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Australian rubella serosurvey 2012–2013: On track for elimination?

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ABSTRACT

Background: The World Health Organization has targeted rubella virus for elimination regionally. Australia was one of the first countries to implement a nationally funded rubella immunisation program, in 1971, and conducts regular national rubella serosurveillance studies. We aimed to estimate the seroprevalence of rubella-specific IgG antibody in the Australian population by age and sex in 2012–2013, to compare the results with three previous serosurveys conducted in 1996–1999, 2002 and 2007 and to estimate the effective reproduction numbers (R_n).

Methods: This study used 2729 serum and plasma specimens, randomly selected from a specimen bank collected in 2012–2013 across Australia. Age groups included in the sample ranged from 1 to 49 years. Sera were tested for rubella-specific IgG-antibody using the Enzygnost anti-rubella IgG enzyme immunoassay and classified as positive, negative or equivocal according to rubella-specific IgG concentrations of >7 IU/ml, <3 IU/ml and 3–7 IU/ml, respectively.

Results: The overall proportions seropositive, seronegative and equivocal for rubella-specific IgG were 92.1% (95% CI, 91.0–93.2), 6.7% (95% CI, 5.7–7.7) and 1.2% (95% CI, 0.8–1.6), respectively. The proportion of males seropositive was significantly lower than females in the 30–34 (83.1% vs. 96.8%, p = 0.003), 35–39 (86.1% vs. 96.3%, p = 0.02) and 40–44 (86.1% vs. 95.7%, p = 0.03) year age groups. R_n for rubella in 2012–2013 was estimated to be 0.33 (95% CI 0.28–0.39).

Discussion: The 2012–2013 national serosurvey showed levels of rubella-specific IgG seropositivity in the Australian population are relatively high with no evidence of decrease compared to previous serosurveys conducted in 1996–1999, 2002 and 2007. The lower proportion of seropositive males aged 30–44 years likely reflects the initial immunisation program targeting females only. To our knowledge this study represents the longest period of serosurveillance following introduction of a nationally funded rubella immunisation program. The lack of evidence of decreasing rubella-specific IgG seropositivity is therefore reassuring for Australia and other countries with longstanding high vaccine coverage.

1. Introduction

Rubella is an acute communicable disease of humans caused by the rubella virus, an RNA virus belonging to the *Togaviridae* family [1]. Both children and adults are susceptible to rubella infection with clinical disease characterised by skin rash, fever and lymphadenopathy. Rubella was considered a mild self-limiting viral infection until 1941 when the association of rubella virus infection in pregnant women and Congenital Rubella Syndrome (CRS) was recognised [1]. If a woman has rubella infection in the first trimester of pregnancy approximately 65–85% of fetuses will develop CRS [1]. The first vaccine for rubella became available in 1969 [1,2]. Australia was among the first countries to implement vaccination against rubella, with a nationally funded school-based program for girls aged 10–14 years introduced in 1971 [3]. In 1989 measles-mumps-rubella (MMR) vaccine was funded on Australia's National Immunisation Program for all children at 12 months of age. In 1992 a second MMR vaccine dose was recommended and funded for both males and females, with boys aged 10–14 years

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offered catch-up vaccination under school-based programs in 1993 and 1994 [3,4]. In 1998, the second dose of MMR vaccine was moved to 4–5 years of age with a one-off school-based catch-up vaccination program for children aged 5–12 years as part of the national Measles Control Campaign [4]. The age of administration of the second dose was fixed at 4 years of age in 2000. In 2001, a funded young adult (18–30 years) MMR vaccination campaign was conducted; however, uptake was poor [5]. In July 2013, the second MMR vaccine dose was moved to 18 months of age, given as measles-mumps-rubella-varicella (MMRV) vaccine [4]. The Australian Immunisation Register shows coverage by two years of age for the first dose of MMR increased from 83.3% in 1998 to 93.9% in 2012, and for the second dose of MMR was 91.6% in 2012 [6]. Rubella was a notifiable disease in Australia from 1942 to 1978 and then since 1991 [7]. The notification rate for rubella dropped from 653.9 per 100,000 in 1943 to 1.9 per 100,000 in 1977 [7] and dropped further to 0.18 per 100,000 in 2012 [8]. The number of CRS cases in Australia decreased from 120 to 200 annually in the pre-vaccination era [7] to 35 cases in total over the 1993–2003 period and two cases for the 2004–2007 period [9]. One case of CRS was reported in 2012 [10] and two cases in 2013 [11]; all of these cases were acquired overseas.

