FIVE YEARS OF MOLECULAR TYPING OF *MYCOBACTERIUM TUBERCULOSIS* ISOLATES IN NEW ZEALAND, 2003 TO 2007

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by

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DISCLAIMER

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TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

Notified cases, 2003 to 2007

- Over the period 2003 to 2007, there were a total of 4 456 notifications of tuberculosis (TB) reported with an average annual rate of 8.6 per 100 000 population.
- There were 1 683 notifications classified as new cases of TB disease and 92 as relapse or reactivations of TB disease, giving a total of 1 775 cases of TB disease.
- The highest age-specific average notification rate occurred in the 20 to 29 years age group (15.1 per 100 000 population).
- The highest average notification rate of TB disease occurred in the "Other" ethnic group (55.5 per 100 000 population), followed by the Asian ethnic group (44.4 per 100 000 population), Pacific Peoples (26.2 per 100 000 population) and Maori (10.4 per 100 000 population).
- Of the 1 775 notifications of TB disease, there were 1 736 cases due to *Mycobacterium tuberculosis*, 25 cases due to *M. bovis* and 14 cases due to other mycobacterial species.

Matched cases, 2003 to 2007

- Of the 1 736 notifications of TB disease due to *M. tuberculosis*, 1 328 were matched to TB molecular typing data, giving a match rate of 76.5%.
- The average annual rate of TB disease for the matched cases was 6.4 per 100 000 population.
- Of the 1 328 matched cases, 1 254 (94.4%) were new cases of TB disease and 74 (5.6%) were relapse or reactivation of TB disease.
- The median time between the date of specimen collection and the date of DNA extraction for typing was 9.0 weeks, with a range of one to 135 weeks.
- Of the 1 328 matched cases, 462 cases (34.8%) had a non-unique TB typing result and were classified as cluster cases, while the remaining 866 cases (65.2%) had a unique typing result and were classified as non-cluster cases.

Cluster cases were significantly more likely to be:
- Aged less than one year, 1 to 4 years, 10 to 14 years or 15 to 19 years.
- Maori or Pacific ethnicity.
- From Northland, Counties Manukau, Taranaki, Hawke's Bay, Whanganui or Hutt Valley District Health Boards (DHBs).

And also, cluster cases were significantly more likely to have the following risk factors:
- Contact with a confirmed case of TB.
- Born in New Zealand or a Pacific Island country.
- Pulmonary TB disease.

Whereas, non-cluster cases were significantly more likely to be:
- Aged between 30 to 39 years or over 70 years.
- Asian.
- From Auckland or Nelson Marlborough DHBs.

And also, non-cluster cases were significantly more likely to have the following risk factors:

- Recent current residence with a person born outside New Zealand
- Born in Asia, North West Europe or South and Central America
- Exposure to TB in a healthcare setting

Cluster cases, 2003 to 2007

- The 462 cluster cases were distributed between 140 different cluster groups.
- The number of cases within a cluster ranged from one to 57 cases, with a mean of 3.3 cases and a median of 2.0 cases.
- The 462 cluster cases were from 18 different DHBs, with the exception of Tairawhiti, South Canterbury and Southland DHBs.
- There were 69 clusters (42.9%) that solely involved cases from the same DHB, whereas the remaining 80 clusters (57.1%) involved cases from more than one DHB.
- The number of DHBs associated with any one cluster ranged from one to 13 DHBs.
- There were 70 clusters that contained cases born in New Zealand. Of these, 16 clusters involving 23 cases consisted solely of cases born in New Zealand.
- There were 109 clusters that contained cases born outside New Zealand. Of these, 68 clusters involving 135 cases consisted solely of cases born outside New Zealand.

1 INTRODUCTION

Worldwide, tuberculosis (TB) is one of the most common causes of death from communicable disease. Infection is usually curable with a combination of specific antibiotics but relies upon full compliance. The annual incidence rate of TB disease in New Zealand was approximately 9 cases per 100 000 population in 2006. Based on the 2006 statistics reported by the World Health Organization, this incidence rate is higher than the United States (4 per 100 000 population), Canada (5 per 100 000 population) and Australia (6 per 100 000), but lower than the United Kingdom (15 per 100 000) (1).

Molecular typing of *Mycobacterium tuberculosis* isolates has been available in New Zealand through LabPlus in Auckland since 1998. Initially, molecular typing was only used in certain circumstances, for example to investigate a suspected cross-contamination event or to support an epidemiological investigation. Universal molecular typing of isolates from TB cases was introduced in July 2002. All of the TB molecular typing work in New Zealand is undertaken by LabPlus under contract to the Institute of Environmental Science and Research (ESR) with funding by the Ministry of Health.

