A measles epidemic controlled by immunisation

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Abstract

Introduction

In 1997, an immunisation campaign, using measles-mumps-rubella (MMR) vaccine, was planned for children aged 2-10 years to prevent a measles epidemic predicted by mathematical modelling. The epidemic started earlier than anticipated. The impact of the immunisation campaign on the epidemic is described here.

Methods

Measles hospitalisation, notification, and laboratory data were combined. Rates were calculated using 1996 census data, age standardised to the total New Zealand population.

Results

The epidemic started in April 1997 and was largely over by January 1998. No deaths were identified, and only one hospitalisation was coded as measles encephalitis, compared to 7 deaths and 10 cases of measles encephalitis in the 1991 epidemic. For the 12 months from 1 March 1997 there were 2,169 (60 per 100,000) measles cases identified, 314 (9 per 100,000) of whom were hospitalised. Over two thirds of hospitalised cases were not notified.

The age-standardised measles incidence rates were 33, 34, 174 and 43 per 100,000 for Europeans, Maori, Pacific people, and ‘Others’, respectively. The respective age-standardised hospitalisation rates were 4, 9, 32 and 7 per 100,000. Incidence declined with age, with rates per 100,000 of: 904 for under one year olds; 689 for one year olds; 198 for 2-4 year olds; 112 for 5-10 year olds, 27 for 11-16 year olds; 73 for 17-22 year olds; 35 for 23-29 year olds; and 5 for those age 30 years and over. Most cases were aged 10 years and under, and this group were the main drivers of virus transmission.

Conclusions

The immunisation campaign prevented about 90-95% of predicted cases (allowing for under notification). The campaign appropriately targeted children aged 2-10 years for immunisation, but could have placed greater emphasis on protection for one year old children. Despite large numbers of susceptibles among young adults who were not targeted by the campaign, the epidemic was limited by preventing disease among 2-10 year old children.
**Introduction**

Measles vaccine was introduced to New Zealand in 1969 but had insufficient coverage to change the pattern of 2-3 yearly epidemics until 1980. A campaign that aimed to eliminate measles epidemics, launched in 1978, increased coverage sufficiently to defer subsequent epidemics to 1985 and 1991. Until 1980, many hospitalisations occurred in non-epidemic years. Since 1980, nearly all measles hospitalisations have occurred in epidemic years.

In March 1996, the World Health Organization (WHO) advised the New Zealand Ministry of Health to consider adopting the successful measles control strategy used in the Americas: immunising all children regardless of previous immunisation or disease history. A similar campaign had prevented a measles epidemic, predicted by mathematical modelling, in the United Kingdom. However, it was not certain that New Zealand needed such a campaign, given that it had introduced a two dose measles schedule in 1992, and that such a schedule had eliminated measles from Finland.

To further evaluate WHO's advice the Ministry developed a mathematical model that predicted an epidemic, of similar scale to that of 1991, was likely to happen in 1997 or 1998. The model's prediction had inherent uncertainties given its many assumptions and a 1998 epidemic was considered more likely. This later timing was consistent with a mathematical prediction based on previous epidemic experience. A more sophisticated model also predicted an epidemic in 1997. These predictions were based on coverage estimates of just over 80% for the first dose of measles-mumps-rubella vaccine (MMR).

To prevent the epidemic, a mass immunisation campaign was planned for July 1997 (at the start of the third school term). All children aged 2-10 years were to be offered MMR to immunise previously unimmunised children, and to protect children who had not responded to their first dose. By the middle of April 1997 it was clear that the epidemic had started. The campaign was brought forward to May/June, and the recommended timing for the first dose of MMR was shifted from 15 to 12 months. The age for the first dose was brought forward further to 6 months in Auckland in May 1997 in response to high disease rates in under one year olds in that region.

