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Impact of the Australian Measles Control Campaign on immunity to measles and rubella

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SUMMARY

To evaluate the impact of the 1998 Australian Measles Control Campaign on immunity to measles and rubella, 4400 opportunistically-collected sera, submitted to diagnostic laboratories across Australia from subjects aged 1–49 years, and 3000 from subjects aged 1–18 years, were tested before and after the campaign, respectively. The proportion of individuals aged 1–18 years who were immune to measles rose from 85% before, to 90% after, the campaign ($P < 0{\cdot}001$). The greatest increase was in preschool (7%, $P < 0{\cdot}001$) and primary school (10%, $P < 0{\cdot}001$) children, who were actively targeted by the campaign. Rubella immunity in 1–18 year-olds rose from 83% to 91% ($P < 0{\cdot}001$), again with significant increases in preschool (4%, $P = 0{\cdot}002$) and primary school (16%, $P < 0{\cdot}001$) children. 94% of individuals aged 19–49 years were immune to rubella. These serosurveys confirm other evidence of the effectiveness of the Australian Measles Control Campaign and demonstrate the value of serosurveillance using opportunistically collected sera.

INTRODUCTION

The Australian Measles Control Campaign took place between July and December 1998. It was conducted when the age for the second dose of measles-mumps-rubella (MMR) vaccine was lowered from 10–16 years to 4–5 years (prior to school entry) and was accompanied by a major media programme. The campaign had three components: (1) all primary school aged children were offered MMR vaccine regardless of their existing immunization status; (2) reminder letters were sent to parents of children aged 12–42 months whose first dose of MMR vaccine (scheduled at the age of 12 months) was due or overdue, according to the Australian Childhood Immunisation Register; (3) an information pack was sent to secondary school students and their parents to encourage students to obtain a second dose of MMR.

National serosurveys were undertaken before and immediately after the campaign to help evaluate its impact. Previous experience in Italy [1], Taiwan [2], England and Wales [3, 4] had indicated that this would be useful for evaluation. Unlike some other countries, where national serosurveillance for key vaccine preventable diseases has been in place for some years [4–6], Australia had no such programme until the establishment of the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases in August 1997.

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In this paper, we report the results of serosurveys using a national sample of opportunistically collected sera to determine the baseline prevalence of immunity to measles and rubella before the campaign, and to measure its impact.

METHODS

Serum samples

All major public and private diagnostic laboratories throughout Australia were invited to contribute sera that had been submitted for diagnostic testing and would otherwise have been discarded; 45 of these 52 laboratories agreed to participate. Sera from subjects who were known to be immunocompromised, to have received multiple transfusions in the past 3 months, be infected with human immunodeficiency virus, or to have had serum collected for diagnosis of measles were excluded. Only one sample from any subject was tested. Samples collected up to 2 years before the campaign were used for the pre-campaign survey and between January and May 1999 for the post-campaign survey.

Study population

Approximately 3000 sera, from children aged 1–18 years, were tested in each survey. In addition, a sample of approximately 1400 sera from adults aged 19–49 years was retrieved at the same time as the pre-campaign survey and tested for rubella IgG, to obtain a broader perspective of rubella immunity in Australia. These sera will also be tested for measles IgG and the results presented elsewhere.

Serum samples were stratified into 1-year age groups for subjects aged up to 19 years, 5-year age groups for those aged 20–29 years and 10-year age groups for those aged 30–49 years. Within each age group, States and Territories were sampled proportionally to their population size. Sample sizes were calculated to achieve confidence intervals of approximately $+/-5\%$ for each age group, based on the expected level of immunity to measles (or rubella for subjects aged over 18 years). Approximately equal numbers of sera from males and females were tested.

Antibody assays

Sera were tested and interpreted according to manufacturer's instructions using the Enzygnost (Behring Diagnostics, Marburg, Germany) anti-measles and anti-rubella IgG enzyme immunoassays (EIA), at the Institute of Clinical Pathology and Medical Research, Sydney, Australia.

