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Age-specific prevalence of IgG against measles/rubella and the impact of routine and supplementary immunization activities: A multistage random cluster sampling study with mathematical modelling

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A B S T R A C T

Background: Vietnam continues to have measles and rubella outbreaks following supplementary immunization activities (SIA) and routine immunization despite both having high reported coverage. To evaluate immunization activities, age-specific immunity against measles and rubella, and the number of averted Congenital Rubella Syndrome (CRS) cases, must be estimated.
Methods: Dried blood spots were collected from 2091 randomly selected individuals aged 1-39 years. Measles and rubella virus-specific immunoglobulin G (IgG) were measured by enzyme immunoassay. Results were considered positive at ≥120 mIU/mL for measles and ≥10 IU/mL for rubella. The number of CRS cases averted by immunization since 2014 were estimated using mathematical modelling.
Results: Overall IgG seroprevalence was 99.7% (95%CI: 99.2-99.9) for measles and 83.6% (95%CI: 79.3-87.1) for rubella. Rubella IgG seroprevalence was higher among age groups targeted in the SIA than in non-targeted young adults (95.4% [95%CI: 92.9-97.0] vs 72.4% [95%CI: 63.1-80.1]; $P < 0.001$). The estimated number of CRS cases averted in 2019 by immunization activities since 2014 ranged from 126 (95%CI: 0-460) to 883 (95%CI: 0-2271) depending on the assumed postvaccination reduction in the force of infection.
Conclusions: The results suggest the SIA was effective, while young adults born before 1998 who remain unprotected for rubella require further vaccination.

Introduction

Measles and rubella continue to be global public health priorities as vaccine-preventable causes of morbidity and mortality. Measles only vaccine was introduced in the 1960s, and, globally, there were an estimated 2 million measles deaths annually before vaccination coverage increased during the 1980s. In 2019,

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measles still caused more than 207,500 deaths globally due to repeated epidemics, and most were among children aged <5 years [1]. Rubella is mainly a mild childhood illness, but rubella virus infection early in pregnancy can cause Congenital Rubella Syndrome (CRS) in the child characterized by the classic triad of cataract, congenital heart disease, and hearing impairment. Recent estimates suggest that around 120,000 CRS cases were born globally in 1996, and around 32,000 cases in 2019 after introduction of rubella-containing vaccine into an increasing number of low- and middle-income countries [2]. Increasing supplementary immunization coverage in 92 low- and middle-income countries may prevent 131,000 CRS deaths and loss of 12.5 million disability-adjusted life years due to CRS during 2001-2030 [3].

Measles and rubella outbreaks continue to occur in Vietnam, despite the introduction of the measles and rubella combined vaccine (MRCV) [4]. An estimated 3788 (95% confidence interval (95%CI): 3283-4143) CRS cases occurred in the whole country during a nonepidemic year before MRCV was introduced, with 234 (95%CI: 207-262) cases per 100,000 live births [5]. Vietnam borders China, Lao PDR, and Cambodia, which have all reported recent outbreaks of measles and rubella. Thus, Vietnam has a high risk of importation of wild virus [4,6]. Vietnam introduced measles only vaccine into its routine immunization schedule in 1981 and MRCV in 2014 as part of routine and supplementary immunization activities (SIA). For both diseases, the reported immunization coverage exceeds the level required for elimination [4]. Thus, the reasons for the continuing outbreaks are unclear. Serosurveys from representative populations have been recommended for accurately estimating population immunity and number of CRS cases averted by immunization [7], but no population immunity gaps have been reported since MRCV was introduced in Vietnam.

In this work, we conducted a seroepidemiological survey using multistage random cluster sampling of children and adults in the South Central provinces of Vietnam in 2019 to estimate population immunity by measuring the prevalence of measles and rubella IgG, and to estimate the number of CRS cases averted by immunization activities since 2014 through mathematical modelling.

Materials and methods

A seroprevalence survey was conducted during the end of May 2019 in 4 South Central provinces (Khanh Hoa, Ninh Thuan, Quang Ngai, and Binh Dinh), deemed to have average affluence in rural Vietnam [8] (Figure 1). Both routine immunization and SIA are provided free of charge, and routine immunization coverage of measles only vaccine for infants <1 year old is reported as 97.0-97.5% in Khanh Hoa, 97.3-98.8% in Ninh Thuan, 96.3-97.2% in Quang Ngai, and 99.0-99.2% in Binh Dinh during 2015-2020 [8]. MRCV was introduced in 2014 with an SIA targeting children aged 9 months to 14 years for catch-up vaccination, followed by two routine doses at ages 9 months with measles only vaccine and 18 months with measles and rubella combination vaccine respectively. To evaluate the difference in IgG prevalence between targeted and non-targeted of MRCV, we collected data from people aged 1-39 years on 20 May 2019.

