Antituberculosis drug resistance in New Zealand, 2003

Surveillance of antituberculosis drug resistance is based on the results of susceptibility testing of isolates in the Mycobacteriology Reference Laboratories at Auckland, Wellington and Waikato Hospitals. The laboratory results are matched with tuberculosis case notifications.

In 2003, 424 cases of tuberculosis were notified, 322 (75.9%) of which were reported by the Mycobacteriology Reference Laboratories as culture positive. Antimicrobial susceptibility testing results were available for all 322 isolates, which comprised 316 *Mycobacterium tuberculosis* and six *M. bovis* isolates. The proportion of isolates resistant to isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin is shown in Table 1, and trends in resistance to these five antimicrobials are shown in Figure 1. Since 1995, there has been a trend of increasing isoniazid ($p=0.0230$) and streptomycin ($p=0.0075$) resistance. However, these trends were only significant among cases born overseas. Pyrazinamide resistance has fluctuated from year to year, with no apparent trend. Rifampicin and ethambutol resistance has remained ≤2%.

Table 1. Resistance to each antimicrobial, 2003

Antimicrobial	Number tested	Number resistant[1]	Percent resistance[1]
Isoniazid	322	32	9.9
Rifampicin	322	2	0.6
Ethambutol	322	5	1.6
Pyrazinamide	322	18[2]	5.6
Streptomycin	322	23	7.1

Notes: 1 includes resistance alone or in combination with other antimicrobials
2 includes the six *M. bovis* isolates

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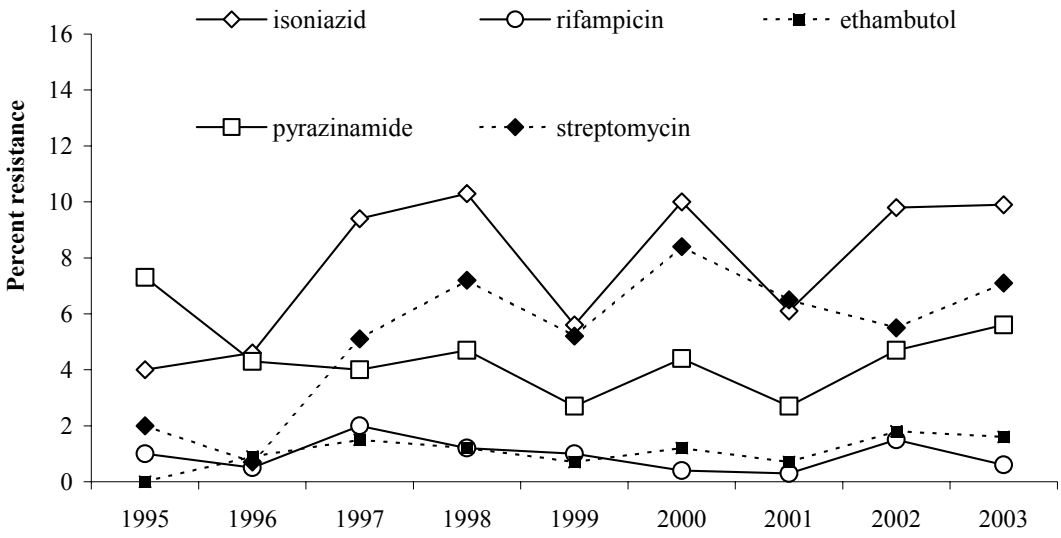
Figure 1. Resistance to each antimicrobial, 1995-2003



In 2003, the majority (81.1%) of the isolates were susceptible to all five antimicrobials tested (Table 2). There were two cases (0.6%) of multidrug-resistant tuberculosis (MDR-TB, resistance to at least isoniazid and rifampicin). MDR-TB is rare in New Zealand, with an average annual incidence of 0.7% and a total of 16 cases recorded in the nine years since national surveillance of antituberculosis-drug resistance began in 1995. Fifteen of the 16 MDR-TB cases identified since 1995 were people born overseas and assumed to have acquired their MDR-TB overseas. Both the 2003 MDR-TB cases had arrived in New Zealand within 15 months of their tuberculosis being diagnosed.

Table 2. Distribution of resistance patterns, 2003

	Number (%)	Resistance pattern[1]	Number (%) of isolates with each pattern
Fully susceptible	261 (81.1)		
Resistant to 1 agent	46 (14.3)	H	18 (5.6)
		Z	16 (5.0)[2]
		S	10 (3.1)
		E	2 (0.6)
Resistant to 2 agents	12 (3.7)	HS	10 (3.1)
		HE	1 (0.3)
		ZS	1 (0.3)
Resistant to 3 agents	2 (0.6)	HRZ[3]	1 (0.3)
		HSE	1 (0.3)
Resistant to 4 agents	1 (0.3)	HRSE[3]	1 (0.3)

Notes: 1 H, isoniazid; R, rifampicin; Z, pyrazinamide; S, streptomycin; E, ethambutol
2 includes the six *M. bovis* isolates
3 MDR-TB, multidrug-resistant tuberculosis, that is, resistant to at least isoniazid and rifampicin

A comparison of resistance among isolates from cases born in New Zealand and cases born overseas is presented in Table 3. Cases born overseas were significantly ($p \leq 0.05$) less likely to be fully susceptible and were more resistant to isoniazid. There were no other significant differences in resistance by place of birth.