1.1 Purpose of the report

The purpose of this report is to summarise the descriptive epidemiology of TB clusters identified in New Zealand from 2003 to 2007.

2 METHODS

2.1 Data sources

This report is based on an analysis of data from two sources: TB notification data reported in EpiSurv, the national notifiable diseases database; and TB molecular typing data from LabPlus.

TB notification data

EpiSurv is the national notifiable diseases database managed by the Institute of ESR on behalf of the Ministry of Health. Clinicians are required to notify all cases of TB infection and disease to their Medical Officer of Health under the Tuberculosis Act (1948).

Once a Public Health Service (PHS) receives a notification, a staff member enters details of the case into EpiSurv according to a standard TB Case Report Form. This case report form includes information such as the type of TB, demographic details, clinical details, laboratory results, risk factors and management.

According to the case definitions used for the TB Case Report Form, the following types of TB are reported:

- Tuberculosis disease – new case
  Active TB in a person who as never been treated for TB before.

- Tuberculosis disease – relapse or reactivation
  Active TB in a person whose TB has been non-infectious or quiescent following full, partial or no treatment.

- Tuberculosis – treatment of latent infection
  A person with all of the following: positive Mantoux test or Mantoux conversion, no evidence of active disease; and placed on chemoprophylaxis with one or more drugs.

- Tuberculosis infection – old disease on preventive treatment
  A person on anti-tuberculosis treatment with multiple drugs in whom active disease is suspected but remains unproven or reactivation is likely to occur.

TB molecular typing data

The national TB molecular typing database is maintained by LabPlus who undertakes all of the human TB molecular typing work in New Zealand. At the time of this report, TB molecular typing data from LabPlus was sent to ESR at periodic intervals. The typing data was then matched to individual cases recorded within EpiSurv.

2.2 Analytical methods

All notifications of TB disease reported from 01 January 2003 to 31 December 2007 were extracted from EpiSurv. This dataset included all notifications of ‘TB disease - new cases’ and ‘TB disease - relapse or reactivation’. This dataset excluded all notifications of

'Tuberculosis - treatment of latent infection' and 'Tuberculosis infection - old disease on preventive treatment'. The notification data was extracted from EpiSurv on 12 February 2008, therefore, any changes to EpiSurv data by PHS staff after this date will not be reflected in this report.

Notified cases of TB disease were subsequently matched to the LabPlus TB molecular typing data using name, NHI and date of birth. The matched dataset was limited to cases of TB disease due to *Mycobacterium tuberculosis* by excluding all cases due to *M. bovis* or other mycobacterial species.

All disease rates, except for ethnicity, have been calculated using mid-year population estimates from Statistics New Zealand. Disease rates for ethnic groups are based on 2006 census data from Statistics New Zealand.

3 RESULTS – NOTIFIED CASES

3.1 Overall TB notifications

There were a total of 4 456 notified cases of TB (disease and infection) recorded in EpiSurv from 2003 to 2007. Of these, 1 683 were classified as new cases of TB disease and 92 as relapse or reactivations of TB disease, giving a total of 1 775 cases of TB disease over the five year period (Table 1).

Table 1: TB notifications by status, 2003 to 2007

Disease name	Status				
	Confirmed	Probable	Under Investigation	Unknown	**Total**
TB disease – new case	1 274	336	53	20	**1 683**
TB disease – relapse or reactivation	76	11	4	1	**92**
TB – treatment of latent infection	12	149	731	1710	**2 602**
TB infection – on preventive treatment	1	19	19	40	**79**
Total	**1 363**	**515**	**807**	**1 771**	**4 456**

3.2 TB disease notifications

From 2003 to 2007, the annual number of notifications of TB disease (new cases and relapse or reactivations) decreased by 31.4% (290 in 2007 compared to 423 in 2003). The annual rate per 100 000 population also decreased by 34.3 % (6.9 in 2007 compared to 10.5 in 2003) with a five year average rate of 8.6 per 100 000 population (Table 2).

Table 2: TB disease notifications[1] by status and year, 2003 to 2007

Year	Status				Total	Rate per 100 000 population
	Confirmed	Probable	Under Investigation	Unknown		
2003	318	92	7	6	423	10.5
2004	282	73	11	9	375	9.2
2005	265	61	3	4	333	8.1
2006	269	81	4	0	354	8.5
2007	216	40	32	2	290	6.9
Total	**1 350**	**347**	**57**	**21**	**1 775**	**8.6**

[1] Includes new cases and relapse or reactivations

Over the five year period from 2003 to 2007 the average annual notification rate of TB disease (new cases and relapse or reactivations) differed by age group, ethnicity and geographical region (Table 3). The TB disease (new cases and relapse or reactivations) rates for males and females were similar (8.7 per 100 000 population and 8.4 per 100 000 population, respectively).