A brief face-to-face questionnaire asking about age, sex, number of family members, and time to the nearest health centre was conducted. The sample size calculation, sampling method, analysis methods, and mathematical modelling are described below.

Sample size

Calculation of sample size was based on expected IgG seroprevalence of 90%. For a 5% level of significance with precision of ±5% considering an assumed design effect of 1.5, the required sample size was calculated as 208 for each 5-year age group [9].

Sampling design

Using probability proportionate-to-size (PPS) sampling, four-stage cluster sampling was conducted in 4 provinces (Khanh Hoa, Ninh Thuan, Quang Ngai, and Binh Dinh; total population of 4,856,210 in 2018). In the first stage, 3 districts were randomly selected from each province using PPS sampling based on the population census in 2015. In the second stage, 2 communes were randomly selected from each selected district by PPS sampling. In the third stage, two villages were randomly selected from each selected commune by PPS sampling. In total, 48 villages were selected as clusters. In each selected village, 40 households were randomly selected and all household members aged 1-39 years were recruited to fulfil the registered number in each age group [9].

Measles IgG and rubella IgG titres

Finger-prick blood samples were collected from consenting participants using Whatman 903 Protein Saver filter paper (Whatman, Maidstone, Kent, UK) and dried in air for ≥4 h. Each filter paper was sealed in a plastic bag and transported to Japan within a few weeks of collection. After the extraction of blood samples, IgG levels were measured by enzyme-linked immunosorbent assay (ELISA) kits (Enzygnost Anti-Measles Virus/IgG and Anti-Rubella Virus/IgG, Siemens Healthcare Diagnostics) in accordance with the manufacturer's instructions. The analyses were performed at the WHO Global Specialized Laboratory for Measles and Rubella in the Department of Virology 3, National Institute of Infectious Diseases, Japan as previously described [10,11]. Based on the recommendation by WHO, IgG titres were regarded as positive at ≥120 mIU/mL for measles [12] and ≥10 IU/mL for rubella [13]. Enzygnost IgG is among the most widely used ELISA kit and has a sensitivity and specificity of more than 90% [14]

Estimating the number of CRS cases averted

Using previously reported methods [10,11,15,16], we fitted four age-stratified catalytic models ("models A-D") to the observed weighted age-stratified serological data using maximum likelihood to estimate the force of infection (FOI: the rate at which susceptible people are infected) for rubella before vaccination was introduced in 2014.

The prevaccination FOI was allowed either to differ for those aged <15 and ≥15 years (models A and B) or to be identical for all ages (models C and D). The sensitivity of the rubella serological (antibody) assay was either estimated (models A and C) or assumed to be 100% (models B and D). The fitting used only data collected from people aged ≥22 years because they would not have been vaccinated. Since the reduction in FOI after 2014 was unknown, we fitted the catalytic model using 5 different values for the reduction in the FOI, compared with that before 2014, namely 0%, 25%, 50%, 75%, and 100%. Table A1 summarizes the equations for the proportion susceptible or seronegative in each model. The incidence of CRS was estimated based on models selected according to biological plausibility [15,16].

The best-fitting FOI value for each model and assumed reduction in the FOI after 2014 was then used to estimate the CRS incidence per 100,000 live births in 2019 among women in 5-year age groups between 15 and 49 years and among all women aged 15-49 years. We also estimated what the incidence would have been without the introduction of MRCV.

CRS incidence per 100,000 live births in a given 5-year age group A (I_{CRS} (A)) was calculated as:

$$I_{CRS}(A) = 0.65 \times s_u(A)\left(1 - e^{-16\lambda_o(1-r)/52}\right) \times 100000 \qquad (1)$$