Vaccine supplies were limited until the end of May 1997, when school-based programmes(for children aged 5-10 years) started. The school programme was over by early July. General practitioners immunised preschool children until around September, and continued routine immunisation. Community workers and a mobile clinic delivered additional immunisation in areas of Auckland with increased measles activity from June to September. In February 1998, the Ministry of Health advised a return to the normal immunisation schedule.

This paper describes the 1997 epidemic in the context of the immunisation campaign, and specifically examines the hypotheses that: targeted mass immunisation of 2-10 year old children was sufficient to prevent epidemic measles transmission in all age groups; and mass immunisation after the commencement of the measles epidemic substantially reduced the number of expected measles cases.

**Method**

Probable measles cases are defined by clinical features of fever $\geq 38^\circ$C, and generalised maculopapular rash lasting 3 or more days, and either cough, coryza, conjunctivitis or Koplik’s spots. Confirmed cases require laboratory confirmation or epidemiological linkage to a laboratory-confirmed case. Laboratory confirmation was by IgM antibody in all except four cases where it was based on a rise in IgG antibody titre.
Measles cases were identified from three sources: notifications, laboratory and hospitalisations. The national communicable disease surveillance centre (ESR) linked notification and laboratory data from January 1997 to May 1998 to provide a notification dataset and a laboratory dataset from positive laboratory test result without a matching notification. The New Zealand Health Information Service provided all hospital discharges with a primary or secondary diagnosis of measles (ICD-9 code 055) from January 1997 to March 1998.

The three datasets were combined into one by electronic matching (using dates of birth and hospitalisation) and comparison of records to remove duplicates from the three datasets (eg, a hospitalised case who had also been notified) or from the same data source (eg, readmissions and duplicate entries in the notification database). When removing records, the preference was to remove the one with the least information. Notification data were corrected if necessary (eg, to indicate the case was hospitalised even though not reported as such).

Analysis was by measles onset date (notified or estimated). For the 70% of notifications and 55% of hospitalisations with an onset date, the mean time from onset was 7 and 3 days respectively. Onset date was estimated for the other hospitalisations by subtracting 3 days; for the other notifications by subtracting 7 days; and for laboratory data, by subtracting an arbitrary 5 days. Geographical analysis was by the four (then) regional health authorities: Northern, Midland, Central, Southern.

Ethnicity was recorded for notifications and hospitalisations, but not for the laboratory data. Age at disease onset was calculated and the following age groups constructed: under one year; one year; 2-4 years; 5-10 years; 11-16 years; 17-22 years; 23-29 years; and 30 years and over. These age groups were chosen for the following reasons:

- the campaign targeted children aged 2-10 years with schoolchildren (5-10 years) offered immunisation at school (except in the Southern region)
- children aged 11-16 years were likely to have received a second dose of measles vaccine at age 11 years, as this immunisation event had been introduced in 1992
- for people born in 1974 or earlier (aged 23 years and over), measles vaccine was recommended at 10 months of age and achieved low coverage so disease exposure was similar to the pre-vaccine era
- people born in 1967 or earlier (aged 30 years and over) were likely to have had measles before immunisation was introduced (in 1969).

The total 1996 census New Zealand population was used for calculating age-standardised rates, using the age strata described above. The 95% confidence intervals (CI) were calculated according to Rothman and Greenland, using the Wald method for rate ratios.

Results

Data sources and undernotification

A total of 2,257 measles case were identified from the 2,085 notifications, 339 hospitalisations, and 158 laboratory reports, once duplicates were removed. Of these, 317 (14%) were hospitalised and 131 (6%) were identified from a laboratory report only.

Of the 317 hospitalisations 214 (68%) had been notified but 55 of these 214 had been incorrectly notified as ‘not hospitalised’. There were also 57 notifications recorded as ‘hospitalised’ for whom no matching hospitalisation records were identified; presumably referred to hospital, but not admitted, and hence not considered ‘hospitalised’ in the analysis.
There were 141 cases with a positive laboratory report who were not notified; 10 of these were matched to a hospitalisation. Of notified cases 1,075 (53%) were laboratory confirmed. Thus, 88% of laboratory confirmed cases were notified.