The highest age specific annual average rate was reported in the 20 to 29 years age group (15.1 per 100 000 population, 412 cases), followed by the over 70 years age group (11.9

per 100 000 population, 209 cases), the 30 to 39 (10.5 per 100 000 population, 314 cases) and the 60 to 69 years age groups (10.1 per 100 000 population, 167 cases).

Table 3: TB disease notifications[1] demographic factors, 2003 to 2007

Category	Sub-category	Number of cases	Five year average rate per 100 000 population
Age (years)	<1	16	5.5
	1 to 4	54	4.8
	5 to 9	41	2.8
	10 to 14	61	3.9
	15 to 19	104	6.8
	20 to 29	412	15.1
	30 to 39	314	10.5
	40 to 49	226	7.3
	50 to 59	169	6.9
	60 to 69	167	10.1
	70+	209	11.9
Sex	Male	880	8.7
	Female	885	8.4
Ethnicity (prioritised)[2]	Maori	295	10.4
	Pacific Peoples	296	26.2
	Asian	756	44.4
	Other	94	55.5
	European	211	1.6
	Unknown	123	14.7
District Health Board	Northland	80	10.6
	Waitemata	248	10.0
	Auckland	340	16.0
	Counties Manukau	311	14.0
	Waikato	123	7.1
	Lakes	17	3.4
	Bay of Plenty	42	4.3
	Tairawhiti	3	1.3
	Taranaki	25	4.7
	Hawke's Bay	79	10.4
	Whanganui	13	4.0
	MidCentral	74	9.1
	Hutt	54	7.7
	Capital and Coast	163	11.9
	Wairarapa	11	5.6
	Nelson Marlborough	23	3.5
	West Coast	7	4.4
	Canterbury	116	4.9
	South Canterbury	11	4.0
	Otago	25	2.7
	Southland	10	1.8

[1] Includes new cases and relapse or reactivations.
[2] Ethnic groups were prioritised in the following order: Maori; Pacific Peoples; Asian; Other; European; Unknown.

Cases classified in the "Other" ethnic group had the highest TB disease rate (55.5 per 100 000 population, 94 cases) followed by Asian (44.4 per 100 000 population, 756

cases) and Pacific Peoples (26.2 per 100 000 population, 296 cases) and Maori (10.4 per 100 000 population, 295 cases).

Auckland DHB had the highest rate (16.0 per 100 000 population, 340 cases) followed by Counties Manukau DHB (14.0 per 100 000 population, 311 cases) and Capital and Coast DHB (11.9 per 100 000 population, 163 cases).

3.3 TB disease notifications by isolated organism

Of the TB disease notifications from 2003 to 2007, 97.8% (1 736/1 775) of cases were *Mycobacterium tuberculosis*, while only 25 cases (1.4%) were *M. bovis* and 14 cases (0.8%) were due to other mycobacterial species (Table 4).

Table 4: TB disease notifications[1] by isolated organism, 2003 to 2007

Year	*M. tuberculosis*[2]	*M. bovis*	*M.* other	Total
2003	410	5	8	423
2004	369	5	1	375
2005	329	4	0	333
2006	343	8	3	354
2007	285	3	2	290
Total	**1 736**	**25**	**14**	**1 775**

[1] Includes new cases and relapse or reactivations.
[2] Includes TB disease notifications where the isolated organism is not recorded.

4 RESULTS – MATCHED CASES

Over the five year period from 2003 to 2007 there were 1 736 notifications for TB disease attributed to *M. tuberculosis*, of which 1 328 were matched to available TB molecular typing data. The following results are based on the 1 328 matched cases of TB disease due to *M. tuberculosis.*

4.1 Matched TB disease cases by year

Of the 1 328 matched cases, 94.4% (1 254 cases) were notifications of new cases of TB disease and 5.6% (74 cases) were notifications of a relapse or reactivation of disease (Table 5). From 2003 to 2007, there was a decrease in the number of matched cases from 303 to 221 cases. However, the proportion of all notified cases matched to TB typing results has remained relatively constant for each year, ranging between 72.6% and 78.1% of overall TB disease cases matched per year (data not shown).

