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Vaccine failures and vaccine effectiveness in children during measles outbreaks in New South Wales, March–May 2006

Vicky Sheppeard, Bradley Forssman, Mark J Ferson, Conrad Moreira, Sue Campbell-Lloyd, Dominic E Dwyer, Jeremy M McAnulty

Abstract

During March to May 2006 the highest incidence of measles in New South Wales since 1998 provided an opportunity to estimate the effectiveness of the measles-mumps-rubella (MMR) vaccination program in preventing childhood measles, and describe any differences in clinical presentation between vaccinated and unvaccinated children. We reviewed records of all 33 notified cases of measles in children aged 1–14 years during a state-wide outbreak in New South Wales from March – May 2006. Six of the children had a confirmed history of vaccination with at least 1 dose of MMR. The children with previous vaccination tended to have milder disease than those without vaccination as judged by their reported number of symptoms and hospitalisation rates. The vaccinated children were less likely to have a typical measles rash. Two of the cases in previously vaccinated children may be due to secondary vaccine failure, although a lack of complete diagnostic testing limits our ability to confirm this. Vaccine effectiveness after receiving at least 1 dose of MMR is estimated to be 96% (95% CI 77.8–99%). MMR vaccination was effective in preventing measles in children during these outbreaks. *Commun Dis Intell* 2009;32:21–26.

Keywords: measles-mumps-rubella vaccine, vaccine effectiveness, disease outbreaks, child

Introduction

From March to May 2006, there were 59 cases of measles in New South Wales.[1] There were 2 distinct outbreaks during this period – the first was associated with transmission in a hospital emergency department, and the second with an Australian tour by a spiritual group from a measles-endemic country. This represented the highest incidence of measles in New South Wales since the Measles Control Campaign (primary school catch-up) in 1998 and the introduction in the same year of the 2nd scheduled dose of measles vaccine (MMR) at 4 years of age.[2] From 1999 to 2005 there was an average of only 20 cases annually in New South Wales.[3]

Since 1999 New South Wales has maintained high vaccination rates, with approximately 93% of children receiving the 12-month dose of MMR, and 85% receiving the recommended 2 doses before school entry (measured at age 6 years).[4]

It has been reported that previously vaccinated children who develop measles may have a milder course, or have different characteristics compared to vaccine naive children.[5–7] Primary vaccine failure (a failure to mount an immune response to MMR) is well recognised and thought to occur in about 5%–10% of cases after 1 dose of measles vaccine given at 12 months of age.[8] However, the entity of secondary vaccine failure (clinical infection despite a prior immune response to vaccination) is less well understood for measles.[8]

We sought to determine whether the clinical presentation of children with measles differed according to vaccination status; the reason for vaccine failure; and to estimate MMR vaccine efficacy among children in New South Wales.

Methods

Setting

New South Wales is the most populous state in Australia. Most of its 7 million residents live in the Sydney metropolitan areas (population >4 million). Public health services are mainly provided by public health units located in 8 Area Health Services, coordinated by the NSW Department of Health. Public health unit surveillance officers (PHUSO) investigate cases of notifiable diseases and enter details into the state's Notifiable Disease Database (NDD).

Case definition

In Australia, a confirmed case of measles is defined as either: positive measles-specific IgM serology; or detection of measles virus by immunofluorescence (IF), polymerase chain reaction (PCR) or culture in the presence of a compatible illness; or clinical measles (fever and/or cough and/or coryza and/or conjunctivitis and maculopapular rash) with an epidemiological link to a laboratory confirmed case.[9]

Data collection

In New South Wales measles is notifiable under the *Public Health Act 1991* by laboratories, hospitals, clinicians, school principals and childcare centre operators, hence it is assumed that all confirmed cases of measles in New South Wales are reported to the NDD. We obtained data on all cases of confirmed measles in Australian residents aged 1–14 years reported to the New South Wales NDD between 1 March and 31 May 2006.

Data on symptoms and signs were obtained by PHUSO from cases' parents and/or guardians and their health care providers and recorded on a standardised reporting form.[10] A rash was classified as typical measles when described as maculopapular and spreading from the head to the trunk then extremities.

