

Population immunity to measles, rubella, mumps, and varicella among adults in Khanh Hoa province, Socialist Republic of Vietnam; residual sample analysis from multistage cluster sampling survey

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Research note

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Abstract

Objective: Measles, rubella, mumps, and varicella are currently endemic in Vietnam, but population immunity to the four diseases among the general population has not been well investigated. This study measured specific immunoglobulin (Ig)G in 362 randomly selected adults between 20 and 70 years old, using residual serum samples to evaluate age-specific immunity to the four diseases in Khanh Hoa province.

Results: Age-specific anti-measles IgG prevalence was lowest, at 89.3% (95% confidence interval 71.8–97.7%) at 20–24 years old, below the herd immunity threshold of 95% to prevent epidemics. About 71.4–90.3% of women of child-bearing age (20–49 years old) were seropositive for rubella, indicating that a certain proportion of babies are at risk of congenital rubella syndrome. A large proportion of young adults (20–29 years) are susceptible to mumps and varicella, with population immunity of 71.4–78.1% to mumps and 48.8–53.6% to varicella. Population-based seroprevalence surveys of both children and adults are needed to evaluate population immunity and improve current immunization programs by expanding the target ages for immunization and introducing new vaccines.

Introduction

Measles, rubella, mumps, and varicella (MMRV) are vaccine-preventable diseases that may cause significant morbidity and mortality. The Expanded Program on Immunization (EPI) was introduced in Vietnam in 1981 with six antigens [1]. A measles-containing vaccine was nationally introduced in 1985 [1] and vaccination coverage reached 97% in 2018 [2]. A rubella-containing vaccine was introduced in 2014 as a measles and rubella combination vaccine [3]. Modelling analysis revealed that the incidence and mortality of most vaccine-preventable diseases have decreased over the last 30 years [1]. However, measles and rubella remain endemic in many areas of Vietnam, and the government has set elimination targets for measles and rubella. Meanwhile, routine immunizations for mumps and varicella have yet to be implemented in Vietnam. Neither is currently classified as a notifiable disease, so epidemiological information remains scarce. The objective of the present study was to clarify the current epidemiological situation of MMRV among a representative adult population in Khanh Hoa province, Vietnam. This study used residual serum samples collected in a multistage cluster sampling survey conducted in 2014 to measure hemoglobin A1c and evaluate the prevalence of diabetes mellitus in Khanh Hoa province [4].

Materials And Methods

Study population and sampling

Three-stage cluster sampling with probability proportionate to size sampling was applied in the 2014 survey [4]. In total, 10 of 137 communes/wards were randomly selected in the first stage, and 3 villages from each selected commune/ward were randomly selected in the second stage. Sixteen adults between 20 and 70 years old were then randomly selected from the residential list of each village in the third

stage. Among the 480 expected participants, blood samples were able to be obtained from 376 participants for the measurement of hemoglobin A1c [4]. Residual serum samples were stored at -20°C in a stockroom of the Pasteur Institute of Nha Trang (Nha Trang, Vietnam) until measurement. After exclusion of 14 samples due to insufficient residual volumes, 362 samples (75.4%) were available for analysis in the present study.

Anti-measles, anti-rubella, anti-mumps, and anti-varicella immunoglobulin (Ig)G measurement

IgG levels specific to measles, rubella, mumps, and varicella for the 362 samples were measured in the virology department of the Pasteur Institute of Nha Trang. Measurements were made in 2016 and 2018 using commercially available enzyme-linked immunosorbent assay (ELISA) kits: IBL® Anti-measles Virus/IgG, IBL® Anti-rubella Virus/IgG, IBL® Anti-mumps (Parotitis) Virus/IgG, and IBL® Anti-varicella zoster Virus/IgG (IBL International, Hamburg, Germany). Specific IgG levels were determined as positive ($\Delta A > 0.200$), equivocal ($0.100 \leq \Delta A \leq 0.200$), or negative ($\Delta A < 0.100$) according to the instructions from the manufacturer. Only samples determined as positive were regarded as 'positive' for the present analysis.

Data entry and statistical analysis

All collected data were double-entered and cleaned in an Excel 2016 spreadsheet (Microsoft, Redmond, WA, USA). Statistical analysis was performed and IgG seroprevalence was calculated using Stata Statistical Software: Release 13 and 14 (StataCorp LP, College Station, TX, USA).

Ethical considerations

The institutional ethics boards at both the Pasteur Institute of Nha Trang (Nha Trang, Vietnam) and National Center for Global Health and Medicine (Tokyo, Japan) approved all study protocols.