Overall, 1,223 notified cases (60%) were confirmed (remainder by epidemiological linkage). Confirmation rates increased with age from 47% for under one year olds to 66% for 11-16 year olds, and was 85% for those aged 17 years and over (97% for 23-29 year olds).

No deaths were identified in the hospitalisation or notification data. Only one hospitalisation was coded as measles encephalitis. Excluding two cases for whom measles was lower than the fourth diagnosis, the mean length of hospitalisation was 2.6 days. Europeans had shorter mean stay (2.0 days) than Maori (3.3 days) and Pacific people (2.7 days).

**Time**

The epidemic started in April 1997, peaked in June (with a secondary peak for hospitalisations in September) and ended in January 1998 (Figure 1). For the 12 months covering the epidemic from 1 March 1997, there were 2,169 measles cases (crude rate of 60 per 100,000), 314 of whom were hospitalised (crude rate of 9 per 100,000).

**Place**

The epidemic affected the Auckland and Waikato areas first but had affected all districts by May 1998. Most (65%) of the cases were in the Northern region, with Central having the lowest proportion (9%) of cases during the epidemic. Most of the cases in Southern region occurred late in the epidemic (Figure 2). The age and ethnicity standardised incidence per 100,000 was: North 94, Midland 44, Central 20, and Southern 36. In the same regional order the age standardised incidence per 100,000 Europeans was: 58, 32, 14, and 28; for Maori: 62, 29, 13, and 20; and for Pacific people: 220, 72, 63 and 62.

**Age**
Age was recorded for all but 35 (1.6%) of cases. The incidence of measles increased from the age of two months with a plateau from age seven months (Figure 3). The number of cases then dropped at ages 13 and 16 months, ie, one month after the recommended ages for immunisation (normally 15 months, brought forward to 12 months during the epidemic). After the first year, the incidence of measles continued to decline with age. The 11-16 year olds had very few cases, while young adults aged 17-22 years had relatively increased numbers.

**Figure 3. Number of measles cases and hospitalisations, by age**

![Graph 3](image3)

The recommendation to immunise children aged 6 months to one year in Auckland had a limited impact on disease incidence in this age group. Children aged 6-11 months in the Northern region had a measles incidence of 2,570 per 100,000 compared with rates of 1,265, 536, and 693 per 100,000 for Midland, Central, and Southern regions respectively. This age group accounted for 18%, 22%, 20%, and 13% of all notifications in the four regions respectively. At the time that the recommendation was made, over 25% of Auckland cases were aged 6-11 months.

The case hospitalisation rate (based on hospitalisations divided by all cases) was 20% in the first year of life, declined to 13% in 1-4 year olds, and 3% in 5-7 year olds, then increased to 10% in 8-14 year olds, and 20% in 15-34 year olds, and was 6% in people aged 35 years and over. Some of the variation in case hospitalisation rates by age may be due to differences in completeness of notification by age.

The primary role of children aged 10 years and under can be seen in Figure 4. Most cases were in this age group. Older age groups were affected later than this age group. Once viral transmission was reduced in children aged 10 years and under, the incidence in the older age groups also declined. Figure 4 also suggests increased viral transmission among young adults later in the epidemic that could not be sustained while disease transmission among the children was declining.

**Figure 4. Number of measles cases per month, by age**

![Graph 4](image4)

Sex

1997 measles epidemic
Sex was recorded for all but 10 (0.5%) of cases. Differences in sex distribution, although statistically borderline or non-significant, showed an interesting pattern. Under fives with measles were more often male (54% of cases and 57% of hospitalisations), while cases aged five years and over were less often male (48% of cases and 43% of hospitalisations). But, 61% of cases in the 11-16 year old group were male reflecting greater uptake of MMR at age 11 years among girls than boys.

