

Previous vaccination modifies both the clinical disease and immunological features in children with measles

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ABSTRACT

INTRODUCTION: Measles that develops in previously vaccinated cases has been reported to be associated with modified disease, although severity has usually been assessed by the presence or absence of symptoms. To date no studies have attempted to subjectively grade the severity of the clinical features.

AIM: To investigate both the objective and subjective severity of measles in vaccinated and unvaccinated cases in the context of a community outbreak.

METHODS: A retrospective observational cohort study conducted in Christchurch in 2009 using notified data compared the presentation of measles in 14 confirmed cases that had received at least one MMR (measles, mumps, rubella) vaccination and 14 age-matched unvaccinated confirmed cases. Additional details on the subjective and objective severity of the illness were obtained from parents/guardians using a standardised telephone questionnaire.

RESULTS: The vaccinated group had significantly fewer clinical features on presentation ($p=0.01$, $RR=1.3$, 95% CI 1.1–1.6) and a less severe illness objectively, as measured by height and duration of fever, the number of days needing medication other than paracetamol and days required in bed. Unvaccinated cases were 2.8 times more likely to have more severe clinical features than vaccinated cases ($OR=2.8$, 95% CI 1.5–5.0). Unvaccinated cases were 3.0 times more likely to develop IgM antibody ($RR=3.0$, 95% CI 0.9–9.3).

DISCUSSION: Previously vaccinated children who develop measles are likely to have less severe disease and serology results that may be inconclusive, particularly for IgM antibody if tested in the first few days after the rash onset.

KEYWORDS: Immunoglobulin M; measles; measles-mumps-rubella vaccine; polymerase chain reaction; vaccination

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Introduction

Measles vaccination is highly effective and primary vaccine failure after two vaccinations is rare, with less than 1% failing to seroconvert.¹ Primary vaccine failure, following challenge with wild measles virus results in an illness of typical severity.² However, secondary vaccine failure, when measles develops after initial seroconversion, occurs in up to 6% of those vaccinated after one dose^{3,4} and has been reported to be associated

with milder or modified disease^{2,5–8} and a lower case fatality rate.⁹ In these studies, severity of disease has usually been assessed by the presence or absence of symptoms and none have attempted to subjectively grade the severity of individual clinical features.

Case definitions for probable measles based on the presence of clinical features alone¹⁰ are not accurate diagnostic guides in vaccinated communities^{2,11} because of the incidence of modified

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disease; in vaccinated cases diagnosis may even be more difficult if the symptoms that are present are less florid. Our aim was to investigate both the objective and subjective severity of measles in vaccinated and unvaccinated cases, as significant differences between these groups would have patient management and surveillance implications for primary care and public health services.

Methods

A measles outbreak occurring between June and September 2009 in Christchurch, New Zealand, provided the opportunity to investigate whether previous vaccination modified the presentation and severity of measles. A retrospective observational cohort study was conducted, with cases identified from the notification database¹² that captured the incidence of six presenting symptoms and laboratory serology (ELISA) results. All suspected probable and confirmed cases notified by general practitioners to the local public health service between June and September 2009 were reviewed. Cases were included if they met the study case definition for a confirmed case.

Case definition

For the purpose of this study, the definition of a confirmed case of measles was based on the New Zealand Communicable Disease Control Manual.¹³ This definition is as follows:

At least 12 months of age with either

1. an illness characterised by a maculopapular rash and fever, plus at least one of the following: cough, coryza, conjunctivitis or Koplik spots who was epidemiologically linked to a laboratory confirmed case, or
2. an illness characterised by either a maculopapular rash or fever with at least one of the following: cough, coryza, conjunctivitis or Koplik spots, that was confirmed by laboratory testing as measles. Confirmatory laboratory tests were demonstration of either: (i) measles virus RNA by PCR (polymerase chain reaction) except where this was within 10 weeks of an MMR (measles, mumps and rubella) vaccination, or (ii) measles-specific IgM antibody, except where this was within 12 weeks of an MMR vaccination.