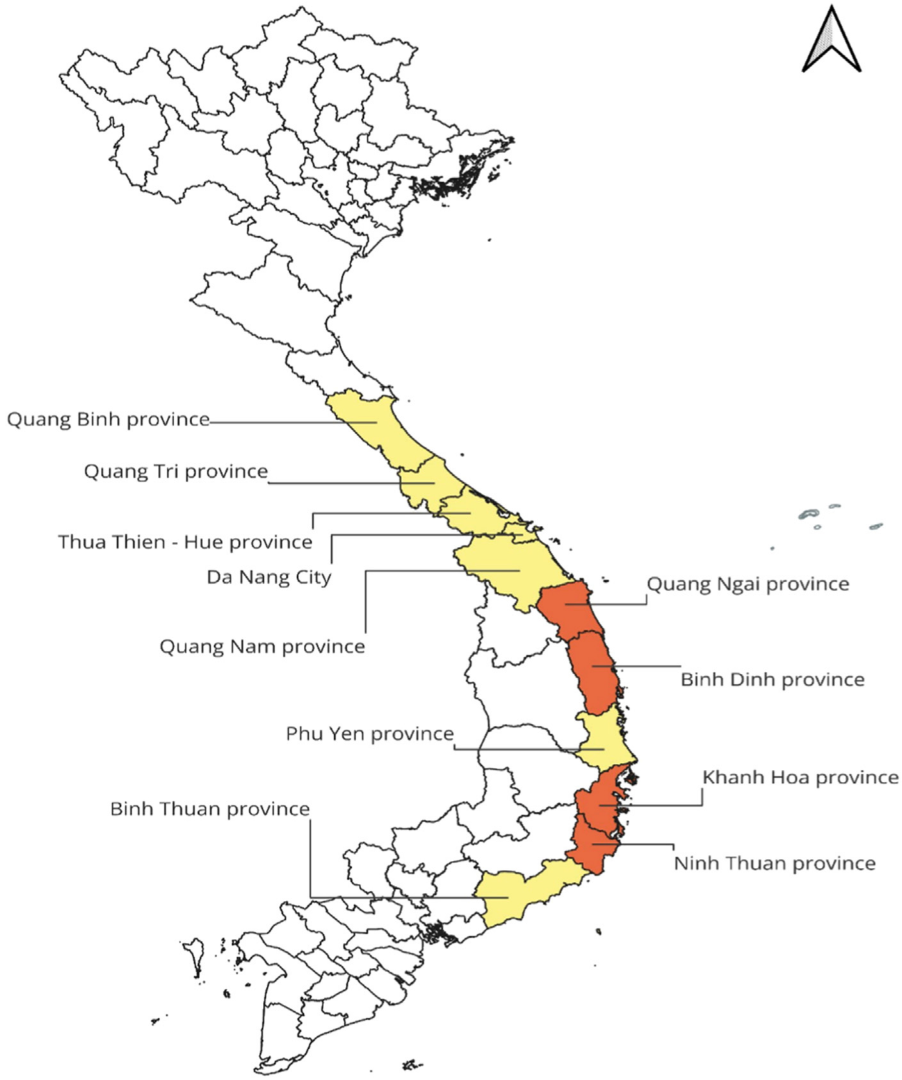

Figure 1. Map showing whole country and selected provinces in South Central region, Vietnam. Selected 4 provinces are coloured in red. The borders indicated on this map represent approximate borders and do not imply the expression of the author's opinions.

In equation 1, for each model and assumed reduction (r) in the average in the FOI after 2014 $s_u(A)$ is the proportion of women in age group A that were susceptible and λ_0 is the best-fitting FOI among women aged ≥15 years before MRCV was introduced, and r is the average reduction in the FOI after 2014. We assumed that the risk that a child was born with CRS if the mother was infected was 65% during the first 16 weeks of pregnancy and zero thereafter, based on Miller et al. [17], as assumed elsewhere [2,18]. When calculating the CRS incidence, the expression for the proportion of women in a given age group that were susceptible depended on whether the age group included vaccines (Appendix, Equations A1-A3). For a given age a in the range 15-21 years, $s_u(a)$ was calculated using the observed data and the model-based estimated or assumed sensitivity of the antibody assay. For the other age groups, and when calculating the CRS incidence if vaccination had not occurred, $s_u(a)$ was calculated using the model (Table A1).

The CRS incidence per 100,000 live births among women aged 15-49 years was calculated as the weighted average of the CRS incidence per 100,000 live births in each 5 year maternal age group. The weights were the number of live births in each maternal age in 2019, calculated by multiplying the corresponding age-specific fertility rates by the number of females, extracted from UN population databases [19].

The total number of CRS cases born in 2019 was calculated by summing the number of CRS cases born to women in each 5 year age group over the range 15-49 years. These were calculated by multiplying the age-specific CRS incidence per live birth among women by the number of live births among women in 2019 in the corresponding age-range.

The number of CRS cases averted in 2019 by introducing MRCV in 2014 was calculated as the difference between the total number calculated assuming that vaccination was in place and that estimated if vaccination had not occurred.

