Declining measles antibodies in the era of elimination: Australia's experience

Heather F. Gidding [a,b,*], Helen E. Quinn [b], Linda Hueston [c], Dominic E. Dwyer [c], Peter B. McIntyre [b]

[a] School of Public Health and Community Medicine, UNSW Medicine, The University of New South Wales, Sydney, NSW, Australia
[b] National Centre for Immunisation Research and Surveillance, Westmead, NSW, Australia
[c] Centre for Infectious Diseases and Microbiology Laboratory Services, New South Wales Health Pathology—Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, NSW, Australia

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ABSTRACT

Background: Australia is one of only a few countries with a long-standing and consistent serosurveillance program. We conducted a national serosurvey in 2012–2013 to estimate population seroprevalence of measles-specific IgG and the effective reproduction number, R, and compare the results with the three previous serosurveys (1996–1999, 2002 and 2007) to examine trends following a decade of sustained measles control.
Methods: 2729 residual sera from 1 to 49 year olds were tested using the Enzygnost anti-measles IgG enzyme immunoassay (EIA). All sera in the equivocal range by EIA on re-testing and a random sample of low positive and negative sera were later tested by a microneutralisation assay. R was calculated from weighted estimates of the proportion seronegative by age using a previously developed contact matrix.
Results: In the 2012–13 serosurvey, anti-measles IgG seropositivity for 1–49 year olds was 80.8% (95% CI: 79.4–82.3%) and 8.9% (95% CI: 7.8–10.0%) had equivocal antibody levels. The increasing proportion of seronegative and equivocal individuals in age groups 10–39 years continued a trend seen in previous serosurveys. There was also an increase in equivocal results among 2–4 and 5–9 year old children, >90% of whom were recently vaccinated. R increased from 0.57 in 1999 to above the epidemic threshold of 1 in 2012–13 (R = 1.7). All 20 EIA negative sera, 238/241 (98.8%) equivocal sera, and 89/92 (96.7%) low positive sera had a titre <10 (negative) in the measles microneutralisation assay.
Conclusions: A number of countries with sustained measles control have now demonstrated that measles-specific IgG antibodies decline with time since vaccination. As there is good epidemiologic evidence of population-level protection, the implications of declining measles-specific IgG antibody levels for maintaining measles elimination are unclear. Novel studies to determine correlates of protection against measles transmission and disease in the post-elimination era are needed to help answer this question.

1. Background

Australia has had a longstanding measles vaccination program; the vaccine was first licensed in 1968 and included on the national immunisation program schedule for infants at 12 months of age in 1975. As part of efforts to eliminate measles, various government funded catch-up campaigns, along with high coverage with the routine infant vaccination program, have attempted to ensure that anyone born since the 1970s has received the recommended two doses of measles vaccine [1–3]. The first national survey of coverage for one dose of a measles containing vaccine (in 1983) was 65% for children aged 1–6 years [4]. This increased to 86% in 1989–90 and 92% by the third survey in 1995 [5]. For cohorts born since 2001 coverage at 2 years of age for the first dose of measles-mumps-rubella vaccine (MMR1; assessed using the Australian Childhood Immunisation Register, established in 1996) has been relatively constant at 94% and coverage with the second dose (MMR2), due at 4 years of age between 1998 and mid 2013 (after which it was due at 18 months), has been above 91% since 2012 [6]. Based on a range of evidence, the World Health Organization announced on March 20, 2014 that measles elimination had been

* Corresponding author at: School of Public Health and Community Medicine, UNSW, Sydney, NSW 2052, Australia.
E-mail addresses: hgidding@unsw.edu.au (H.F. Gidding), helen.quinn@health.nsw.gov.au (H.E. Quinn), Linda.Hueston@health.nsw.gov.au (L. Hueston), dominic.dwyer@sydney.edu.au (D.E. Dwyer), peter.mcintyre@health.nsw.gov.au (P.B. McIntyre).

achieved in Australia [7]. However, as isolated outbreaks continue to occur [8], triggered by imported cases, continued efforts to maintain elimination are required. These include high quality epidemiological and laboratory surveillance systems to detect measles cases and to monitor population immunity.

Population immunity can be measured using national serosurveys, and these have been an important part of measles surveillance programs in many countries, including Australia [9]. However, only a handful of countries have conducted multiple serosurveys during periods of sustained measles control [10–13] and to our knowledge none has consistently used the same laboratory testing and population sampling methods to enable adequate comparisons between serosurveys. In Australia, national serosurveys were conducted in 1996–1999, 2002 and 2007, using consistent sampling and laboratory testing methods [1,14,15]. In this study, we used the 2012–2013 national serosurvey to estimate population seroprevalence of measles-specific IgG and the effective reproduction number, R (where maintenance of R < 1 is an indicator that measles elimination is sustained [16]). The results are compared with the three previous serosurveys to examine trends following a decade of sustained measles control.