Cases were considered vaccinated if documentation of the date was provided for at least a single measles vaccination given at over 12 months of age. Cases were considered unvaccinated if they were reported as having never been vaccinated.

A total of 14 cases previously vaccinated with MMR met the case definition. They were all aged less than 17 years and were individually age-matched to control for age-related severity,¹ with 14 unvaccinated cases.

Evaluation of severity

To obtain information on the severity of the illness, a standard telephone questionnaire was administered by a doctor or health protection officer to parents/guardians of all cases. The questionnaire was developed, applying a standard rating scale for evaluating severity, using information from the literature on measles signs and symptoms. The questionnaire covered the following objective measures of severity:

- height and duration of fever
- requirement for analgesia/antipyretic (paracetamol) or other medication
- days of confinement to bed or equivalent
- hospitalisation
- visits to a doctor
- time to complete recovery.

Parents/guardians were also asked to subjectively grade the severity 0 to 5 (with 5 being severe) of each of the following 14 clinical features: rash, cough, coryza, conjunctivitis, otitis media, bronchitis, pneumonia, laryngitis or croup, headache, irritability, confusion, vomiting, diarrhoea and photophobia. Parents/guardians were unaware of the reason for the study.

Ethics approval was not required for this study under Section 11 of the Ethical Guidelines for Observational Studies.

Data analysis

Chi-square tests were used to compare the percentages of cases with diagnostic clinical features in the vaccinated and unvaccinated groups. Paired Student *t* tests were used to compare both the

objective and subjective severity of measles. Subjective grades of severity for the 14 clinical features were further grouped into three categories, with only the mild (0–1) and more severe (4–5) included in the analysis. The numbers of grades in these two categories were compared by a Chi-square test. The Chi-square test was used to examine the difference of the immune response between the two groups. The Student *t* test was used to detect any association between the timing of the serology test and the presence of IgM antibody,^{14,15} and any difference in the timing of the serology test between the two groups (vaccinated and unvaccinated cases) to determine if timing confounded an apparent association between the immune response and vaccination. All analyses were conducted using SPSS 17.0 statistical package (SPSS Inc. Chicago, USA).

Results

Of 168 notified suspected, probable and confirmed measles cases, 64 met the study inclusion criteria. Fourteen had documentation of previous vaccination and 50 reported being unvaccinated. The characteristics of the matched groups were similar (Table 1). On presentation, vaccinated cases were less likely to have Koplik spots and had significantly fewer clinical features ($p=0.01$, RR=1.3, 95% CI 1.1–1.6; see Table 2).

WHAT GAP THIS FILLS

What we already know: In previously vaccinated cases, measles signs and symptoms are likely to be less frequent compared with unvaccinated cases. There is some evidence that, in vaccinated cases, measles-specific IgM is less likely to be positive if tested in the first few days after the rash onset.

What this study adds: In this study of a New Zealand community outbreak of measles, previously vaccinated children were likely to develop subjectively less severe disease compared with unvaccinated cases.

Table 1. Characteristics of the study groups

| | Vaccinated n*=14 | Unvaccinated n*=14 |
|---|---------------------|-----------------------|
| Mean age | 9.6 ± 5.9 years | 9.3 ± 5.2 years |
| Range | 1–16 years | 2–16 years |
| Males: females | 11: 3 | 10: 4 |
| Ethnicity—European: Maori | 12:2 | 13:1 |
| Vaccination | | |
| 1 MMR | 5 | — |
| 2 MMR | 9 | — |
| PCR positive | 10 | 11 |
| IgM antibody positive [†] | 2 [‡] | 9 |
| Clinical criteria met plus contact with confirmed case [§] | 4 | 1 |