The 95% CIs on the FOI and CRS incidence, and the number of CRS cases averted by vaccination activities since 2014, were obtained by bootstrapping, using 1000 bootstrap datasets [20].

Data entry and statistical analysis

Completed questionnaires were taken to the Pasteur Institute in Nha Trang, and all the data were double-entered into Microsoft Excel files. Statistical analysis was performed using STATA version 16 (Stata Corp., College Station, TX). IgG prevalence among the participants was calculated considering the multistage cluster sampling design and sampling weight of each participant to obtain representative, unbiased results. The chi-square test and Fisher's exact test were used for comparisons of IgG prevalence by birth year. The level of statistical significance was set as $P < 0.05$.

Ethical considerations

The survey objectives and procedures were explained to the local authorities and selected participants verbally and in writing. All participants provided written informed consent. For minors (age <18 years), the survey objectives and procedures were explained and consent was obtained from their parents or legal guardians. Participants' names were not recorded. The study protocol was reviewed and approved by the Pasteur Institute in Nha Trang, the National Center for Global Health and Medicine (Japan, NCGM-G-3091), and the National Institute of Infectious Diseases (Japan, NIID-1011).

Results

Survey teams visited all 48 selected villages and obtained blood samples from 2091 participants. Women and girls comprised 61.1% of the participants. Of 2091 samples collected, 12 were excluded as they were not from participants in eligible age groups. For rubella, 1 sample with insufficient blood volume was discarded. Table 1 provides the background characteristics of the participants.

Estimated measles IgG prevalence

From the 2079 samples tested, 2074 were positive for measles IgG. Estimated IgG prevalence was 99.7% (95%CI: 99.2-99.9%) after accounting for the sampling design and individual sampling weights (Figure 2).

Table 1
Background characteristics and anti-measles IgG and anti-rubella IgG prevalence among participants in South Central region, Vietnam, 2019 (n = 2079 for measles and 2078 for rubella).

	n	M-IgG (+)	95%CI		n	R-IgG (+)	95%CI	
Province								
Khanh Hoa	534	100	99.31	100	533	77.86	74.09	81.31
Nhin Thuan	523	100	99.30	100	523	83.36	79.89	86.46
Quang Ngai	524	99.43	98.34	99.88	524	84.54	81.16	87.53
Binh Dinh	498	99.60	98.56	99.95	498	86.74	83.45	89.60
Sex								
Male	806	99.75	99.11	99.97	805	86.34	83.77	88.63
Female	1270	99.76	99.31	99.95	1270	80.94	78.67	83.07
No. of family members								
>=10	35	1	90.00	100	35	82.86	66.35	93.44
5-9	911	99.67	99.04	99.93	911	84.41	81.89	86.70
<=4	1133	99.82	99.36	99.98	1132	81.98	79.61	84.18
Time to nearest HF (min)								
<15	1646	99.76	99.38	99.93	1645	82.61	80.69	84.41
15-30	362	99.72	98.47	99.99	362	85.36	81.29	88.84
>=30	71	100	94.94	100	71	81.69	70.73	89.87

CI, confidence interval; HF, health facility; M-IgG, measles immunoglobin G prevalence; R-IgG, rubella immunoglobin G prevalence.