2. Methods

2.1. Population and study design

We randomly sampled 2729 sera and plasma specimens by age group and region from a bank of 12,411 specimens collected opportunistically from 32 laboratories around Australia in 2012 and 2013. Sera were identified at the referring laboratory by sex, age or date of birth, residential postcode, and date of collection: a unique identifier was used to ensure that only one sample from any subject was tested. Information about vaccination status was not available. Subjects who were immunocompromised, had received multiple transfusions in the past three months, or were known to be infected with human immunodeficiency virus were excluded.

Ethical approval was obtained from the Western Sydney Human Research Ethics Committee, the South Australian Department of Health Human Research Ethics Committee, Melbourne Health Human Research Ethics Committee and the Government of Western Australia Child and Adolescent Health Service Research Ethics Committee.

2.2. Sample size calculations

Sample sizes were calculated for 1 and 2–4 year olds, then 5-year age groups up to 45–49 years. They were based on the expected proportions of individuals seropositive for anti-measles IgG in each age group at a national level, with a precision of at least ±5% (±3% for ages 2–4, 20–24, 35–39, 40–44, 45–49 years) for each point estimate. Within each age group, the sample was stratified to be proportional to the age distribution of the population in each state and territory.

2.3. Antibody assays

Sera were tested and interpreted according to the manufacturer's instructions using the Enzygnost (Behring Diagnostics, Marburg, Germany) anti-measles IgG enzyme immunoassay (EIA). Measles-specific IgG levels were interpreted as follows: corrected optical density (OD) <0.1 negative (susceptible), OD between 0.1 and 0.2 equivocal, and OD >0.2 positive (immune). All sera for which the anti-measles IgG result was classified as equivocal were retested using the same method and reclassified if the result was

negative or positive. All sera with anti-measles IgG in the equivocal range by EIA on re-testing and a random sample of low positive (corrected OD >0.020 and ≤0.514) and negative sera were further tested by a microneutralisation assay according to the method by Grist el at [17]. Briefly, sera were screened using dilutions from 1/10 to 1/40, a known concentration of the ATCC strain measles virus (100 $TCID_{50}$) was then added and allowed to incubate at 37 °C with 5% CO_2 for 1hr. This was followed by the addition of baby hamster kidney (BHK) cells. Plates were incubated for 3–4 days at 37 °C with 5% CO_2. The endpoint was the last well displaying 90% or more cytopathic effect (CPE; ie BHK cell destruction).

2.4. Analysis

2.4.1. Estimating seroprevalence

The proportions equivocal, positive, and equivocal or positive for ages 1–49 years combined (and 1–34 years to allow comparison with the 2002 serosurvey) were calculated for the Australian population. Age group-specific estimates were also calculated for Australia. Estimates were weighted to be proportional by sex, age group, state and territory as appropriate [18]. Analysis was performed in SAS version 9.4 using the Proc surveyfreq procedure which calculates 95% confidence intervals (CIs) using the Taylors series expansion method to estimate variance.

2.4.2. Estimating the effective reproduction number, R

To estimate the effective reproduction number (R), population weighted estimates for susceptibility (xi; seronegative for measles-specific IgG antibody) were determined for five age groups: 0–4, 5–9, 10–14, 15–19 and 20+ years. As only 1–49 year olds were tested, we assumed 0 year olds had 50% immunity and used prior serosurveys for estimates of susceptibility in older cohorts (assuming that no immunity would be acquired through natural infection). Using the calculated susceptibility profiles for the five age groups, R was determined as previously described [19] using values for R_{0ij} from studies in the UK and Canada [20], where R_{0ij} is the average number of secondary cases in the ith age group (rows) caused by an infectious individual in the jth age group (columns) if all individuals in the ith age group are susceptible to infection. If only a proportion, xi, of the ith age group are susceptible to infection, then R_{ij}, the number of secondary infections in that group caused by an infectious individual in the jth age group, is given simply by $R_{ij} = R_{0ij}$ xi. The overall R is calculated as the leading eigenvalue of the next generation matrix R_{ij} [21].

$$(R_{0ij}) = \begin{pmatrix} 0.96 & 0.43 & 0.43 & 0.43 & 0.43 \\ 0.48 & 4.99 & 1.80 & 0.48 & 0.48 \\ 0.48 & 1.80 & 7.48 & 0.48 & 0.48 \\ 0.48 & 0.48 & 0.48 & 8.73 & 0.48 \\ 5.23 & 5.23 & 5.23 & 5.23 & 5.23 \end{pmatrix}$$

3. Results

The population weighted proportion of individuals with either a positive (80.8%) or equivocal (8.9%) anti-measles IgG result was 89.7% (Table 1). Seroprevalence varied by age group/birth cohort, with the lowest levels of seropositivity in 1 year olds, adolescents and young adults (Table 1, Fig. 1). Adolescents and young adults also had the highest levels of anti-measles IgG equivocal results. Of note is the significant increase in proportion of equivocal results and decrease in proportion of positive results between the 2–4 and 5–9 year age groups, despite high coverage with MMR2 due at 4 years. Within the 5–9 year age group, seroprevalence also varied,