Measles IgG antibody tests

Measles IgG levels were interpreted as follows: < 150 mIU/ml negative, 150–343 mIU/ml equivocal and > 343 mIU/ml positive. All sera for which the result was equivocal were retested. A proportion of those that remained equivocal was tested by plaque reduction neutralization (PRN) assay [7] at the Victorian Infectious Diseases Research Laboratory, Melbourne, Australia. The PRN titre was calculated as the highest serum dilution that reduced the number of plaques in measles virus-infected Vero cell monolayers by 50%. PRN titres were interpreted as follows: < 8 negative, 8–119 low positive (indicating past immunization or infection but possible susceptibility to clinical measles), 120–899 protective against measles disease, $\geqslant 900$ protective against infection [8]. Individuals with a measles antibody level > 343 mIU/ml by EIA or a PRN titre > 900 were defined as seropositive (immune).

Rubella IgG antibody tests

Rubella IgG levels were interpreted as follows: < 3 mIU/ml negative, 3–7 mIU/ml equivocal and > 7 mIU/ml positive. Sera for which results were equivocal were retested and those that remained equivocal were tested by haemagglutination inhibition (HAI), using trypsinized, human group O red blood cells [9]. HAI titres were interpreted as follows: < 10 negative, 10–40 low positive (indicating past immunization or infection but possible susceptibility to rubella infection), > 40 positive and generally protective against infection. Individuals with a rubella antibody level > 7 mIU/ml by EIA or an HAI titre > 40 were defined as seropositive (immune).

Statistical analysis

The percentages of individuals with positive, negative and equivocal results were determined for each age group and sex for the pre- and post-campaign surveys. To determine the impact of the campaign, sera were grouped according to the age-specific interventions as follows: infants (aged 1 year), preschool (aged 2–5 years), primary school (aged 6–11 years) and secondary school (aged 12–18 years) groups. The chi-

Table 1. *Immunity to measles and rubella pre and post Australian Measles Control Campaign by age group and sex*

Antibody	Infant (1 yr)	Pre-school (2–5 yr)	Primary (6–11 yr)	Secondary (12–18 yr)	Total (1–18 yr)
Measles					
Pre					
No. tested	174	756	958	1048	2936
% positive	70	82	84	89	85
(95% CI*)	(62,76)	(79,85)	(82,87)	(87,91)	(83,86)
Post					
No. tested	184	715	965	1054	2918
% positive	63	89	94	91	90
(95% CI*)	(56,70)	(86,91)	(93,96)	(89,93)	(89,91)
P value†	0·2	< 0·001	< 0·001	0·1	< 0·001
Rubella					
Pre					
No. tested	175	738	935	1011	2859
% positive	70	90	79	85	83
(95% CI*)	(63,77)	(88,92)	(76,82)	(83,87)	(82,85)
Post					
No. tested	183	718	968	1078	2947
% positive	66	94	95	89	91
(95% CI*)	(59,73)	(93,96)	(93,96)	(87,91)	(90,92)
P value†	0·4	0·002	< 0·001	0·003	< 0·001

* CI, confidence interval.

† *P* value for the comparison of the percentage of seropositive results pre and post campaign by age group.

square test was used to compare proportions of seropositive subjects between groups. 95% confidence intervals were calculated where appropriate, and *P* values less than 0·05 were considered statistically significant. Statistical analyses were performed using Epi Info version 6.04b [10] and Confidence Interval Analysis (CIA) [11].

Ethics approval

The study was approved by appropriate institutional ethics committees and the State-wide Health Confidentiality and Ethics Committee of the New South Wales Health Department.

RESULTS

Measles

Measles IgG EIA tests were positive in 85% (Table 1), negative in 12% and equivocal in 3% of sera collected before the campaign. Sera from 91% of children aged 12–15 years, but only 70% of infants, were positive (Fig. 1). After the campaign, 90% of tests were positive (Table 1), 7% were negative, and 3% were equivocal. There were no significant differences between males and females before ($P = 0·4$) or after ($P = 0·9$) the campaign.