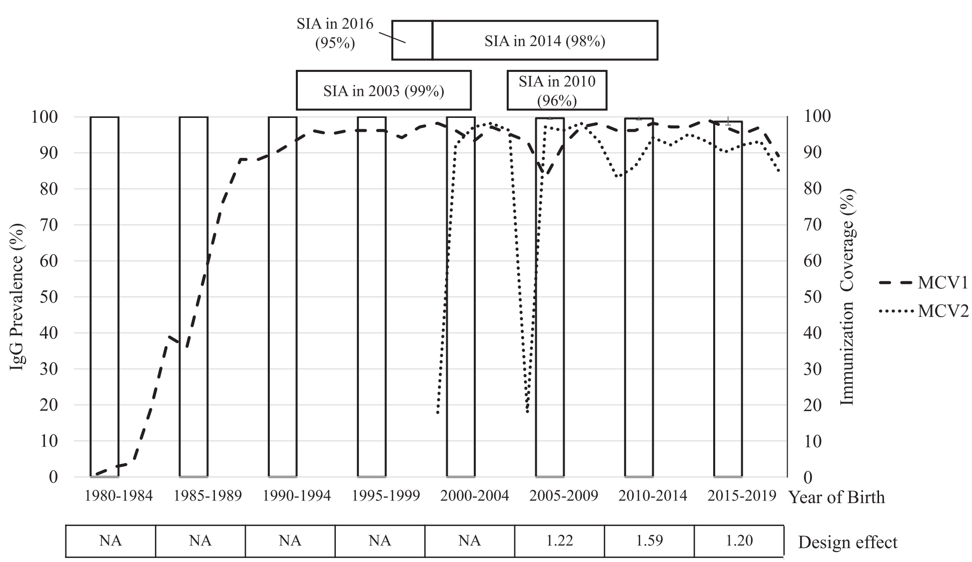

Figure 2. Estimated antimeasles IgG prevalence and reported immunization coverage by year of birth in South Central region of Vietnam (n = 2079). An Enzygnost IgG ELISA value of ≥120 mIU/mL was considered positive. IgG prevalence was calculated considering sampling design and sampling weight of each participant. SIA in 2003 and 2010 used measles only vaccine with target age of 9 months to 10 years old and 9 months to 6 years old, respectively. SIA in 2014 and 2016 used measles and rubella combination vaccine with target age of 9 months to14 years old and 16-17 years old, respectively. Data source: WHO/UNICEF Estimates of National Immunization Coverage, 2022 Revision. Abbreviations: MCV1, percentage of surviving infants who received the 1st dose of measles containing vaccine; MCV2, percentage of children who received the 2nd dose of measles containing vaccine which was switched form measles only vaccine to MRCV in 2015; MRCV, measles and rubella combination vaccine; SIA, supplementary immunization activities.

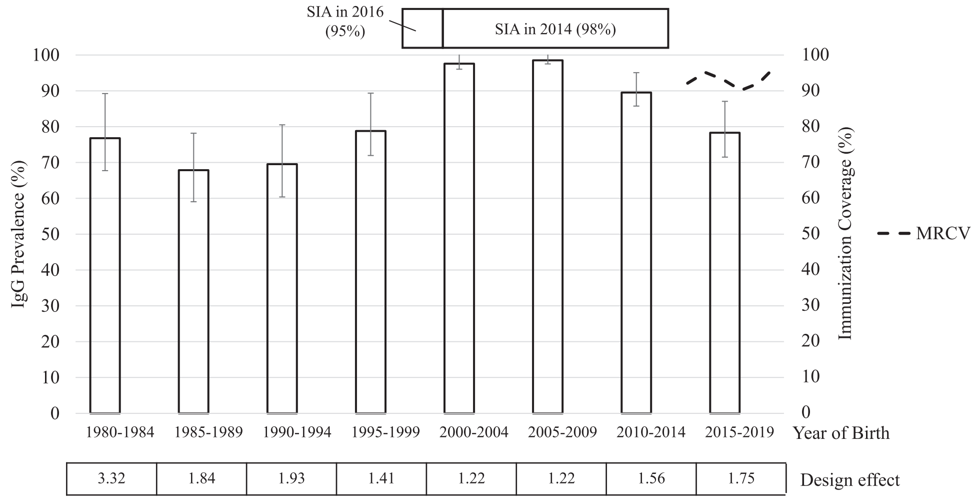

Figure 3. Estimated anti-rubella IgG prevalence and reported immunization coverage by year of birth in South Central region of Vietnam (n = 2078). An Enzygnost IgG ELISA value of ≥120 mIU/mL was considered positive. IgG prevalence was calculated considering sampling design and sampling weight of each participant. SIA in 2014 and 2016 used measles and rubella combination vaccine with target age of 9 months to14 years old and 16-17 years old, respectively. Data source: WHO/UNICEF Estimates of National Immunization Coverage, 2022 Revision. Abbreviations: MRCV, percentage of surviving infants who received the 1st dose of rubella containing vaccine; SIA, supplementary immunization activities

The seroprevalence for measles IgG was >98% in all 8 age groups, regardless of targeting in the SIA. The IgG prevalence was 100% among those born before 1992 who would have been vaccinated through routine immunization alone, albeit with a low reported coverage (1-56% for those born in 1980-1987). The youngest age group, born in 2015-2018, was not targeted in the SIA and showed high IgG prevalence (>98%).

Estimated rubella IgG prevalence

From the 2078 samples tested, 1726 were positive for rubella IgG (83.6% [95%CI: 79.3-87.1%]) (Figure 3). Rubella IgG prevalence among people born in 2000-2013, who were targeted in the 2014 SIA was 95.4% (95%CI: 92.9-97.0), significantly higher than among those born in 1980-1997, who did not have the opportunity to receive RCV or MRCV (72.4% [95%CI: 63.1-80.1]; $P < 0.001$). Younger age groups, born in 2014-2018, would have had the opportunity to receive only routine immunization with MRCV and showed significantly lower IgG prevalence (78.9% [95%CI: 70.5-85.3]) than that of the 2014 SIA target ages, born 2000-2013, (95.4% [95%CI: 92.9-97.0]; $P < 0.001$).