Table 5: Matched TB disease cases by year, 2003 to 2007

Year	TB disease – new case	TB disease – relapse or reactivation	Total TB disease	
			Number of cases	Rate per 100 000 population
2003	285	18	303	7.5
2004	275	12	287	7.0
2005	243	14	257	6.2
2006	244	16	260	6.2
2007	207	14	221	5.2
Total	**1 254**	**74**	**1 328**	**6.4**

4.2 Time from specimen collection to typing result

A total of 1 118 matched cases (84.2%) had both a valid date of specimen collection and a valid date of DNA extraction. Over the period 2003 to 2007, the median length of time between specimen date and extraction date was 9.0 weeks, ranging from one to 325 weeks. Between 2003 and 2007 both the median and mean times to DNA extraction varied. The median time varied from 6.0 to 10.0 weeks, and the mean time from 7.6 to 12.9 weeks (Table 6). The 2007 median and mean times have dropped closer to 2003 levels, and were 7.0 and 7.6 weeks respectively.

Table 6: Median and mean time to typing result by year, 2003 to 2007

Year	Number of cases	Median (weeks)	Mean (weeks)
2003	213	6.0	8.0
2004	286	10.0	12.4
2005	246	9.5	10.6
2006	212	10.0	12.9
2007	161	7.0	7.6
Total	**1 118**	**9.0**	**10.5**

4.3 Number of cluster and non-cluster cases

Of the 1 328 matched cases, a total of 462 cases (34.8%) had a non-unique TB molecular typing result and were classified as cluster cases. These cluster cases were associated with 140 Cluster IDs, i.e. belonged to 140 separate clusters. The remaining 866 cases (65.2%) had a unique typing result and were classified as non-cluster cases.

4.4 Comparison of cluster and non-cluster cases

The 462 cluster cases and 866 non-cluster cases were compared according to demographic factors (Table 7) and risk and protective factors (Table 8). This analysis is based on the proportions of cases belonging to the cluster and non-cluster groups, therefore, it is important to also refer to the actual number of cases reported in the tables when interpreting these results.

Cluster cases were significantly more likely to belong to the following age groups: less than one year, 1 to 4 years; 10 to 14 years; and 15 to 19 years, to be of Maori or Pacific ethnicity, and to reside in Northland, Counties Manukau, Taranaki; Hawke's Bay, Whanganui or Hutt Valley DHBs. Cluster cases were also significantly more likely to have the following risk factors: contact with a confirmed case of TB; born in New Zealand or a Pacific Island country; and pulmonary TB disease.

In contrast, non-cluster cases were significantly more likely to be aged between 30 to 39 years or over 70 years, to be of Asian ethnicity, and to reside in Auckland or Nelson Marlborough DHBs. Non-cluster cases were also significantly more likely to have the following risk factors: born outside New Zealand; born in Asia, North West Europe or South and Central America; current or recent residence with a person born outside New Zealand; and exposure to TB in a healthcare setting.

Table 7: Comparison of demographic factors of cluster and non-cluster cases, 2003 to 2007

Category	Sub-category	Cluster cases (n=462)		Non-cluster cases (n=866)		χ^2	*P*-value	Significant[1]
		No.	%	No.	%			
Age (years)	<1	9	1.9%	1	0.1%	13.5	0.000	***
	1 to 4	8	1.7%	0	0.0%	15.1	0.000	***
	5 to 9	4	0.9%	7	0.8%	0.0	0.912	n/s
	10 to 14	27	5.8%	7	0.8%	30.6	0.000	***
	15 to 19	44	9.5%	33	3.8%	18.0	0.000	***
	20 to 29	114	24.7%	217	25.1%	0.0	0.878	n/s
	30 to 39	75	16.2%	185	21.4%	5.0	0.025	*
	40 to 49	57	12.3%	118	13.6%	0.4	0.509	n/s
	50 to 59	50	10.8%	87	10.0%	0.2	0.658	n/s
	60 to 69	42	9.1%	91	10.5%	0.7	0.413	n/s
	70+	32	6.9%	118	13.6%	13.5	0.000	***
	Unknown	0	0.0%	2	0.2%	1.1	0.301	n/s
Sex	Male	222	48.1%	432	49.9%	0.4	0.525	n/s
	Female	239	51.7%	426	49.2%	0.8	0.378	n/s
	Unknown	1	0.2%	8	0.9%	2.2	0.135	n/s
Ethnicity (prioritised)[2]	Maori	143	31.0%	69	8.0%	118.6	0.000	***
	Pacific Peoples	121	26.2%	84	9.7%	62.8	0.000	***
	Asian	118	25.5%	497	57.4%	122.9	0.000	***
	Other	24	5.2%	57	6.6%	1.0	0.314	n/s
	European	37	8.0%	88	10.2%	1.6	0.201	n/s
	Unknown	19	4.1%	71	8.2%	8.0	0.005	**
District Health Board	Northland	33	7.1%	28	3.2%	10.5	0.001	**
	Waitemata	65	14.1%	132	15.2%	0.3	0.567	n/s
	Auckland	70	15.2%	217	25.1%	17.5	0.000	***
	Counties Manukau	107	23.2%	150	17.3%	6.6	0.010	*
	Waikato	27	5.8%	60	6.9%	0.6	0.447	n/s
	Lakes	1	0.2%	9	1.0%	2.7	0.099	n/s
	Bay of Plenty	11	2.4%	18	2.1%	0.1	0.719	n/s
	Tairawhiti	0	0.0%	2	0.2%	1.1	0.301	n/s
	Taranaki	9	1.9%	6	0.7	4.3	0.039	*
	Hawke's Bay	26	5.6%	13	1.5%	18.0	0.000	***
	Whanganui	5	1.1%	2	0.2%	4.2	0.041	*
	MidCentral	16	3.5%	29	3.3%	0.0	0.913	n/s
	Hutt	20	4.3%	18	2.1%	5.5	0.019	*
	Capital and Coast	31	6.7%	72	8.3%	1.1	0.298	n/s
	Wairarapa	1	0.2%	5	0.6%	0.9	0.350	n/s
	Nelson Marlborough	1	0.2%	12	1.4%	4.2	0.039	*
	West Coast	1	0.2%	2	0.2%	0.0	0.958	n/s
	Canterbury	33	7.1%	65	7.5%	0.1	0.810	n/s
	South Canterbury	0	0.0%	5	0.6%	2.7	0.102	n/s
	Otago	5	1.1%	14	1.6%	0.6	0.435	n/s
	Southland	0	0.0%	7	0.8%	3.8	0.058	n/s