The significant increase (5·2%; 95% CI 3·5–6·9%) in the proportion of immune subjects after the campaign was largely due to improved immunity in the age groups actively targeted by the campaign (Fig. 1, Table 1). The increase was greatest in primary schoolchildren (6–11 years) (10·0%; 95% CI 7·2–12·7%), followed by preschool children (2–5 years) (6·7%; 95% CI 3·1–10·2%).

Seventy-three of 173 (42%) sera with equivocal EIA results were tested by the PRN assay. All had neutralizing antibody titres < 900 (non-immune); titres were 8–119 in 41 sera and 120–899 in 32 sera. The proportions of equivocal results were similar before and after the campaign (3%), did not differ by sex ($P = 0·4$), and increased with age (χ^2 for trend = 21·7, $P < 0·001$) from 2% in preschool and primary schoolchildren to 4% in secondary schoolchildren.

Rubella

Before the campaign rubella IgG EIA tests were positive in 83% (Table 1), negative in 16% and

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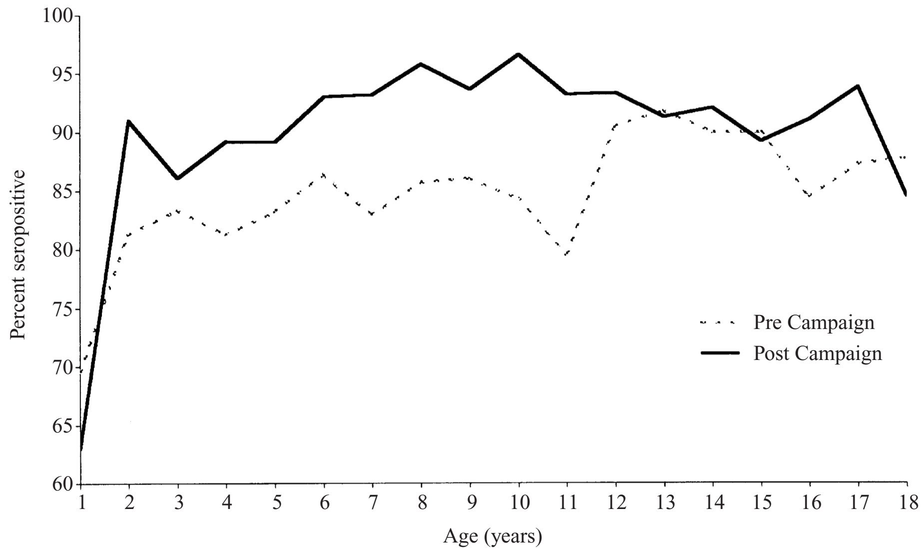

Fig. 1. Percentage of sera positive for measles IgG antibody before and after the Australian Measles Control Campaign by age (1–18 years).