* Number of cases

† Nine cases in each group had serology completed

‡ Another case was equivocal

§ Does not include cases who were also laboratory confirmed

Table 2. Clinical features of measles in the study groups

| Clinical feature | Diagnostic clinical features as notified by general practitioners n (%) | | RR (95% CI) | p-value |
|---|--|-----------------------|----------------|---------|
| | Vaccinated n=14 | Unvaccinated n=14 | | |
| Fever | 10 (83)* | 12 (86) | 1.0 (0.7–1.4) | 1.00 |
| Maculopapular rash | 12 (86) | 14 (100) | 1.2 (0.9–1.4) | 0.48 |
| Cough | 10 (71) | 13 (100) [†] | 1.4 (1.0–2.0) | 0.05 |
| Coryza | 11 (85) [‡] | 9 (82) [‡] | 1.0 (0.7–1.4) | 1.00 |
| Conjunctivitis | 6 (43) | 6 (50)* | 1.2 (0.5–2.7) | 1.00 |
| Koplik spots | 2 (17)* | 9 (82) [†] | 4.9 (1.3–17.9) | 0.003 |
| Percentage of total clinical features present when notified | 65% | 84% | 1.3 (1.1–1.6) | 0.01 |

RR relative risk

* 2 cases unknown

† 1 case unknown

‡ 3 cases unknown

Table 3. Objective severity of measles as assessed by parents/guardians

| Clinical feature | Average objective severity level | | Mean difference (95% CI) | p-value |
|------------------------------|---|---|--------------------------|---------|
| | Vaccinated n=14 mean (standard deviation) | Unvaccinated n=14 mean (standard deviation) | | |
| Height of fever | 38.8°C (0.9)* | 39.8°C (0.8) | 1.0°C (0.2–1.7) | 0.02 |
| Days of fever | 2.3 (1.2) | 4.3 (1.3) | 2.0 (1.2–2.6) | <0.001 |
| Days given other medication† | 0.3 (0.8) | 2.5 (3.1) | 2.2 (0.4–4.1) | 0.02 |
| Days in bed | 2.1 (1.4) | 5.3 (2.8) | 3.2 (1.7–4.8) | <0.001 |
| Days until full recovery‡ | 8.6 (4.7) | 17.0 (16.1) | 8.4 (-0.2–17.0) | 0.05 |

* 2 cases unknown

† medication other than paracetamol

‡ able to participate in usual activities

The vaccinated group had several objective measures of severity that were significantly lower: the height and duration of fever, the number of days taking medication other than paracetamol, and days in bed (Table 3), but not time taken to recover ($p=0.05$), days requiring paracetamol, or visits to the doctor. Two unvaccinated patients were admitted to hospital; however, this finding was not significant due to the small sample size.

The vaccinated group also had significantly lower subjective severity grades for maculopapular rash ($p=0.004$), vomiting ($p=0.04$), diarrhoea ($p=0.04$) and photophobia ($p=0.001$) but not for cough, coryza, conjunctivitis, otitis media, bronchitis, laryngitis/croup, headache, irritability or confusion. Two cases in the unvaccinated group developed pneumonia, but there were no cases with pneumonia in the vaccinated group. This finding was not significant due to the small sample size. When the numbers in each group were compared for the 14 clinical features that were subjectively graded as either mild (0–1) or as more severe (4–5), unvaccinated cases were 2.8 times more likely to have more severe (grades 4–5) clinical

features than vaccinated cases (OR=2.8, 95% CI: 1.5–5.0; see Table 4).

The immune response differed significantly ($p=0.01$), with unvaccinated cases being 3.0 times more likely to develop IgM antibody compared with the vaccinated group (RR=3.0, 95% CI 0.9–9.3). Although the mean duration of the interval between the onset of the rash and the serology test was 1.4 days less in the vaccinated group (mean=1.3 days, median=1.5 days, range=0–3 days) compared with the unvaccinated group (mean=2.7 days, median=2 days, range=0–6 days), this difference was not significant ($p=0.17$). Of 10 vaccinated cases that had serology tests, two were IgM antibody positive, six were negative and two were equivocal (the two that had equivocal antibody and the two without a rash were excluded from the analysis). Six were IgG antibody positive, two were negative and two were equivocal. Of nine unvaccinated cases that had serology, all were IgM antibody positive and IgG antibody negative.