Table 3. Resistance by case's place of birth, 2003[1]

	Percent		P value[3]
	New Zealand-born cases (n=75)	Overseas-born cases (n=221)	
Fully susceptible	90.7	77.4	0.0117
Resistant to:[2]			
Isoniazid	0	14.0	0.0006
Rifampicin	0	0.9	1.0000
Ethambutol	0	2.3	0.3346
Pyrazinamide	5.3	5.0	1.0000
Streptomycin	4.0	9.1	0.1581
MDR-TB[4]	0	0.9	1.0000

Notes: 1 information on place of birth unknown or not reported for 26 cases; these 26 cases included one isoniazid-resistant case and three pyrazinamide-resistant cases.
2 includes resistance alone or in combination with other antimicrobials
3 rates compared by the Chi-square test or Fishers Exact test, as appropriate
4 multidrug-resistant tuberculosis, that is, resistant to at least isoniazid and rifampicin

The geographic distribution of resistant isolates, based on aggregated health districts, is shown in Table 4. There were no statistically significant differences ($p \leq 0.05$) in resistance rates between the areas.

Table 4. Geographic distribution of resistance, 2003

Antimicrobial	Percent resistance (number resistant/number tested)[1]			
	Northern[2]	Midland[2]	Central[2]	Southern[2]
Isoniazid	10.4 (22/211)	2.9 (1/35)	14.6 (8/55)	4.8 (1/21)
Rifampicin	0.5 (1/211)	0 (0/35)	0 (0/55)	4.8 (1/21)
Ethambutol	1.4 (3/211)	0 (0/35)	0 (0/55)	9.5 (2/21)
Pyrazinamide	4.7 (10/211)	11.4 (4/35)	1.8 (1/55)	14.3 (3/21)
Streptomycin	9.0 (19/211)	5.7 (2/35)	1.8 (1/55)	4.8 (1/21)

Notes: 1 includes resistance alone or in combination with other antimicrobials
2 the Northern area includes the Northland, North West Auckland, Central Auckland, and South Auckland Health Districts; the Midland area includes the Waikato, Tauranga, Eastern Bay of Plenty, Gisborne, Rotorua, Taupo, Taranaki, and Ruapehu Health Districts; the Central area includes the Hawkes Bay, Wanganui, Manawatu, Wairarapa, Hutt, Wellington, and Nelson-Marlborough Health Districts; and the Southern area includes the Canterbury, South Canterbury, West Coast, Otago, and Southland Health Districts

Eighteen (5.6%) of the 322 culture-positive cases in 2003 were reported to be tuberculosis disease reactivations. Thirteen of these reactivation cases were originally diagnosed with tuberculosis overseas – in Korea (4 cases), Philippines (2), Cambodia (1), China (1), India (1), Nepal (1), Samoa (1), South Africa (1), and Zimbabwe (1). Four of the reactivation cases were originally diagnosed with tuberculosis in New Zealand. These four cases included two Maori, one Chinese, and one European. The place of original diagnosis was not reported for the remaining reactivation case. Information on previous treatment was recorded for 17 of the 18 reactivation cases. All but one were recorded as receiving previous antituberculosis-drug treatment. The one exception was the European case whose original disease was diagnosed in New Zealand in 1948.

Compared with new cases of disease, reactivation cases were less likely to be fully susceptible to all five antimicrobials tested, and significantly ($p \leq 0.05$) more resistant to isoniazid and ethambutol (Table 5). One of the two MDR-TB cases was a reactivation case.

Table 5. Resistance among new cases and reactivations of tuberculosis disease, 2003

	Percent		
	New disease (n=304)	**Disease reactivations (n=18)**	**P value[2]**
Fully susceptible	82.2	61.1	0.0553
Resistant to:[1]			
Isoniazid	8.9	27.8	0.0237
Rifampicin	0.3	5.6	0.1088
Ethambutol	0.7	16.7	0.0014
Pyrazinamide	5.6	5.6	1.0000
Streptomycin	7.2	5.6	1.0000
MDR-TB[3]	0.3	5.6	0.1088

Notes: 1 includes resistance alone or in combination with other antimicrobials
2 rates compared by the Chi-square test or Fishers Exact test, as appropriate
3 multidrug-resistant tuberculosis, that is, resistant to at least isoniazid and rifampicin

Clinical commentary by Tim Blackmore, Clinical Microbiologist and Infectious Diseases Physician:

It is pleasing that the rates of resistance overall remain quite low in New Zealand. It is also interesting that the rate of resistance is higher in cases of so called reactivated disease. I suspect that the definition of reactivation may need to be reassessed because most tuberculosis disease would be expected to be reactivation after a period of latent infection. If it were genuinely the case that only 5.6% of culture-positive cases were reactivation, it would imply that most disease was primary. Primary disease would only be expected to be identified in the settings of paediatric disease and in large-scale outbreaks. The lack of major clustering identified on molecular

strain analysis also supports this notion. It seems possible that the category of reactivation is most likely to be used if resistance is present, and as such represents confounded data.

Perhaps the most important finding is the difference in isoniazid resistance between NZ- and overseas-born persons with active tuberculosis. This supports the empiric choice of four first-line drugs for overseas-born persons as recommended in the *Guidelines for tuberculosis control in New Zealand, 2003*.

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This report is available at www.surv.esr.cri.nz/antimicrobial/tuberculosis.php