**Ethnicity**

For 24% (n=529) of cases and 12% (n=39) of hospitalisations no ethnicity was recorded, so not included in ethnic specific rates which are therefore are underestimates. The overall crude rate of measles during the epidemic year (March 1997 to February 1998) was 60 per 100,000. The ethnic specific rates were 29, 58, 275, and 52 per 100,000 for Europeans, Maori, Pacific people, and ‘Other’ respectively. The age-standardised rates for these ethnic groups were 33, 34, 174 and 43 per 100,000. The age-standardised hospitalisation rates were 4, 9, 7 and 32 per 100,000.

Maori and Europeans had the same age-standardised measles rate, but Maori rates were significantly higher for under one and 2-4 year olds and lower for those aged 17 years and over (Table 1). Maori hospitalisation rates were higher in most age groups (Table 2), with the age-standardised rate ratio (SRR) being double the European rate (2.1, 95% CI 1.5-2.8). Pacific people had a higher incidence of measles than Europeans in all age groups, both for total cases (SRR 5.2, 95% CI 4.7-5.9) and hospitalisations (SRR 7.7, 95% CI 5.8-10.4).

**Table 1. Age-specific and age-standardised measles incidence rates (per 100,000), and relative risk by ethnicity**

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence rate</th>
<th>Rate ratio compared to European (95%CI)</th>
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<tbody>
<tr>
<td></td>
<td>Incidence rate</td>
<td>Rate ratio compared to European (95%CI)</td>
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<tr>
<td></td>
<td>Age std*</td>
<td>European</td>
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<tr>
<td>0 yr</td>
<td>904.2</td>
<td>398.0</td>
</tr>
<tr>
<td>1 yr</td>
<td>688.5</td>
<td>367.2</td>
</tr>
<tr>
<td>2-4 yr</td>
<td>197.9</td>
<td>91.3</td>
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<tr>
<td>5-10yr</td>
<td>112.2</td>
<td>67.8</td>
</tr>
<tr>
<td>11-16yr</td>
<td>26.8</td>
<td>18.0</td>
</tr>
<tr>
<td>17-22yr</td>
<td>73.0</td>
<td>56.9</td>
</tr>
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<td>23-29yr</td>
<td>35.2</td>
<td>26.8</td>
</tr>
<tr>
<td>30+yr</td>
<td>4.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* Includes both cases and population counts with ‘Other’ ethnic group, and no specified ethnicity.
* Overall rates standardised to New Zealand population structure; includes cases with no age specified.
* Stratum with 5 or less cases, so CI may be unreliable.
### Table 2. Age-specific and age-standardised measles hospitalisation rates (per 100,000), and relative risk by ethnicity

<table>
<thead>
<tr>
<th>Age</th>
<th>Incidence rate (per 100,000)</th>
<th>Rate ratio compared to European (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All†</td>
<td>European</td>
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<tr>
<td>0 yr</td>
<td>184.5</td>
<td>54.1</td>
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<tr>
<td>1 yr</td>
<td>100.7</td>
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<tr>
<td>2-4 yr</td>
<td>22.3</td>
<td>7.9</td>
</tr>
<tr>
<td>5-10 yr</td>
<td>7.3</td>
<td>3.4</td>
</tr>
<tr>
<td>11-16 yr</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>17-22 yr</td>
<td>12.0</td>
<td>9.4</td>
</tr>
<tr>
<td>23-29 yr</td>
<td>9.9</td>
<td>7.7</td>
</tr>
<tr>
<td>30+ yr</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Rate ratio compared to European (95% CI)

| Age std* | 8.7 | 3.6 | 2.08 (1.5-2.8) | 7.73 (5.8-10.4) | 1.80 (1.1-3.0) |

† Includes both cases and population counts with ‘Other’ ethnic group, and no specified ethnicity.

* Overall rates standardised to New Zealand population structure; includes cases with no age specified.