[1] *** $p<0.001$, ** $p<0.01$, * $p<0.05$, n/s = not significant

[2] Ethnic groups were prioritised in the following order: Maori; Pacific Peoples; Asian; Other; European; Unknown.

Table 8: Comparison of risk and protective factors of cluster and non-cluster cases, 2003 to 2007

Category	Sub-category	Cluster cases (n=462)		Non-cluster cases (n=866)		χ^2	*P*-value	Significant[1]
		No.	%	No.	%			
Contact with a confirmed case	Yes	156	33.8%	111	12.8%	82.3	0.000	***
	No	173	37.4%	536	61.9%	72.4	0.000	***
	Unknown	133	28.2%	219	25.3%	1.9	0.169	n/s
Exposure in a healthcare setting	Yes	18	3.9%	65	7.5%	6.7	0.010	**
	No	350	75.8%	603	69.6%	5.6	0.018	*
	Unknown	94	20.3%	198	22.9%	1.1	0.291	n/s
Born outside NZ	Yes	247	53.5%	712	82.2%	124.1	0.000	***
	No	182	39.4%	119	13.7%	113.1	0.000	***
	Unknown	33	7.1%	35	4.0%	6.0	0.015	*
Current or recent residence with person born outside NZ	Yes	236	51.5%	564	65.1%	24.8	0.000	***
	No	145	31.4%	170	19.6%	23.0	0.000	***
	Unknown	81	17.5%	132	15.2%	1.2	0.279	n/s
Birth country region	Asia	109	23.6%	515	59.5%	155.7	0.000	***
	Australia	0	0.0%	3	0.3%	1.6	0.205	n/s
	New Zealand	182	39.4%	118	13.6%	114.4	0.000	***
	North Africa & the Middle East	2	0.4%	7	0.8%	0.6	0.427	n/s
	North America	1	0.2%	1	0.1%	0.2	0.651	n/s
	North West Europe	3	0.6%	18	2.1%	4.0	0.47	*
	Pacific Islands	93	20.1%	76	8.8%	35.0	0.000	***
	South & Central America	0	0.0%	8	0.9%	4.3	0.038	*
	Southern & Eastern Europe	1	0.2%	6	0.7%	1.3	0.253	n/s
	Sub-Saharan Africa	35	7.6%	75	8.7%	0.5	0.495	n/s
	Unknown	36	7.8%	39	4.5%	6.1	0.013	*
Current or recent residence in an institution	Yes	12	2.6%	25	2.9%	0.1	0.760	n/s
	No	359	77.7%	678	78.3%	0.1	0.806	n/s
	Unknown	91	19.7%	163	18.8%	0.1	0.699	n/s
Has immunosuppressive illness	Yes	77	16.7%	144	16.6%	0.0	0.986	n/s
	No	333	72.1%	647	74.7%	1.1	0.299	n/s
	Unknown	52	11.3%	75	8.7%	2.3	0.126	n/s
On immunosuppressive medication	Yes	18	3.9%	45	5.2%	1.1	0.288	n/s
	No	388	84.0%	738	85.2%	0.4	0.550	n/s
	Unknown	56	12.1%	83	9.6%	2.1	0.150	n/s
Vaccinated with BCG	Yes	172	3.72%	364	42.0%	2.9	0.089	n/s
	No	80	17.3%	106	12.2%	6.4	0.011	*
	Unknown	210	45.5%	396	45.7%	0.0	0.924	n/s
Pulmonary disease	Yes	329	71.2%	518	59.8%	16.9	0.000	***
	No	96	20.8%	287	33.1%	22.4	0.000	***
	Unknown	37	8.0%	61	7.0%	0.4	0.522	n/s