Estimated number of CRS cases averted by immunization since 2014

Following criteria described elsewhere [15,16], we selected catalytic model B for estimating the CRS burden in South Central Vietnam. Estimates from all the models are in Table A.2.

The fit of the selected model to the data was similar for all assumed FOI reductions since 2014 (Figure 4). The best-fitting values for FOI were also similar among the selected models but had wide CIs (Table 2). Assuming that FOI was decreased by 50% since 2014, FOI until 2014 was estimated as 75 (95%CI: 51-95) and 14 per 1000 susceptible (95%CI: 0-36) for those aged <15 and ≥15 years, respectively.

The estimated CRS incidence after RCV introduction depended on the assumed reduction in the FOI, ranging from 69 (95%CI: 0-186) to 17 per 100,000 live births (95%CI: 0-47) with a 0% and 75% reduction in the FOI, respectively, corresponding to 1100 (95%CI: 0-2963) and 276 (95%CI: 0-743) CRS cases born in 2019 (Table 2), respectively.

If RCV had not been introduced in 2014, the estimated CRS incidence was 74 per 100,000 live births (95%CI: 0-198), decreasing

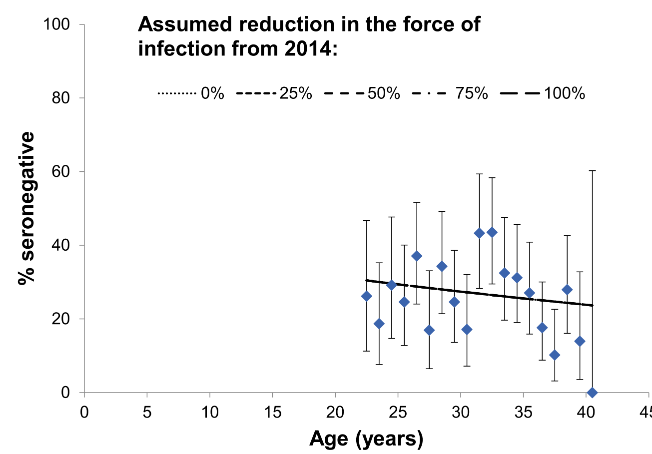

Figure 4. Comparison between the age-specific percentage seronegative predicted using the selected catalytic model and the observed data. Bars show the 95% confidence intervals for the observed data. Lines indicate predictions from the selected model assuming 0%, 25%, 50%, 75%, or 100% reductions in the force of infection since 2014. Similar best-fitting values were obtained for the seronegative percentage from the selected model for each of the assumed reductions in the force of infection since 2014.

with maternal age from about 85 to 60 per 100,000 live births among those aged 15-19 and 40-44 years, respectively (Table SI.1), based on the model which assumed that the FOI decreased by 50% since 2014 (Table 2). This corresponds to about 1180 CRS cases born in 2019 (95%CI: 0-3149) nationwide.

The estimated numbers of CRS cases averted in 2019 following immunization activities since 2014 ranged from 126 (95%CI: 0-460) to 885 (95%CI: 0-2273) (Table 2). The greatest reduction in the age-specific estimated CRS incidence occurred for mothers aged 15-19 years, for example, from 85 (95% CI: 0-282) to 4 (95% CI: 0-13) per 100,000 livebirths, assuming a 50% reduction in the FOI from 2014 (Table SI.1).

Discussion

We had results from 2079 and 2078 samples for measles and rubella respectively from participants aged 1-39 years in 1070 households in 48 villages in South Central Vietnam. Three major

Table 2
Summary of the best-fitting values of the FOI in South Central region, Vietnam before the introduction of RCV among those aged <15 and ≥15 years, as obtained by the selected model (model B) for different assumptions about the reduction in the FOI after the introduction of MRCV in 2014, and the incidence of CRS per 100,000 live births among women aged 15-49 years after weighting by the number of live births among women in different maternal age groups.