Results

Mean age was 42.5 years (standard deviation, 12.5 years), with females accounting for 61.9% of participants (Table 1). In this study, overall immunity rates were 98.1% (95% confidence interval (CI) 96.1–99.2%) for measles, 88.7% (95%CI 85.0–91.7%) for rubella, 88.7% (95%CI 85.0–91.7%) for mumps, and 83.2% (95%CI 78.9–86.9%) for varicella.

Table. Characteristics of respondents (N=362)

	Variable	n	%
Age group (years)	20-24	28	7.7
	25-29	41	11.3
	30-34	42	11.6
	35-39	46	12.7
	40-44	43	11.9
	45-49	45	12.4
	50-54	45	12.4
	55-59	36	9.9
	60-64	25	6.9
	65-70	11	3.0
Sex	Male	138	38.1
	Female	224	61.9
Residential area	Rural	215	59.4
	Urban	145	40.1
	Missing	2	0.6
Ethnicity	Kinh	328	90.6
	Others	34	9.4
Education level	No schooling or primary school uncompleted	63	17.4
	Primary school completed	104	28.7
	Lower secondary school completed	91	25.1
	Higher secondary school completed	102	28.2
	Missing	2	0.6
Occupation	Manual <u>laborer</u>	147	40.6
	Office worker	36	9.9
	Service worker	60	16.6
	Homemaker, student, or unemployed	74	20.5
	Retired	19	5.3
	Other	26	7.2

Age-specific IgG prevalence

The seroprevalence of anti-measles IgG was lowest (89.3%, 95%CI 71.8–97.7%) in participants 20–24 years old compared to other age groups (Fig. 1a). Seroprevalence for measles increased with age, reaching 97.6–100% in participants > 25 years old. The seroprevalence of anti-rubella IgG was also lowest in those 20–24 years old (78.6%, 95%CI 59.0–91.7%), showing a tendency toward a small increase with age in those > 25 years old (Fig. 1b). Anti-mumps IgG seroprevalence rate was lowest in those 20–24 years old (71.4%, 95%CI 51.3–86.8) and highest in those 60–64 years old (100.0%, 95%CI 86.3–100.0%) (Fig. 1c). The seroprevalence of anti-varicella IgG for participants 25–29 years old was the lowest, at 48.8% (95%CI 32.9–64.9%), followed by those 20–24 years old. Seroprevalence gradually increased with age, reaching 100% in participants > 55 years old (Fig. 1d).

Discussion

To the best of our knowledge, this represents the first set of data on MMRV IgG seroprevalence in a randomly selected, representative population in south central Vietnam. Several epidemiological reports have been published from the northern and southern cities of Vietnam [5–7], but few reports in the English literature are available for the south central region of the country. For example, serological study using samples from biobank showed seroprevalences against measles reached above 90% after 25 years old and 95% after 30 years old [5].

Measles

In this study, overall immunity to measles was higher than those to rubella, mumps, or varicella. Participants in the present study were not targeted in supplementary immunization activities (SIA) using measles-containing vaccine in 2003 (target age, 9 months to 10 years) and 2010 (target age, 12–59 months), or in SIA using measles- and rubella-containing vaccine in 2014 (target age, 9–24 months), 2015 (target age, 1–14 years) and 2016 (target age, 16–17 years) [8]. Individuals over 29 years old as of 2014 thus had no public opportunities to undergo vaccination, and were likely to have been exposed to wild measles viruses leading to acquisition of immunity. Conversely, individuals 28 years old or younger might have received vaccination with measles-containing vaccine in infancy. Participants 20–24 years old who were born after implementation of the measles immunization program in 1985 showed the lowest anti-measles IgG prevalence, below the herd immunity threshold of 95% necessary to meet the World Health Organization (WHO) goal for measles elimination [9, 10], while other groups showed rates $\geq 95\%$. As the majority of epidemics occurred among children [11, 12], anti-measles IgG prevalence should also be investigated in younger ages.