The vaccination status of cases aged 1–7 years was confirmed against the Australian Childhood Immunisation Register.[4] For older cases, vaccination status was confirmed by parent-held or general practitioner childhood vaccination records.

Data on immunisation rates in New South Wales were obtained from the Australian Childhood Immunisation Register (ACIR), for children born between April 1998 and March 2005 (1–7 years of age during the outbreak).[4]

Laboratory testing

All positive IgM serology tests were either performed initially or confirmed using the Enzygnost Anti-Measles-Virus IgM immunoassay for measles virus-specific IgM method (Dade Behring, Marburg, Germany) at one of 4 New South Wales reference laboratories. Measles virus was detected using either IF or PCR on nasal or pharyngeal specimens as previously described.[11]

Statistical analysis

Oddsratios (comparing vaccinated and unvaccinated cases) and significance levels were calculated using Epi Info version 3.2.[12] Levels of significance were obtained using Fisher's exact test. Age-corrected vaccine effectiveness was calculated for New South Wales resident children aged 1–7 years according to the screening method described by Farrington.[13] We tested for confounding by location by calculating vaccine effectiveness by Area Health Service of residence.

Results

Between 1 March and 31 May 2006 there were 59 notifications of measles in New South Wales. Figure 1 demonstrates the onset of cases by age group during the study period. Thirty-three of these notifications met the case definition for this study. Age distribution by vaccination status is illustrated in Figure 2. Only six of the 33 children (18%) had received at least 1 dose of MMR.

Figure 1. All measles cases onset, New South Wales, 1 March to 31 May 2006, by age group

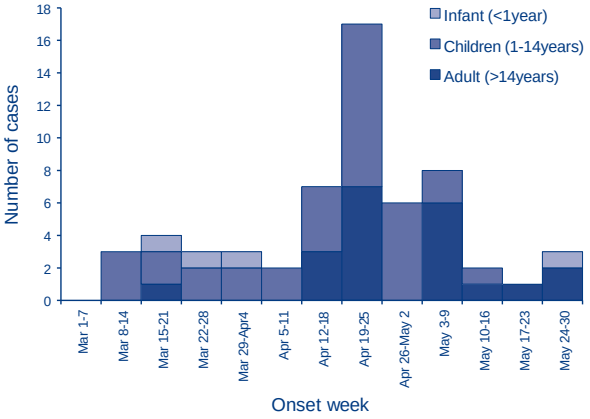
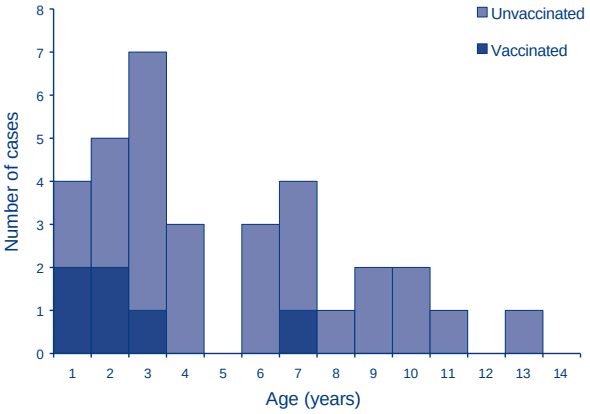


Figure 2. Age of children with measles, by vaccination status



The 6 previously vaccinated children ranged in age from 13 months to 7 years. All had received their first MMR vaccine at 12 months of age. Only one was old enough to have received a scheduled second MMR vaccine (at 4 years of age). The time elapsed since vaccination varied from 1 month to 3 years. All cases apart from one were residents of the Sydney Metropolitan region. Their characteristics are summarised in Table 1.

Table 2 compares the clinical characteristics by vaccination status of all 33 children, and also separately provides characteristics of the group of unvaccinated children aged 1–7 years for comparison, as all vaccinated children were in this age group.