Assumed reduction in FOI since 2014 (%)	FOI per 1000 susceptible people before 2014		Log-likelihood deviance (degrees of freedom)	Weighted CRS incidence per 100,000 live births		No. of CRS cases in 2019		
	<15 years	≥15 years		Without vaccination	With vaccination	Without vaccination	With vaccination	Prevented
0	75 (51.95)	14 (0.36)	39 (17)	77 (0.216)	69 (0186)	1223 (0.3448)	1100 (0.2963)	126 (0.460)
25	76 (54.95)	14 (0.36)	39 (17)	75 (0.206)	52 (0.140)	1202 (0.3289)	826 (0.2224)	376 (0.1054)
50	77 (57.95)	14 (0.36)	39 (17)	74 (0.198)	35 (0.93)	1182 (0.3149)	551 (0.1486)	628 (0.1659)
75	78 (60.95)	14 (0.36)	39 (17)	73 (0.189)	17 (0.47)	1161 (0.3018)	276 (0.744)	885 (0.2273)
100	80 (63.95)	14 (0.36)	39 (17)	72 (0.181)	0 (0.0)	1141 (0.2884)	0 (0.0)	1141 (0.2884)

Confidence intervals were obtained by bootstrapping. Columns labelled "without vaccination" refer to the estimated CRS incidence that might have occurred in 2019 if the MRCV had not been introduced.
CRS, congenital rubella syndrome; FOI, force of infection; MRCV, measles and rubella combination vaccine.

findings were obtained: 1) measles IgG prevalence in all 8 age groups exceeded 98%; 2) rubella IgG prevalence was higher among age groups targeted in the 2014 SIA than among younger children and nontargeted young adults; and 3) immunization activities since 2014 averted an estimated 126 (95%CI: 0-460) to 885 (95%CI: 0-2273) CRS cases in 2019.

Measles IgG prevalence

Measles IgG prevalence was >98% for all ages, exceeding the level needed for elimination [1,13]. This high prevalence was likely achieved by immunization and natural infection in people born after measles only vaccine was introduced in 1981 (Figure 2) and by only natural infection in people born before 1981. Participants born shortly after its introduction (aged 32-39 years during the survey) received routine immunization with low reported coverage (1-56% during 1981-1987, Figure 2), and they were 100% IgG positive; thus, some of them probably achieved immunity after exposure to wild measles viruses and adults aged ≥40 years may well have nearly 100% IgG prevalence against measles, as found in other southeast Asian countries [6,11].

Despite this high level of immunity, Vietnam has still been experiencing measles outbreaks in recent years: 1249 cases in 2018 and 5004 cases in 2019 [4]. There are several possible explanations. First, some areas could have low population immunity and the virus circulates among these pockets [21]. Such communities cannot always be detected by multistage cluster sampling, so our survey may have missed some of them. To detect specific areas and populations, it is necessary to analyse vaccination history as well as the geographical and age distributions of recent measles cases. Second, inflow of unvaccinated immigrants after a successful SIA could cause outbreaks. To achieve long-term measles control and elimination, we must reach and vaccinate those who have not been infected or vaccinated, though their immunization records are difficult to obtain [22]. Third, although the serological threshold of protection (120 IU/mL) has been widely used [12], it is not an absolute indicator of protection against clinical measles [23]. Re-evaluation of the cut-off point could be needed.

A recent seroprevalence study in Thailand revealed that those aged 6 months to 30 years had a lower seroprevalence than those aged ≥30 years (75.5% vs 98.7%, $P < 0.001$). [24]. In Cambodia, a high vaccine coverage (>95%) was achieved, although a serological study in 2012 found that those aged 15-19 years had lower IgG seropositivity than older groups (89·6% vs 97·4%, $P < 0.001$) [25]. These countries plan to conduct further SIAs targeting cohorts with lower IgG prevalence, while the present study found no specific cohorts with low IgG prevalence.

Rubella IgG prevalence

Rubella IgG prevalence was significantly higher in the age groups targeted in the 2014 SIA (95.4% [95%CI: 92.9-97.0], born in 2000-2013) than in those aged 22-39 years who were not targeted (72.4% [95%CI: 63.1-80.1], born in 1980-1997) (Figure 3), and exceeded the recommended population immunity threshold of 80% [13] that is required to avoid a potential increase in the CRS burden following RCV introduction. Among participants born after the 2014 SIA, who had the opportunity for routine immunization only, the IgG prevalence was insufficient to eliminate rubella (78.9% [95%CI: 70.5-85.3]). Although detailed characteristics of rubella cases during 2015-2019 have not been reported, younger and older people not targeted in the 2014 SIA should be covered in future SIAs to prevent future CRS cases occurring [26].

Similarly, serological studies in Cambodia and Thailand revealed specific age cohorts with low seroprevalence: more than 25% of women of childbearing age were susceptible to rubella in Cambodia [25] and 7-28 year olds had lower anti-rubella IgG seroprevalence in Thailand (83.9%) [24].