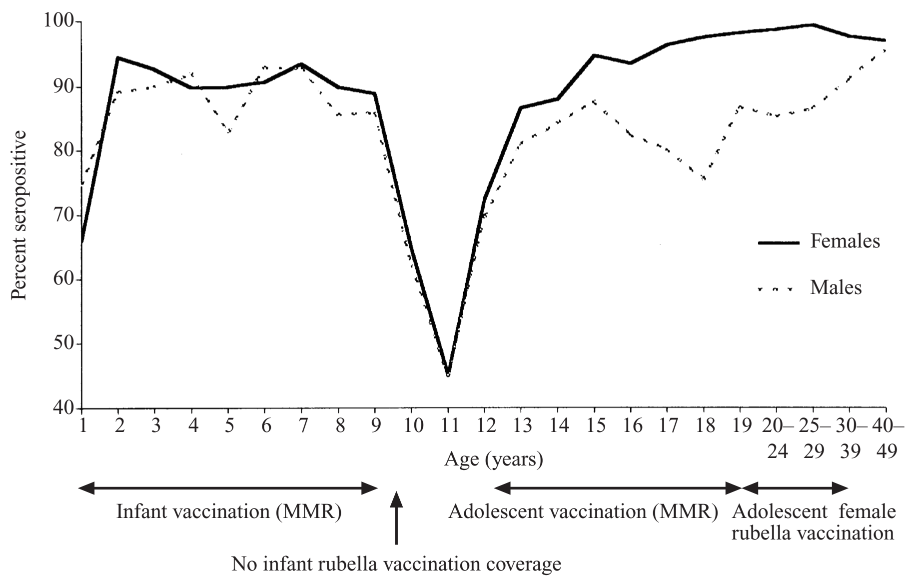

Fig. 2. Percentage of sera positive for rubella IgG antibody prior to the Australian Measles Control Campaign, by age (1–49 years), sex and vaccination cohort.

equivocal in 1% of sera from individuals aged 1–18 years. Fewer infants (70%) than 2–9 year old children (90%) were immune (Fig. 2), while 10–12 year olds had the lowest proportion of immune subjects (60%; 95% CI 55–65%). Immunity increased with age in those aged over 11 years. 94% of sera from adults aged 19–49 years were positive, 6% were negative, and 0·4% were equivocal.

After the campaign, rubella IgG EIA tests were positive in 91% (Table 1), negative in 8% and equivocal in 1% of sera from individuals aged 1–18 years. The proportion of immune subjects increased after the campaign by 7·5% (95% CI 5·7–9·2%) in the 1–18 year age group. The increases occurred in all age groups except infants (Table 1), and were most marked in 10–12 year olds (32%; 95% CI 26–37%) (Fig. 3).

Up to age 16 years the proportions of males and females who were immune were comparable both before ($P = 0{\cdot}3$) and after ($P = 0{\cdot}7$) the campaign (Figs 2, 3). Similarly, in the pre-campaign sample of 40–49 year olds there was no difference between the

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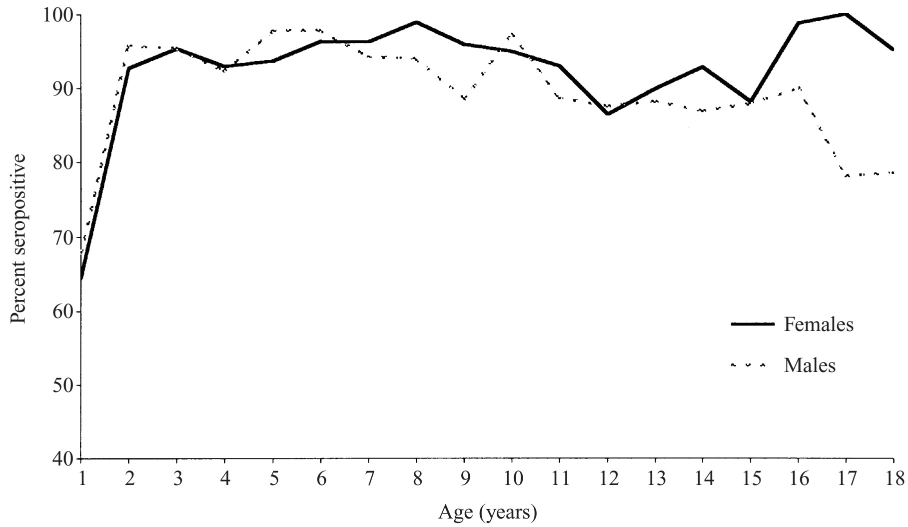

Fig. 3. Percentage of sera positive for rubella IgG antibody after the Australian Measles Control Campaign, by age (1–18 years) and sex.

sexes ($P = 0{\cdot}6$). However, there were significantly more females than males immune to rubella in both the pre-campaign sample of 16–39 year olds (97% *vs.* 85%, $P < 0{\cdot}001$) and the post-campaign sample of 16–18 year olds (98% *vs.* 82%, $P < 0{\cdot}001$).

