Skin | 5 | † | |
| CSF | 10 | † | |

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

One pleural biopsy and four pleural fluids were smear positive

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

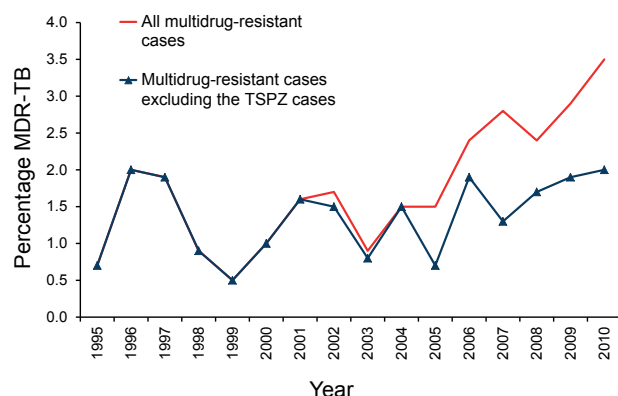
Table 3: Drug resistance patterns in multi-drug resistant strains of tuberculosis, Australia 1995 to 2010

| Resistance pattern (standard drugs)* | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
|--------------------------------------|---------|----------|----------|---------|---------|---------|----------|----------|---------|----------|----------|----------|----------|----------|----------|----------|
| H+R only | 3 | 10 | 6 | 2 | 2 | 3 | 8 | 8 | 4 | 7 | 5 | 16 | 16 | 10 | 21 | 18 |
| H+R+E | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 3 | 1 | 2 | 3 | 1 | 1 |
| H+R+Z | 1 | 4 | 5 | 2 | 1 | 3 | 3 | 1 | 1 | 1 | 1 | 0 | 5 | 3 | 7 | 15 |
| H+R+E+Z | 0 | 0 | 2 | 1 | 0 | 1 | 0 | 2 | 0 | 2 | 3 | 5 | 1 | 5 | 2 | 3 |
| XDR-TB | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| TOTAL (%) | 5 (0.7) | 15 (2.0) | 14 (1.9) | 6 (0.9) | 4 (0.5) | 8 (1.0) | 12 (1.6) | 12 (1.7) | 7 (0.9) | 12 (1.5) | 12 (1.5) | 22 (2.4) | 24 (2.8) | 21 (2.4) | 31 (2.9) | 37 (3.5) |

* the streptomycin result was not considered for this table

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

Figure 2: Percentage MDR-TB in Australia; all cases excluding the TSPZ zone



additional resistance to a fluoroquinolone and an injectable (kanamycin, amikacin, capreomycin).¹⁰ In 2010, there was a single case of XDR-TB in a 33 year old male where the isolate was resistant to amikacin and ciprofloxacin (but was susceptible to moxifloxacin). One other MDR-TB isolate also had resistance to a quinolone.

Mono-resistance to isoniazid (INH) was detected in 49 isolates; mono-resistance to RIF (n=3), EMB (n=1), and PYZ (n=4) was also detected (Table 4). One hundred and ten isolates demonstrated resistance to INH at a concentration of 0.1 mg/L. Of these, 62 (56.3%) demonstrated resistance to INH at the higher level of 0.4 mg/L. Among MDR-TB strains, 15/37 (40.5%) demonstrated INH resistance at the higher concentration (0.4 mg/L). Forty-seven (37.3%) of 126 of specimens culture-positive for drug resistant strains, including 38 of 88 (43.2%) sputum or bronchoscopy specimens, were smear-positive for acid-fast bacilli. The single *M. bovis* isolate which is inherently resistant to pyrazinamide, was not included in the above analyses.

Results of testing for streptomycin (STR) were available for 345 of 1,050 (32.9%) isolates with 54 demonstrating resistance to at least STR; 8 had mono-resistance, 19 were resistant to STR and INH, and 25 of 31 MDR-TB strains reporting a S-result were also STR-resistant.