Rubella

The percentage of participants seropositive for rubella antibodies was 88.7% in the present study sample. This immunity would have been acquired via natural infection, because participants had no public opportunities for vaccination with rubella containing vaccines [8]. Women of childbearing age (20–49 years) were at higher risk of rubella infection (71.4–90.3% were seropositive, see additional file 3), below the WHO recommendation (95%) for the elimination of rubella and the prevention of congenital

rubella syndrome (CRS) [11, 12]. Studies in Vietnam at different levels and geographic areas both nationally [13] and in Khanh Hoa Province [14] found that a substantial proportion of women of childbearing age lacked immunity against rubella. One modeling study estimated that 3,788 babies (95%CI 3,283–4,143 babies) were born with CRS annually throughout the whole country, based on seroepidemiological results from the Khanh Hoa Province during a non-epidemic year [14], while 292 infants with CRS were confirmed by laboratory tests and clinically through the national surveillance system during 24 months after a rubella epidemic [13]. This huge discrepancy between modeling estimates and surveillance data could be attributed to under-reporting caused by a variety of reasons, such as poor reporting systems, limited human resources, and a lack of diagnostic equipment [13]. Serological assessment using population-based data covering both children and adults, especially in women of child-bearing age, is needed to estimate population immunity against rubella.

Mumps

Age-specific seroprevalence of mumps IgG antibodies ranged from 71.4–100.0%, suggesting widespread transmission of mumps virus in Khanh Hoa province, where mumps vaccine has yet to be implemented (Fig. 1c). Studies on age-specific seroprevalences of anti-mumps IgG before the introduction of mumps-containing vaccines have been conducted in different regions of the world: Europe [15], Africa [16], and the Lao People's Democratic Republic [17], while mumps epidemiology has not been well investigated in Vietnam [6, 7]. Age-specific serosurveys are thus needed to formulate an immunization policy for mumps. An IgG prevalence against mumps in Vietnam and Lao People's Democratic Republic was similar. For example, the prevalence was 71.4–89.1% in those 20 to 39 years old in Vietnam, and 79.0–83.6% in those 22 to 39 years old in Lao People's Democratic Republic [17], however, comparison of data from different ELISA kits must be careful in interpretations [12, 15].

Varicella

The present study found that a certain proportion of young adults (20–29 years old) was susceptible to varicella. The age-specific seropositivity of varicella in this study was similar to previous findings from Spain, Switzerland, and Iran [18–20]. The disease burden of varicella in Vietnam is not well known, but varicella is one cause of central nervous system infections in northern [6] and southern Vietnam [7]. Serological assessment using nationwide population-based data covering both children and adults is needed.

Four diseases showed different proportions of susceptible population. This phenomenon might be caused by differences in force of infection, as such findings were common in the pre-vaccine era [15]. A previous study in Vietnam found marked discrepancies between estimated levels of population protection and vaccine coverages of measles [5]. Reported immunization coverage does not necessarily offer reliable information with which to estimate population immunity [12, 21, 22].

In conclusion, this is the first study to describe the age-specific seroprevalence of antibodies against measles, rubella, mumps, and varicella in a representative adult population from south central Vietnam. A study to investigate age-specific IgG seroprevalence to the four diseases including both children and

adults will offer valuable information to evaluate immunization policy and plan the introduction of mumps- and varicella-containing vaccines.

Limitations

First, the number of participants was insufficient to estimate population immunity against the four diseases. As the sampling design of the present study was derived from other purposes, comparison with results from different times (past and future) and different places (regions in Vietnam and other countries) is difficult. To reveal the current population immunity and to contribute to the formulation of immunization policy, more samples (i.e., $\geq 2,000$ samples) from wider geographical areas are needed [12, 21].

Second, numerous ELISA kits are commercially available and have been used in previous studies investigating anti-measles, anti-rubella, anti-mumps, and anti-varicella IgG seroprevalences, but cutoff values for IgG levels measured using different kits have not been standardized [23]. The present study followed the instructions of the manufacturer to determine IgG levels as positive, whereas other studies used different quantitative ELISA values. Direct comparison of age-specific IgG seroprevalences is therefore not valid. To better assess seroepidemiological data, cutoff values and methods for comparison among different test kits need to be standardized [15, 23].

Third, the present study did not include a pediatric population (< 20 years old), so virus circulation, particularly for the most affected age stratum, was difficult to estimate. Age-specific IgG prevalence in the younger population may provide more accurate estimation of virus circulation [21, 22], and allow us to calculate the force of infection for each disease in local settings. The present residual serum sample analysis is regarded as a pilot study, and a population-based seroprevalence survey covering both children and adults in wider geographical areas is needed to evaluate population immunity in Vietnam.