Forty-nine of 60 (82%) sera in which EIA results were equivocal were tested by HAI; 40 (82%) were negative and titres in the remainder were 10–20. The proportion of equivocal results was similar before (0·9%) and after (0·8%) the campaign.

DISCUSSION

This national serosurvey was the first in Australia and provided objective evidence of an increase in immunity to measles (5·2%) and rubella (7·5%) in subjects aged 1–18 years, as a result of the 1998 Measles Control Campaign. The increase in measles immunity in the targeted age groups (2–5 years, 82–87%; 6–12 years, 84–94%) after the campaign was similar to that following the 1994 vaccination campaign in England and Wales [3, 4].

Ideally, sera tested in mass serological surveys would be collected from subjects randomly selected to represent the study population, and the results interpreted in the light of potentially confounding factors such as vaccination and medical history [1, 2, 12]. However, such studies are costly and difficult to perform. In addition, there is the risk of non-participation bias [4]. Our large convenience sample of sera submitted to diagnostic laboratories throughout Australia was obtained at a considerably lower cost than a population based random sample. Any selection biases are likely to be limited because first, all Australians have free access to health care; and second, the sera were obtained from most major laboratories around Australia. These laboratories offer a wide range of diagnostic services, therefore reasons for which the sera were submitted are unlikely to differ between laboratories or over time [4].

Our testing methods and cut-off levels differed from those used in some other studies [1–4]. We classified subjects with equivocal serological results as non-immune because functional antibody levels in their sera were below those reliably associated with protection against subclinical infection [7, 13, 14]. The role of subclinical infection in transmission of measles is uncertain [13], and subclinical rubella can cause serious adverse foetal effects [14].

Susceptibility to rubella varied considerably between age groups and by sex. Before the campaign 40% of children aged 10–12 years were susceptible to rubella. They were too old to have received rubella vaccine in infancy and too young to have received an adolescent dose. These differences disappeared after the campaign and only 6% of preschool and 5% of primary school aged children remained susceptible.

The serosurvey showed that more females than males aged over 16 years were immune to rubella. This difference was due to the school-based rubella immunization programmes, which excluded males between 1971 and 1993, and post-partum immunization of susceptible women. Despite high levels of immunity among women of child-bearing age, congenital rubella syndrome occurred in 1 in 67000

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liveborn Australian children between 1992 and 1997, a higher rate than in the United Kingdom or the United States of America [15]. The increased levels of immunity in young children after the campaign will reduce the risk of exposure of susceptible women to rubella. However, many adolescent and young adult males remain susceptible, so routine antenatal screening and postpartum immunization of susceptible women are still needed.

This study shows the value of testing opportunistically collected sera for serological surveillance and evaluation of interventions. The results accurately reflect historical changes in immunization policies before, and confirm other measures of vaccine uptake (based on parental surveys and vaccination records) during the campaign [16]. This suggests that there is little systematic bias among large numbers of sera collected this way in Australia.

The $30 million campaign achieved high rates of vaccine uptake in targeted groups [16]. However, maintenance of high rates of routine vaccine uptake and vigilant surveillance, including laboratory confirmation of cases [17], will be required to effect and document the interruption of measles transmission within Australia. In addition, improved immunity in young adults is needed, as most cases in outbreaks since the campaign have been from this age group [18]. With this in mind, in August 2000 the Australian Government allocated $22 million to cover the cost of MMR vaccine for young adults aged 18–30 years. Rubella control and surveillance are more difficult because of subclinical infection and lack of uniform diagnostic criteria. Indirect surveillance measures (immunization rates, levels of susceptibility among pregnant women and modelling based on sero-surveillance data) will be required to monitor the risk of rubella outbreaks. Additional national serosurveys, similar to the ones reported here, should be helpful in tracking progression towards elimination of these diseases.

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