Compared to the presence of atypical or no rash in four of the 6 vaccinated children, only three of the 27 unvaccinated children were reported to have an atypical rash ($\chi^2_{1df} = 9.13$, $P = 0.003$). Vaccinated children tended to have a shorter prodrome, although this was not statistically significant.

Diagnostic tests

Results of diagnostic testing on the 6 vaccinated children are summarised in Table 1. Of the 27 unvaccinated children, 10 had positive IF tests for measles antigen, six were confirmed by positive measles-specific IgM serology and 11 were diagnosed on the basis of clinical features and epidemiological links.

Calculation of vaccine effectiveness

Population rates of measles were estimated for vaccinated and unvaccinated New South Wales resident children aged between one and 7 years (excluding 1 case from this age group, resident in Queensland). There were 605,623 children born during the period 1 April 1998 to 31 March 2005 in New South Wales with records on the ACIR. The proportion of this population reported as vaccinated (PPV) is 92.9% for 1 dose and 86.6% for 2 doses of MMR (Table 3). The age-corrected vaccine effectiveness of at least 1 dose of MMR is estimated at 96% (95% CI 78.1–99.3). Cases arose in six of the 8 Area Health Services. For the Area Health Services where vaccine effectiveness could be calculated the point estimates were within these confidence intervals.

Table 1. Characteristics of measles cases in previously vaccinated children 1–14 years of age

Age	Lifetime doses MMR	Time between MMR and onset	Days from symptom onset to serum sample	IgM	IgG	Nasal swab IF
13 months	1	4 weeks	2	negative	equivocal	+
14 months	1	7 weeks	n/a	not done	not done	+
2 years	1	11 months	2	negative	+	+
2 years	1	10 months	6	low +	+	not done
3 years	1	2 years	4	negative	+	+
7 years	2	3 years	12	+	not done	not done

Table 2. Comparison of clinical characteristics of children (1–14 years), by vaccination status

	Vaccinated n=6		Unvaccinated n=27		Unvaccinated (1–7 years, n=20)		Odds ratio*	*P* value
Mean age	2.7 years		5.4 years		3.8 years			
Age range	1–7 years		1–13 years		1–7 years			
Sex (female)	3	(50%)	17	(63%)	11	(55%)	0.59	0.66
Signs and symptoms								
Fever	5	83%	27	100%	20	100%	0	0.18
Cough	4	67%	22	81%	17	85%	0.45	0.58
Coryza	3	50%	18	67%	13	65%	0.5	0.64
Conjunctivitis	3	50%	21	78%	15	75%	0.29	0.31
Koplik's spots	0	0%	4	15%	3	15%	0	1.00
Typical rash	2	33%	24	88%	20	100%	0.06	0.01†
≤2 prodromal symptoms‡	3	50%	4	15%	3	15%	5.75	0.09†
Median duration prodrome; range	2 days 1–7 days		3 days 0–7 days		3 days 0–7 days			NS
Hospitalised	0	0%	4	15%	3	15%	0	1
Median number of visits§ range	2.5 1–3		1 0–4		1 0–4			NS

* Comparing vaccinated and all unvaccinated children.

† Chi-squared, Fisher's exact test.

‡ Presence of only one or two of symptoms: fever, cough, coryza, conjunctivitis.

§ Visits to emergency department or general practitioner.

NS Not significant.

Table 3. Rate of measles, New South Wales resident children aged 1–7 years, by vaccination status

	Number in New South Wales	PPV	Number of cases	Rate per 100,000
One MMR (age 1–3 years)	260,738	93.3%	5	1.9
Two MMR (age 4–7 years)	344,884	86.6%	1	0.3
No MMR	42,949	0	19	44.2
Total population (age 1–7)	605,623		25	

MMR Measles-mumps-rubella

PPV Proportion of population reported as vaccinated.

Discussion

In these outbreaks we observed a differing clinical presentation in children with and without a history of MMR vaccination. The previously vaccinated children were significantly more likely to have fewer symptoms, had a non-significant shorter duration of prodrome, were significantly more likely to have an atypical rash, and none were hospitalised. This demonstrates that previously vaccinated children experienced milder disease.