New or previously treated cases, and country of birth

Of the 126 *M. tuberculosis* isolates resistant to at least one of the standard drugs, 61 (48.4%) were from new cases, 7 (5.5%) from previously treated cases, and no information was available on the remaining 58 cases. Nine were Australian-born, 116 were overseas-born, and the country of birth of one case was unknown. The 116 overseas-born persons with drug resistant disease were from 20 countries; most frequently from Papua New Guinea (including

Table 4: Drug resistance profiles, 2010

| | 2010 |
|---|-------------|
| ANY RESISTANCE | |
| S | 54 |
| H | 110 |
| R | 40 |
| E | 7 |
| Z | 26 |
| MONO RESISTANCE | (65) |
| S | 8 |
| H | 49 |
| R | 3 |
| E | 1 |
| Z | 4 |
| MDR-TB | (37) |
| HR | 4 |
| HRZ | 7 |
| HREZ | 1 |
| SHR | 15 |
| SHRE | 1 |
| SHRZ | 7 |
| SHREZ | 2 |
| XDR-TB | (1) |
| HRZ + resistance to amkican, capreomycin, ciprofloxacin | 1 |
| POLY RESISTANCE | (24) |
| SH | 19 |
| SHE | 1 |
| SHEZ | 1 |
| Total isolates | 1,051 |
| Total isolates and DST completed | 1,050 |
| Fully susceptible | 924 |

TSPZ) (n=23), India (n=14), Vietnam (n=13), China (n=10), Philippines (n=8), and Myanmar (n=6).

Isolation of *M. bovis* (BCG)

There were 18 isolations of *M. bovis* (BCG) in 2010. Thirteen were cultured from males (4 aged ≤ 5 years) and from 5 females (4 aged ≤ 5 years). Seven isolations were from the vaccination site or axilla, and all were children aged ≤ 5 years. Nine males (age range: 60 to 86 years) had *M. bovis* (BCG) isolated from urine. In addition, *M. bovis* (BCG) was isolated from an ankle biopsy from a two-year old female, and also buttock pus from a 22 year old female.

Discussion

The detection of 1,051 laboratory-confirmed cases of TB in 2010 representing 4.7 cases per 100,000 population is slightly lower than the 4.9 cases per 100,000 population reported in 2009.³ Previously, the incidence of bacteriologically confirmed TB was between 3.5 and 4.4 cases per 100,000 population (see previous AMRLN reports) but has now risen above the upper limit twice in the past two years. As expected, the number of cases notified to the NNDSS was higher than for bacteriologically confirmed TB.³ The most frequent reasons postulated for the extra cases reported in the NNDSS database include: diagnosis of childhood and extrapulmonary TB based on clinical, radiological and epidemiological information, and submission of extrapulmonary samples in formalin precluding bacteriological investigations. There were 1,311 notifications of tuberculosis in 2010 compared with 1,051 (80.2%) cases confirmed bacteriologically.⁴ In the past decade, the proportion of notifications confirmed by culture has stayed within a range of 70-80% bacteriological confirmations (see previous AMRLN reports).

The number of isolates with resistance to any drug (including streptomycin) was 126 (12.0%), a reduction from the peak of 15.9% recorded in 2009.³ Mono-resistance to INH remains the most frequently encountered mono-resistance profile in Australia. Resistance to INH at higher MIC levels was observed in 56.3% of isolates. High level INH resistance is associated with mutations in *katG* whilst low level INH resistance is associated with mutations in *inhA* and *ethA*.^{7,8,9} Strains with low-level INH resistance may have cross-resistance to ethionamide, a structural analogue of INH.^{8,9} Ethionamide is a second-line drug used commonly in standard regimens for treatment of drug-resistant TB.¹⁰

MDR-TB remains at a low but concerning level. Since the AMRLN began preparing annual reports in 1985, the proportion of patients with MDR-TB has stayed within a band of 0.5-2.0%, but since 2000, the influence of MDR-TB cases occurring in people moving within the TSPZ has pushed the percentage above 2%. In 2010, when the 16 TSPZ isolates were included, the MDR-TB rate was 3.5%, the highest level since records began in 1985. When the TSPZ isolates were excluded, the proportion of MDR-TB isolates was 2.0%. In 2010, there were no TSPZ patients with mono-rifampicin resistance compared with three patients in 2009.