[1] *** $p<0.001$, ** $p<0.01$, * $p<0.05$, n/s = not significant

5 RESULTS – CLUSTER CASES

There were 1 328 notifications of TB disease due to *M. tuberculosis* from 2003 to 2007 that were subsequently matched to TB molecular typing data, as described in the previous results section. Of these matched cases, 34.8% (462/1 328) had a non-unique typing result and were assigned a Cluster ID. The following results are based on the 462 cluster cases.

5.1 Cluster size

The 462 cluster cases were distributed between 140 different Cluster IDs (Table 9). The number of cases within a cluster ranged from one[1] to 57 cases, with a mean of 3.3 cases and median of 2.0 cases. Clusters with two or fewer cases comprised 75.0% of the cluster IDs but contained fewer than 40% of the cases. There were four clusters with 20 or more associated cases.

Table 9: Distribution of clusters and associated cases by cluster size, 2003 to 2007

Cluster size (number of cases)	**Number of clusters**	**% of all clusters** (n=140)	**Number of cases associated**	**% of all cases Associated** (n=462)
1	26	18.6	26	5.6
2	79	56.4	158	34.2
3	10	7.1	30	6.5
4	6	4.3	24	5.2
5	4	2.9	20	4.3
6	5	3.6	30	6.5
7	3	2.1	21	4.5
8	1	0.7	9	1.9
10	1	0.7	10	2.2
12	1	0.7	12	2.6
20	1	0.7	20	4.3
22	1	0.7	22	4.8
23	1	0.7	23	5.0
57	1	0.7	57	12.3
Total	**140**	**100.0**	**462**	**100.0**

5.2 District Health Board involvement in clusters

There were 60 clusters (42.9%) that solely involved cases from the same DHB, whereas the remaining 80 clusters (57.1%) involved cases from more than one DHB (Table 10). Of those clusters involving multiple DHBs, almost three-quarters (57/80) involved only two different DHBs.

The number of DHBs associated with any one cluster ranged from one to 13 DHBs, with a mean and a median of 2.0 DHBs per cluster. The cluster named the Rangipo cluster was associated with the most DHBs and involved 13 different DHBs and 57 associated cases.

[1] A cluster can contain just one case when the other cases within that cluster were either not notified on EpiSurv or notified outside the study time period from 2003 to 2007.

Table 10: Number of DHBs associated with clusters, 2003 to 2007

Number of DHBs associated with cluster	Number of clusters	% of all clusters (n=140)
1	60	42.9
2	57	40.7
3	11	7.9
4	3	2.1
5	6	4.3
6	1	0.7
7	1	0.7
13	1	0.7
Total	**140**	**100.0**

Overall, the 462 cluster cases resided in 18 different DHBs, with no cluster cases reported from Tairawhiti, South Canterbury and Southland DHBs, where no cluster cases were identified. Auckland and Counties Manukau DHBs were linked to approximately 40% of the clusters (Table 11). Waitemata, Waikato and Capital and Coast DHBs were each linked to 20 or more clusters.

Table 11: Number of clusters by DHB, 2003 to 2007

DHB	Number of clusters	% of total clusters (n=140)
Northland	13	9.3
Waitemata	36	25.7
Auckland	54	38.6
Counties Manukau	53	37.9
Waikato	20	14.3
Lakes	1	0.7
Bay of Plenty	9	6.4
Tairawhiti	0	0.0
Taranaki	7	5.0
Hawke's Bay	8	5.7
Whanganui	4	2.9
MidCentral	10	7.1
Hutt	14	10.0
Capital and Coast	20	14.3
Wairarapa	1	0.7
Nelson Marlborough	1	0.7
West Coast	1	0.7
Canterbury	19	13.6
South Canterbury	0	0.0
Otago	4	2.9
Southland	0	0.0

5.3 Clusters with cases born in New Zealand

In total, there were 70 clusters that contained cases born in New Zealand. Of these, 16 clusters involving 23 cases consisted solely of cases born in New Zealand. For these clusters, the cluster size ranged from one to three cases with a mean of 1.4 cases and median of 1.0 cases.

5.4 Clusters with cases born overseas

There were a total of 109 clusters that involved cases born outside of New Zealand. The number of cases born overseas in these clusters ranged from one to 20 cases. The cluster named the Southern Cross cluster had the largest number of cases born outside of New Zealand, with 87.0% (20/23) of the associated cases born overseas (mostly Samoa or Tonga).