Many previous case series comparing vaccinated and unvaccinated children are from developing countries where other determinants, such as malnutrition, may be important in influencing the clinical course of measles. Of the hospital-based case series, two found no difference between vaccinated and unvaccinated children in the clinical presentation or complication rate[14,15] whereas Adu in Nigeria, found that signs and symptoms were more severe among the unvaccinated children[5] and Aurangzeb in Pakistan,[6] found that mortality was significantly associated with unvaccinated status. The only community-based series from developing countries, Ibrahim in Khartoum, found that severe measles was as common in vaccinated as unvaccinated children.[16]

In developed countries, however, there have been reports of differences in disease severity related to vaccination status. In a large case series from Wisconsin, the authors found a significant association between milder measles (categorised by fewer symptoms and lower fever) in previously vaccinated children with presumed secondary vaccine failure, compared with previously vaccinated children with primary vaccine failure or unvaccinated children.[17] A case series from The Netherlands where 33 of 37 cases were vaccinated noted that measles infection was detected in patients with relatively few or atypical symptoms.[7]

In this case series the number of visits to primary care providers does not appear to be a good indicator of disease severity. The median number of visits to GPs or emergency departments per case was significantly greater for the vaccinated group of children, which may reflect the difficulty in making a diagnosis in this group of patients rather than the severity of disease. The range of number of visits was greater for the unvaccinated group. Some of this latter group who were contacts of other cases, had no visits at all to health care providers and were managed at home, whereas others repeatedly presented due to ongoing or increasing symptoms. The greater severity of disease in the unvaccinated group was demonstrated by the significantly increased number and duration of prodromal symptoms, and that 15% required hospital admission, compared to none of the vaccinated children.

Measles infection after immunisation is thought to largely arise from primary vaccine failure. In primary vaccine failure the patient fails to develop an immune response to the vaccination. This is reported to occur in 5%–10% of children after 1 vaccination at 12 months, and reduces to 1% after a second vaccination.[8] The causes of primary vaccine failure include failure of the cold chain, inadequate viral dose, and host immune factors, such as persistence of passively acquired maternal immunity.[18]

Secondary vaccine failure has also been postulated, where the patient develops an initial immune response to the vaccine and has detectable IgG antibody to measles. When challenged with wild virus however the immune response is inadequate to prevent disease. The incidence of secondary vaccine failure is not known, but has been reported as developing in 5% of children after 10 to 15 years.[8] Erdman observed 57 measles cases with a prior history of vaccination, and 55 (96%) had detectable IgM antibodies. Of these, 30 (55%) were classified as having a primary antibody response and 25 (45%) a secondary antibody response based on their ratios of IgM to IgG being greater than one (primary failure) or less than one (secondary failure). Differences in the severity of clinical symptoms between these 2 groups were consistent with this classification scheme, with cases categorised as secondary vaccine failure having significantly fewer and less severe symptoms.[19]

The interpretation of the type of vaccine failure in this case series is limited as only routine laboratory tests were available. Quantitative complement fixation on acute and convalescent serology would have assisted in determining whether vaccine failure was primary or secondary, and IgG avidity testing has also been used in this context, but neither are routinely undertaken in New South Wales.[20,21]

The study is however strengthened by the detection of measles antigen by immunofluorescence in four of the 6 vaccinated cases. Detection of measles antigen by immunofluorescence is assumed to have a specificity of 90%–95%, whereas the sensitivity depends on the quality of the specimen and is similar to culture at around 50%.[22,23] Two of the vaccinated cases were diagnosed on the basis of positive measles-specific IgM serology. Specificity of the Dade Behring method in a reference laboratory should be 97%, nevertheless these cases could be false positives. Both cases had atypical prodromal symptoms but developed classical measles rashes.