Abbreviations

MMRV measles, rubella, mumps, and varicella

EPI Expanded Program on Immunization

IgG immunoglobulin G

ELISA enzyme-linked immunosorbent assay

SIA supplementary immunization activity

WHO World Health Organization

CRS congenital rubella syndrome

Declarations

Ethics approval and consent to participate

The institutional ethics boards at both the Pasteur Institute in Nha Trang (Nha Trang, Vietnam) and National Center for Global Health and Medicine (Tokyo, Japan) (NCGM-G-001644-00) approved all study protocols. Written informed consent was obtained from all participants and caregivers prior to the survey.

Consent for publication

Not applicable

Availability of data and materials

Data sets are available as supporting information.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DTH, VQM and LXH supervised the entire survey process, including survey design, training for surveyors, data collection, and interpretation of the data. HKM and NBT performed immunological evaluation and interpreted the results. HTT designed and conducted the survey in close collaboration with local health departments. KK, YI, SM, MLY, and MMT developed the table and figures, analyzed the data, and revised the manuscript. YM and MT designed the experiments and comparison among different ELISA kits. TM advised epidemiological aspects of the survey design and revised the manuscript. MH contributed to design, data collection, and manuscript writing. All authors read and approved the final manuscript.

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Figures

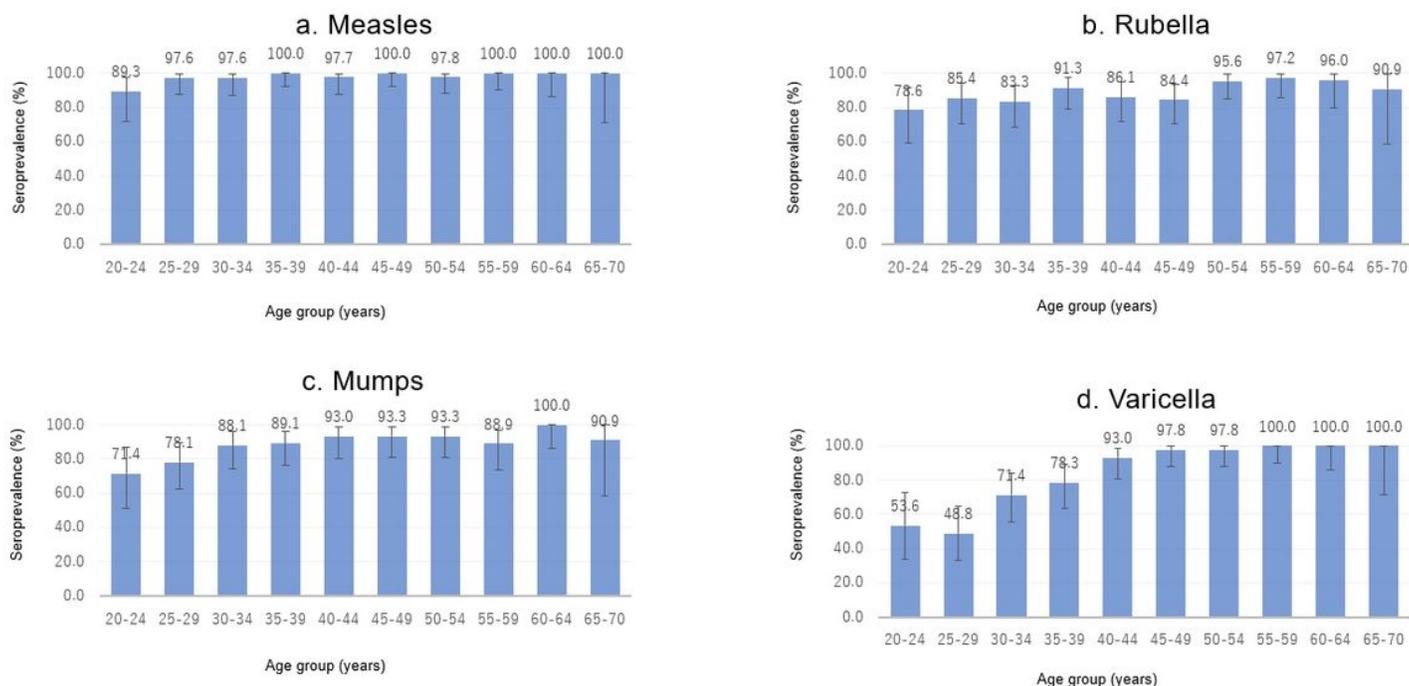


Figure 1

Prevalence of positive IgG. Plots show the prevalence of specific IgG against measles (a), rubella (b), mumps (c) and varicella (d) among adults in Khanh Hoa province, Socialist Republic of Vietnam, 2014 (N=362). Error bars represent 95% confidence intervals.

Supplementary Files

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