For the first time since 2004, an XDR-TB isolate was reported. The isolate from the smear-positive patient was resistant to STR, INH, RIF, EMB, PYZ, amikacin, capreomycin, ofloxacin, and ethionamide. Since 1995, 257 cases of MDR-TB have been documented, and of these, only 2 (0.8%) have been

confirmed using current internationally-recognised breakpoints for drug susceptibility testing (DST) as XDR-TB (see previous AMRLN reports).

The emergence of “totally drug-resistant TB” (TDR-TB) in Iran and now India was the culmination of *M. tuberculosis* acquiring mutations associated with resistance to ever more classes of anti-TB agents.¹¹ The Indian report described four cases from the Hinduja hospital where resistance was documented for all first-line (INH, RIF, EMB, PYZ, STR) and second-line (kanamycin, capreomycin, amikacin, levofloxacin, moxifloxacin, ethionamide and para-amino-salicylic acid, PAS) anti-TB drugs.¹² Erratic treatment by multiple doctors in private practice was held responsible for the emergence of TDR-TB. There are now 14 TDR-TB cases in the Hinduja hospital. In a recent editorial, one of the authors involved in reporting the Indian cases wrote a scathing account of the global failure to utilise anti-TB drugs in a manner that did not generate drug resistance.¹³ Exposure to the wrong drugs and/or to the wrong regimen, and/or to the wrong doses had created a selective pressure for the stepwise accumulation of mutations associated with resistance.

The definition and reliable detection of TDR-TB is confounded by some laboratory issues. Although drug susceptibility testing of the injectables and fluoroquinolones is now well established and shown to provide reliable consistent results; that cannot be said for PYZ, ethionamide, and PAS.¹⁴ Critical concentrations for kanamycin and PAS were not described in the 2008 WHO policy guidance document on DST for second-line anti-tuberculosis drugs, and were provided in a guidance update released at a Global Laboratory Initiative meeting in April 2012.¹⁵ The critical concentration (MGIT 960) for kanamycin is 2.5 µg/ml and 4.0 µg/ml for PAS. The critical concentration for levofloxacin has been reduced from 2.0 µg/ml to 1.5 µg/ml, and moxifloxacin has been revised upwards from 0.25 µg/ml to 0.5 µg/ml and also tested simultaneously at 2.0 µg/ml. There is still no critical concentration for cycloserine in liquid culture. Drug susceptibility testing for ciprofloxacin is no longer recommended.¹⁵

The 2010 laboratory data raise a biosafety issue and a public health issue. Firstly, 27% of bronchoscopy specimens were smear-positive. Bronchoscopic samples are superior to sputa (which may not always be obtainable) so some sputum-smear-negative but bronchoscopy-smear-positive cases will always be expected. Nonetheless, performing bronchoscopy on sputum smear-positive cases subjects them to a needless invasive procedure and exposes healthcare workers to *M. tuberculosis*. Bronchoscopists are therefore encouraged whenever possible to ensure that patients are confirmed as sputum-smear-negative before proceeding to bronchoscopy. Secondly, 65.5%

of the MDR-TB-positive sputum specimens in 2010 were smear-positive and therefore infectious. The state tuberculosis services, in collaboration with the laboratories, medical practitioners, public health authorities, migrant groups and other stakeholders, must attempt to minimise the interval between symptom onset and MDR-TB diagnosis and management, and hence curtail the infectivity of MDR-TB patients.

The much anticipated merging of the AMRLN and NNDSS databases has experienced further delays due to information technology limitations and transitions in various states. A combined database will not be available before 2012 dataset at the earliest. In the interim, Australia must continue to provide a combined prevalence of drug resistance and remains unable to provide comprehensive data to the World Health Organization global reports sub-classifying drug-resistance between new cases and previously-treated patients.

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- 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.
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