There were 68 clusters involving 135 cases where all the associated cases were born overseas. The size of these clusters ranged from one to five cases, with a mean of 2.2 and a median of 2.0 cases.

6 DISCUSSION

This report is a timely review of the TB molecular typing data for two major reasons. Firstly, universal molecular typing of TB isolates has been practiced for a five complete calendar years, ensuring an ample volume of available results for analysis. Secondly, new developments are to be implemented in order to improve the dissemination of and access to TB cluster information, as well as the timeliness of typing results.

This analysis found that over one third of the typed cases could be assigned to a cluster, which is an indication of the potential benefit that typing could play in TB control in New Zealand. Identifying a link between cases without an obvious epidemiological association may lead to a cluster investigation, which could uncover a common source, identify other undiagnosed cases, and direct appropriate control measures.

Applications of molecular typing for TB control

There are numerous applications of molecular typing for TB control such as those proposed by Auckland Regional Public Health Service (2): (i) detecting cross-contamination of clinical specimens or isolates; (ii) distinguishing relapse from exogenous re-infection; (iii) identifying TB outbreaks; (iv) reinforcing (or disproving) epidemiological links; (v) evaluation of contact investigation and management; and (vi) providing a basis for the study of TB epidemiology.

This report addresses the last of these applications by providing descriptive epidemiology of TB molecular typing results over the first five years since universal typing began. When interpreting the results, it should be noted that they are a summary of EpiSurv TB disease notifications matched to LabPlus molecular typing data only. The actual burden of TB associated with any one cluster may also involve the following: cases of TB disease from outside the timeframe of the study; cases of TB disease that could not be matched between the EpiSurv and LabPlus databases; and cases of latent TB infection not included in this analysis.

Risk factors associated with cluster cases

A key outcome of this report was the comparison between cases linked by the same typing patterns (cluster cases) versus cases that have unique typing patterns (non-cluster cases). This analysis identified risk factors associated with cluster cases, which could assist TB control activities at a regional level. Contact tracing efforts would be particularly important for TB cases at higher risk of belonging to a cluster. Also, health promotion programmes could target at-risk groups so that TB disease is detected at an earlier stage to minimise transmission to others.

Of particular note was the association between cluster cases and ethnic group. Cluster cases were more likely to be of Maori or Pacific ethnicity, which is supported by the finding that cluster cases were more likely to be born in New Zealand or in the Pacific. Other New Zealand research has also demonstrated that Maori and Pacific people are disproportionately affected by TB outbreaks (3). It is credible that Maori are at a higher risk of acquiring TB strains that are already circulating in New Zealand. While transmission of the same TB strain could occur within the Pacific community in New

Zealand, it is also possible that multiple TB cases with the same strain could be imported from the Pacific. Examples of such TB outbreak scenarios are recorded within EpiSurv. The association observed for Maori and Pacific people could also be influenced by delayed diagnosis due to poor access to healthcare, as well as household overcrowding, both of which can increase the risk of TB transmission (3).

Results demonstrated that TB cluster cases were less likely to be of Asian ethnicity and less likely to be born in Asia. It is possible that Asian TB cases acquire unique overseas strains of TB and have lower risk of transmitting infection within New Zealand. This is supported by evidence that immigrants from TB endemic countries have a high incidence of TB in New Zealand, but are not an important source of TB transmission within the country (4). Current immigration TB screening policy offers a potential explanation for this observation. Since 2005, TB screening has been compulsory for students, visitors and workers from high-risk countries who apply to live in New Zealand for six months or more. Anecdotal reports indicate that this has led to increased diagnosis and subsequent treatment of asymptomatic cases of TB disease (5). Despite immigration TB screening, Asian immigrants with LTBI, undetected by chest X-ray, may still develop disease once in New Zealand. However, it is possible that these cases are less likely to transmit infection due to early TB treatment, which is influenced by awareness of TB, access to health services, and diagnostic vigilance of clinicians caring for immigrant patients.

It is interesting to note that cluster cases were significantly more likely to be children and adolescents aged less than 20 years, with the exception of the 5 to 9 years age group. Children, particularly those aged less than five years, are more susceptible to infection with TB, which is supported by these results that show children are more vulnerable to TB transmission within the home and the community.

Dissemination of TB molecular typing results

The identification of local and multi-jurisdictional TB outbreaks is an important application of TB molecular typing. This function will be enhanced by new developments to increase the dissemination of TB cluster data to regional and national agencies where appropriate.