# Stratum with 5 or less cases, so CI may be unreliable.

### Immunisation status

The notification forms include immunisation status, but this was recorded as unknown for 58% (n=1,126) of notifications. Only 5% (n=94) had documented receipt of at least one dose of measles containing vaccine (MCV); a further 9% (n=180) were immunised according to parental recall. Eight cases notified as immunised after disease onset date and 40 cases immunised within 10 days of disease onset were not considered to be immunised.

Only four cases had documented receipt of two doses of MCV; all of them were of European ethnicity. There were an additional 18 children who had received two doses of MCV according to parental recall.

Comparison of proportion of cases and population immunised allows an estimate of vaccine efficacy (VE). The estimated VE for one or more doses of MCV was 95% for children aged one year and over, if cases with unknown immunisation status were considered unimmunised, as they were likely to be. Excluding those with unknown immunisation status from the calculation led to a VE of 81%. Assuming higher coverage than 80%, and restricting the analysis to those with documented immunisation histories would increase the calculated VE.

### Impact of the campaign

The overall impact of the immunisation campaign can be seen by comparing measles cases with model predictions (Figure 5). The log scale shows the close match in the early development of the epidemic to that modelled, but masks the scale of the benefit - 97% of cases prevented. The less sophisticated model had predicted fewer cases (45,000) which would equate to just over 95% of cases avoided. Assuming that half the cases were not notified (in fact two-thirds...
of hospitalised cases were notified) then 90-95% of cases were prevented. Even for the Northern region which had the most cases (65%), the estimated percentage of cases prevented was 82-91%, and so greater than 95% of cases were prevented in the three other regions.

The number of cases starts deviating from the model two weeks after the circular letter of 28 April 1998 advising health professionals of the immunisation campaign to limit the epidemic. This interval is consistent with the time that immunisation takes to provide a protective effect.

The impact of the immunisation campaign is also evident from the numbers of cases in the target age groups (2-10 year olds) halving after the campaign, and contributing a smaller proportion of cases.

**Discussion**

Combining three data sources enabled a more comprehensive account of the epidemic and assessment of undernotification. As hospitalisation and laboratory data are fully ascertained, capture-recapture methods would not be appropriate to estimate the size of the epidemic. The notification rates were relatively high: 68% of hospitalisations, and 88% of laboratory confirmed cases. This compares favourably to the 50% or lower notification rate for measles in England in the 1970s, which itself compared favourably to notification rates in other countries. However, notification of measles is legally required, and all cases should be notified, both to enable appropriate and timely the public health response and to allow surveillance of the immunisation programme.

A review of immunisation campaigns to control measles outbreaks in middle and low income countries found limited evidence of efficacy. This immunisation campaign appears successful with 90-95% of expected cases prevented. The number of hospitalisations was high at half that of the 1991 epidemic but there were no deaths, compared with 7 deaths in 1991. There was also only 1 case of measles encephalitis compared with 10 in 1991. The absence of deaths and single case of encephalitis support the estimate that 90-95% of cases were prevented despite the relatively large number of hospitalisations.

The case hospitalisation rate of 14% (7% allowing for under notification) contrasts dramatically with the estimate of 1 to 2% in the 1991 epidemic and the 1976 English rate of 1.4%, but is lower than the 20% reported for the 1989-1991 USA epidemic. The 1996 pertussis epidemic also involved an unexpectedly large number of hospitalisations, possibly related more to social changes (ie, increased deprivation in some groups) than disease incidence although the exact reason is uncertain. The campaign’s lesser impact on hospitalisations could be explained if the most vulnerable people, who are most likely to be hospitalised as a result of infection, are also least likely to have responded to the immunisation programme. An increase in people not accessing primary health care may explain the trend towards the American rate of hospitalisation.

The age distribution of measles cases was as predicted by the models, including the very low attack rates for children aged 11-16 years who had been offered a second dose of MMR at age 11 years. There were more cases among those aged under two years than predicted. The high attack rate may be partly spurious as this age group had the lowest rate of confirmed measles. Infants often have febrile illnesses with rash caused by viruses other than measles.