Given the availability of very effective vaccines, the World Health Organization (WHO) has targeted rubella for elimination regionally, along with measles [12]. The WHO Pan American Health Organization Region was declared rubella-free in 2015 [13]. The Technical Advisory Group on Immunisation and Vaccine Preventable Diseases of the Western Pacific Region of WHO, of which Australia is a member, has recommended a regional rubella elimination target date of 2020 [14].

Communicable disease transmission is influenced by the prevalence of non-immune individuals in a population. Serosurveillance studies are used to estimate the level of population immunity for a given disease, acquired through either natural infection or vaccination [15]. Australia has conducted national serosurveys approximately every five years since the late 1990s to monitor population level immunity and provide information regarding progression towards elimination for selected vaccine preventable diseases including rubella [16]. We aimed to estimate seroprevalence of rubella-specific IgG in the Australian population by age and sex in 2012–2013, compare the results with three previous serosurveys conducted in 1996–1999, 2002 and 2007, and estimate the effective reproduction number (R_n).

2. Methods

This serosurveillance study was conducted using 2729 serum and plasma specimens, selected randomly from a bank of 12,411 specimens collected opportunistically from 32 diagnostic laboratories throughout Australia during the period 2012–2013. The collection method is the same as that used previously although the number of laboratories from which specimens have been collected has varied between the four serosurveys, ranging from 28 to 45 [16,17]. Information available for specimens included sex, age or date of birth, residential postcode and date of collection. Information about vaccination status was unavailable. History of infection with human immunodeficiency virus, any other immunocompromised status and transfusion of blood products within three months of original sample collection were defined exclusion criteria for specimen collection.

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

2.1. Sample size calculation

Sample sizes were calculated for children aged 1–<2 years, 2–4 years, then 5-year age groups up to 45–49 years. Infants were not included. Sample size calculations were based on the expected proportions seropositive for rubella-specific IgG in each age group for Australia, with at least ±5% precision for each point estimate. The number of specimens to be tested in each age group was chosen to reflect the population distribution across the eight states and territories of Australia within each age group, with equal numbers of males and females tested.

2.2. Rubella-specific IgG antibody assay

Sera were tested using the Enzygnost (Behring Diagnostics, Marburg, Germany) anti-rubella IgG enzyme immunoassay (EIA) which contained internal positive and negative controls. Test results were interpreted as <3 IU/ml negative, 3–7 IU/ml equivocal and >7 IU/ml positive, in accordance with manufacturer's instructions and previously published practice [17]. No further testing of specimens with equivocal results was undertaken.

2.3. Statistical analysis

Estimates of the proportion rubella-specific IgG positive, equivocal and negative for the Australian population aged 1–49 years, and age group specific estimates, were calculated, weighted by age group and sex as appropriate using 2011 Australian population estimates [18]. To examine representativeness by geographic remoteness, postcodes of the samples were mapped to the 2011 Australian Statistical Geography Standard (ASGS) for remoteness [19] and the population weighted frequency for each remoteness classification category was compared to that for the Australian population in 2011.

Seropositivity (>7 IU/ml) in the 2012–2013 serosurvey was compared by age group and sex with data from the previous three Australian national serosurveys (1996–1999, 2002, 2007), which all used the same assay. Weighting of the 1996–1999, 2002 and 2007 serosurveys was done using mid-year population estimates by age group and sex for 1996, 2002 and 2007, respectively [18].

R_n for each of the four serosurveys was calculated using a Who-Acquires-Infection-From-Whom (WAIFW) matrix developed for the Australian setting and described previously [16], with 95% confidence intervals calculated using bootstrap sampling [20]. An R_n value of less than 1 indicates that disease incidence is below the threshold for endemic transmission. The following assumptions were made in order to estimate the proportion susceptible (i.e. negative or equivocal combined) by age group in order to estimate R_n. First, immunity developed for rubella due to natural infection or vaccination was assumed to be lifelong. Second, the rubella seropositivity among infants aged <1 year was assumed to be 25% [21]. Additional assumptions for the 2002 serosurvey, in which specimens were only collected and tested for the 1–34 years age group, were as follows: seropositivity of the 35–39 years age was assumed to be the same as the 30–34 years age group; seropositivity of the 40–44 years age group was calculated as the weighted average of seropositivity in the 30–39 and 40–49 years age groups from the 1996–1999 serosurvey; and seropositivity of the ≥45 age group was assumed to be the same as that in the 40–49 years age group from the 1996–1999 serosurvey. Similarly, seropositivity for the ≥50 years age group in the 2007 and 2012–2013 serosurveys was assumed to be the same as that in the 45–49 years age group from the 2002 and 2007 serosurveys, respectively.