Since half way through 2002, typing results were disseminated as follows. After molecular typing had been completed by LabPlus, the result was sent to the requesting clinician, as well as the relevant Medical Officer of Health if known by LabPlus. If cases were identified as belonging to a cluster, an additional report "TB Typing Result – Public Health" was sent to the relevant PHS. This report contained details of the new case, as well as all other previously identified cases belonging to that cluster.

During the study time period, the LabPlus typing results were not being merged with EpiSurv notification data. But since the beginning of 2008, the electronic reporting of TB typing results has been standardised, enabling ESR to match EpiSurv TB notifications with typing results in a more routine and timely manner.

This has allowed ESR to develop a system whereby PHSs will be alerted to new cases belonging to a cluster (including the PHS of the new case, as well as other PHSs with cases already belonging to that cluster). ESR has also set up an online tool within

EpiSurv that allows PHS staff to look up anonymous line listings of all cases within a specific cluster nationwide. Together these processes will replace the existing "TB Typing Result – Public Health" report.

Timeliness of typing results

There was no available data on the date that TB typing results were sent to the requesting clinician and relevant PHS. For the purposes of this report, an estimate of the timeliness of typing results was calculated using the date of specimen collection from the TB case and the date of DNA extraction from that specimen for molecular typing.

It is important to note that the time between specimen date and extraction date will reflect the sum of several time periods: time taken for the local laboratory to culture TB; speed of referral from the local laboratory to one of the three TB reference laboratories; time taken for the reference laboratory to confirm TB; speed of referral from the reference laboratory to LabPlus for typing; and time taken at LabPlus to culture sufficient isolate for typing. Following DNA extraction it then takes approximately two weeks to run the typing procedures, analyse the result and send the report out.

The findings of this report indicated that there could be delays of 10 or more weeks on average before a typing result is received by a PHS. Such long time frames may hinder effective TB control. Therefore, improving the timeliness of typing results is important. This issue will be partially addressed when LabPlus changes to a more rapid typing methodology and ESR commences automated alerts of cluster cases.

Recommendations

- Over one third of TB disease cases could be assigned to a cluster, which indicates the potential use of molecular typing data in TB control. New developments are currently being implemented to increase the dissemination of and access to TB cluster data. The effectiveness of these developments should be evaluated in the future.

- There could be delays of 10 or more weeks on average before a typing result is received by a PHS, which could hinder effective TB control. This delay stems from a lengthy pathway from the collection of the specimen to the dissemination of results. Improvements in timeliness are expected with new developments that relate to the end of this pathway. The timeliness of reporting should be monitored and methods to decrease delays throughout the pathway should also be considered.

- Cluster cases were more likely to be of Maori and Pacific ethnicity. There were also more likely to be children and adolescents aged less than 20 years, with the exception of the 5 to 9 years age group. Contact tracing efforts should be more extensive for TB cases belonging to these at-risk groups. Health promotion initiatives should target these at-risk groups to prevent transmission and improve early detection of TB disease.

- There were 87 outbreaks that involved cases from two or more DHBs. This finding supports the need for a national protocol to manage and investigate multi-jurisdictional TB clusters.

- This report provides a national representation of TB molecular typing in New Zealand over the last five years. Repeating this report every five years would not only provide updated results, but would also allow further analyses, which would be enhanced by a greater volume of historical data.

- Additional analyses that should be considered for future reports include:
  - Summarising the demographic, risk factor and clinical features of the larger TB clusters already present in New Zealand, such as the Rangipo, Southern Cross, Tuvalu, and Weymouth clusters.
  - Summarising important international strains, such as the Beijing strain, are present in New Zealand.
  - Examining the antibiotic resistance patterns within clusters.
  - Identifying risk factors associated with TB disease relapse versus TB re-infection.

7 REFERENCES

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APPENDIX – TB GENOTYPING TECHNIQUES

The two genotyping techniques currently available in New Zealand are Restriction Fragment Length Polymorphism (RFLP) and Mycobacterial Interspersed Repetitive Unit (MIRU).

RFLP

RFLP TB genotyping technique is a southern blot based assay that detects a mobile genetic element called insertion sequence *6110* (IS*6110*), a naturally occurring transposable genetic sequence detected only in *M. tuberculosis* complex. *M. tuberculosis* strains can therefore be described in terms of the number of IS*6110* copies and the position of each copy, providing the basis for a genetic fingerprint.

MIRU

MIRU genotyping is a polymerase chain reaction (PCR) based assay that detects specific segments of *M. tuberculosis* DNA that are prone to containing sequences repeated in a tandem fashion. The sites on the *M. tuberculosis* genome where repeated sequences occur are called MIRU loci. MIRU results are recorded as 12-digit numbers, with each digit corresponding to the number of repeats at one of the 12 MIRU loci listed in a standard order.