False positive clinical diagnoses may be partly responsible for the apparently limited impact of bringing forward immunisation to age six months in Auckland on the very high rates of measles in infants aged 6-11 months, despite an estimated immunisation coverage of 57%. Failure of those most at risk to get immunised also accounts for the limited impact of this strategy, shown...
to be effective in other outbreaks.\textsuperscript{15} Disease in the infants stopped once the epidemic was controlled in the children..

The relatively high rates of susceptibility among young adults suggested by modelling was confirmed in Otago University students: 11\% lacked measles antibody.\textsuperscript{16} Nevertheless, the campaign was targeted at children aged 10 years and under in the belief that they are the main drivers of virus spread, and that children aged 11-16 years would be largely protected from having previously received a second dose of MMR. These assumptions appear to have been correct: once the epidemic had been controlled among children, measles spread was limited.

The higher rate of measles among preschool children than primary school children may reflect increased contact rates now that the majority of pre-schoolers attend early childhood centres (56\% of children aged 0-5 years; 91\% of 3-4 year olds in 1996\textsuperscript{17}). It may also reflect the fact that younger children get more serious illness and that parents of younger children are more likely to attend a doctor. Younger children did have higher case hospitalisation rates based on crude calculations in this paper. Preschool children also probably had lower immunisation coverage delivered over a longer time period than for school children.

Maori had a similar age-standardised measles incidence rate to Europeans, but more measles in the younger age groups. Maori hospitalisation rate was over twice that of European. These findings might reflect one or more of: Maori being less likely to be notified; Maori having poorer access to primary care than European; a lower threshold for hospital admission for Maori; relatively low numbers of susceptible older children among Maori; and increased likelihood of more severe disease among Maori.

In the 1991 epidemic, the age-standardised hospitalisation rate per 100,000 was 97 for Maori, 75 for Pacific people, and 18 for Europeans [Ministry of Health, unpublished report]. Compared to Europeans, the relative risk of hospitalisation in 1997 versus 1991 has doubled for Pacific people and halved for Maori. Some of the reduction in the relative risk of hospitalisation between epidemics for Maori may be due to denominator inflation as the number of people self-reporting as Maori increased from 435,000 in the 1991 census to 523,000 in the 1996 census. The discrepancy cannot be explained by differences in immunisation coverage, as coverage rates were slightly higher for Pacific than Maori children in the 1992 national survey,\textsuperscript{18} and even more so in the 1996 North Health survey.\textsuperscript{19} Household crowding, underestimates of the denominator size, and a proportionately larger susceptible adult population may explain the Pacific difference.

**Conclusions**

The immunisation campaign dramatically limited the size of the 1997 measles epidemic. The target group for the immunisation campaign was appropriate, illustrating the importance of country-specific factors in determining immunisation policy.

A relatively large pool of young adults remain susceptible to measles. Disease in this group was probably limited by the immunisation campaign targeted at children. The most effective way of protecting these individuals is to limit (hopefully eliminate) measles virus circulation among young children.

National coverage figures achieved by the campaign are not available, but local coverage estimates range from 55\% for Auckland to 85\% for the Wellington region.. The campaign’s prevention of 90-95\% of predicted cases demonstrates the protective effect of community immunity. A sustained increase in immunisation coverage may lead to the elimination of measles virus circulation.
The prevention of further measles epidemics requires high coverage with two doses of vaccine. Achieving the target of 95% coverage is likely to require additional mechanisms to reach vulnerable families and groups who are currently missing out. Scheduling the second dose of MMR earlier (e.g., at school entry) may also assist in the elimination of measles.\(^7\)

Measles only became a notifiable disease on 1 June 1996. Although measles cases were reported in the second half of 1991 epidemic, this was the first epidemic with relatively complete community incidence data. Hospitalisation data suggested that a third of cases were not notified, though the proportion may have been higher for non-hospitalised cases. Medical practitioners are actively encouraged to notify measles to support local control measures and provide surveillance data to guide future elimination or control policy.

References