Cases 3 and 5 who had received MMR 11 months and 2 years previously may be examples of secondary vaccine failure as IgG was present at days 2 and 4 of disease respectively and IgM was not detected. The expected immunological response to primary exposure to the measles virus is a rapid rise in IgM from the appearance of the rash, peaking after 1 week. The rise in IgG is slower, and the peak occurs approximately 2 weeks after the rash.[24] The Dade Behring indirect enzyme immunoassay is reported to have a sensitivity of 88.6%, which increases from 70% in the first few days from onset of symptoms to 100% between six and 14 days after onset of symptoms.[20] We are unable to determine if the negative IgM results are false negatives as both these cases' sera were taken early in the course of the disease. False negative indirect IgM assays can also result from insufficient removal of high levels of measles-specific IgG from a test specimen.[25] Due to these factors, where measles is suspected in vaccinated children, specimens should be obtained for viral testing to allow confirmation of the diagnosis.

The comparison of the number of symptoms between the 2 groups should be viewed with caution. Symptoms were not independently verified by the investigators, but were reported by clinicians, or surveillance officers based on patient reports. Knowledge of previous vaccination against measles may have influenced reporting of symptoms, with a tendency for those with previous vaccination to be less likely to report symptoms known to be consistent with measles. The reported duration of a shorter prodrome in vaccinated cases may represent a more robust measure of milder disease as symptom and rash onset dates may be more accurately reported than the actual symptoms. Surveillance officers did use a standard form to record symptom information for each case that may have assisted in reducing measurement error.

It is interesting to note that none of the cases in vaccinated children presented as typical measles and were only confirmed by diagnostic testing. It may be that such cases are not routinely diagnosed in New South Wales, but were detected during this period due to heightened awareness of measles arising from information sent to clinicians and mass media releases.

Use of field observations in outbreaks to monitor vaccine program effectiveness is recommended.[26] The calculated measles incidence rates indicate that the vaccine failure rate in New South Wales children is low. Children who had received at least 1 dose of MMR developed measles infection at only 2.4% of the rate in the unvaccinated population, and children who received 2 doses developed measles at less than 1% of that observed in unvaccinated children. The calculated vaccine effectiveness rate of 96% compares favourably with that observed in an outbreak in Leeds of 95.1%,[13] however the impact of a 2nd dose of vaccine at 4 years cannot be accounted for by this method. The calculation of vaccine effectiveness utilised vaccination rates recorded at the Australian Childhood Immunisation Registry. As survey data indicate that ACIR records underestimate actual vaccination rates by 5%–13% the true vaccine effectiveness may be higher than we have estimated.[27,28]

Use of the screening method to assess vaccine effectiveness can also be confounded by age and location. We tested for confounding by age cohort and by area of residence (data not shown) and found that confounding was not present, indicating similar effectiveness over time and place.

Modelling of expected susceptible population numbers against the epidemic threshold predicted that there would be sufficient unimmunised children in Sydney between 2002 (in the lowest immunisation rate areas) and 2006 (in the highest immunised areas) to sustain a measles epidemic.[29] The introduction of measles to New South Wales in 2006 with a resultant epidemic has illustrated the usefulness of modelling in predicting disease control failure and underlines the importance of improving our current measles immunisation rates.

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Author details

Dr Vicky Sheppeard,[1] Medical Officer, Communicable Diseases Control Branch
Dr Bradley Forssman,[2] Medical Officer, Public Health Unit
Professor Mark J Ferson, Director, Public Health Unit[3], School of Public Health and Community Medicine[4]
Dr Conrad Moreira,[5] Medical Officer, Centre for Population Health
Ms Sue Campbell-Lloyd,[1] Manager, Immunisation Unit
Dr Dominic E Dwyer,[5,6] Microbiologist,
Dr Jeremy M. McAnulty, Director,[1] Communicable Diseases Control Branch

1. NSW Department of Health
2. Sydney South West Area Health Service
3. South East Sydney Illawarra
4. University of New South Wales
5. Sydney West Area Health Service
6. Institute of Clinical Pathology and Medical Research

Corresponding author: Dr Vicky Sheppeard, Locked Bag 7118, PARRAMATTA BC NSW 2150. Telephone: +61 2 9840 3603. Facsimile: +61 2 9840 3608. Email: Vicky.sheppeard@swahs.health.nsw.gov.au

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