Discussion

In our study, we have assumed that all vaccinated cases had secondary vaccine failure because the rate of seroconversion after one and two doses respectively of measles vaccine is approximately 95% and 99%.¹ Two cases, however, were negative for both measles-specific IgM and IgG, but both had had two doses of MMR vaccine. It is not known whether they had an initial antibody response to vaccination and subsequently

Table 4. Subjective severity of 14 clinical features as assessed by parents/guardians

| Grades* | Number of grades | | OR (95% CI) | p-value |
|---------|--------------------|----------------------|---------------|---------|
| | Vaccinated n=14 | Unvaccinated n=14 | | |
| 0–1 | 124 | 92 | 2.8 (1.5–5.0) | 0.001 |
| 4–5 | 21 | 43 | | |

* 0 (none) – 5 (severe)

lost measurable circulating antibody or had no response at all.

A potential bias of the study was the parents'/guardians' reporting of the subjective severity of the illness, as that was not independently validated. However, the pattern of modified disease in vaccinated cases seen in that reporting was also apparent in the objective measures (Table 3), as well as in general practitioners' notification details (Table 2). Another limitation of the study design was the small sample size, which limited the power of some of the statistical analyses to detect significance. For instance, only four individual symptoms were subjectively assessed as significantly less severe in vaccinated cases, although the odds ratio for the unvaccinated group having a greater number of subjectively more severe symptoms was significant. On the other hand, the strengths of the study were that it compared two similar groups of confirmed cases in the same outbreak whose ages were within a relatively narrow age range, and the same laboratory was used for serology and PCR tests.

Of the 27 indicators (Methods and Case definition) reported, only three were either less frequent or less severe in unvaccinated cases. They were coryza as a presenting symptom and coryza and bronchitis as subjectively assessed, but none of these differences were statistically significant. The results support findings of previous studies^{2,5-8} that showed that measles associated with vaccine failure was likely to be less severe. Even following incidental exposure post-vaccination, measles symptoms were ameliorated,¹⁶ a result consistent with the suggestion that partial immunity may account for the findings.^{2,16} Although studies have found few or no differences,^{17,18} one of these studies¹⁸ grouped children vaccinated prior to 12 months of age with unimmunised cases.

Case definitions for suspected measles in vaccinated communities based only on clinical features have been shown to be unreliable,^{2,11,19} in part because the symptoms in vaccinated cases may be modified. This presents a quandary for both surveillance and public health management. The introduction of case definitions with less rigorous clinical criteria capturing presentations with

fewer or milder symptoms would result in a shift from the current situation of under-diagnosis to over-diagnosis, resulting in unnecessary public health intervention. We therefore suggest that in previously vaccinated patients with suspected measles who do not satisfy a clinical case definition, a PCR test (rather than serology) be done to establish the diagnosis if presentation is within three to five days of the rash onset. In our experience and that of others,^{2,4,11} serology in these cases and particularly within this timeframe²⁰ may be associated with false negative IgM results.

This study of measles cases in a community outbreak has shown that children previously vaccinated with MMR who develop measles are likely to have less severe objective and subjective disease, and serology results that may not be conclusive. The findings indicate gains from immunisation despite apparent vaccine failure. The study also identifies the importance of using PCR to assist with the diagnosis, since case definitions for measles based on clinical criteria alone can be unreliable in previously vaccinated children. Diagnostic accuracy is important from a public health perspective, both for surveillance purposes and to inform the response.

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COMPETING INTERESTS

None declared.