Estimates of averted CRS cases

Before MRCV was introduced in Vietnam, the estimated number of CRS cases was 3788 (95%CI: 3283-4143) nationwide [3], while a national sentinel surveillance system in the two largest hospitals reported 292 CRS cases [27], indicating that current surveillance detects only the tip of the iceberg [27]. To evaluate the introduction of MRCV in 2014, a well-designed serosurvey using data from a representative population, as well as mathematical modelling, is needed [7].

Rubella vaccinations are important for preventing CRS. Many countries have recently introduced rubella vaccination through SIAs and routine immunization. A seroprevalence survey is recommended after SIAs with MRCV to estimate the actual coverage achieved [7], however, few reports have discussed the impact of SIAs [10,28-30]. Although vaccinating women of childbearing age is important for preventing CRS cases, our modelling estimates suggest that vaccinating children alone can potentially reduce CRS incidence, supporting the current WHO-recommended strategy of MRCV introduction targeting both sexes over a wide age range (e.g., 9 months to 15 years) [13]. The reduction in CRS incidence depends on the post-vaccination reduction in the FOI which can potentially be estimated given future seroprevalence surveys conducted in the same region [11]. Notably, some older girls and women who were too old to be targeted in the 2014 SIA had not been exposed to wild-type rubella virus and remained susceptible and may be at risk for rubella during pregnancy [26].

Strengths of the study

This study is the first population-based survey of measles and rubella IgG antibody prevalence in the general population for both SIA-targeted and non-targeted ages after MRCV was introduced in Vietnam. We applied multistage random cluster sampling to better represent the general population in the country. The design effect in each age group was distributed from 1.20 to 1.59 for measles (Figure 2) and 1.22 to 3.32 for rubella (Figure 3), suggesting that our sampling strategy was adequate.

Study limitations

This research has some limitations. First, immunization records were not obtained from participants in the SIA-targeted age groups. Vaccinations received during campaigns are not consistently recorded on vaccination cards. To evaluate the effectiveness of immunization, written records are needed to provide additional information on whether individuals actually received the vaccine during the 2014 SIA, but this remains challenging under the current system.

Second, our estimated IgG prevalence among adults may be biased as adults were sampled when the survey teams visited relevant communes and wards. The female proportion was 50.8% among children aged <18 years but 73.2% among adults, indicating potential selection bias.

Third, we collected data from only 4 provinces. The background characteristics, such as the adult education levels, of our sampled population were similar to those from a nationwide population-based study, the Viet Nam SDGCW Survey 2020-2021 [8]. The SDGCW Survey applied multistage stratified cluster sampling and surveyed more than 47,872 individuals in 14,000 households nationwide. A direct comparison of the sampled populations in the two surveys is difficult as their primary objectives differed. One study revealed that the child health coverage in south central region is close to the national average [31]. Nonetheless, our sampled population is likely representative of the Vietnamese general population.

Forth, testing methods in the present study does not measure neutralization capacity and is regarded less sensitive than plaque reduction neutralization tests for measles [14]. Additionally, the test is designed for diagnostic purposes rather than epidemiological studies.

Finally, our estimates of the number of CRS cases averted following the introduction of RCV depended on the assumed reduction in the force of infection following the introduction of RCV, which varied between 0 and 100%. The actual size of this reduction is presently unclear. Analyses of nationwide age-specific seroprevalence data collected in 2014 and 2019 from Laos PDR estimated a 100% reduction in the force of infection following the introduction of RCV in 2014, although the 95% confidence limits were wide (28-100%) [11]. This reduction in the force of infection after the introduction of RCV is compatible with over 30% reductions in the incidence of serologically-confirmed rubella cases following SIAs which have been reported elsewhere [32]. Considering the above, the results should be interpreted carefully.

Conclusions

Both prevalence of measles and rubella IgG reached the levels necessary for elimination among 2014 SIA target ages, thus the 2014 SIA appears to have been effective. Repeated measles and rubella outbreaks need detailed investigation of the characteristics of cases for further targeted vaccination. Mathematical modelling suggests that immunization activities since 2014 were effective in averting CRS cases, but some young adults remain unprotected, requiring further vaccination.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

This study was approved by the Pasteur Institute in Nha Trang, the National Center for Global Health and Medicine (NCGM-G-3091), and the National Institute of Infectious Diseases (NIID-1011). All participants or their representative gave written informed consent for inclusion in the study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107053.

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