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Effectiveness of immunization activities on measles and rubella immunity among individuals in East Sepik, Papua New Guinea: A cross-sectional study

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ABSTRACT

Objectives: This study aimed to assess measles and rubella immunity by measuring virus-specific immunoglobulin G (IgG) prevalence among individuals and evaluate the effectiveness of recent supplementary immunization activities (SIAs) by comparing the antibody positivity rates of the SIA target age groups in 2015 with those in 2019 as measles and rubella are endemic in Papua New Guinea.

Methods: A cross-sectional study. The measles- and rubella-specific IgG levels of patients aged ≥ 1 year at two clinics in East Sepik province, Papua New Guinea were assessed with commercially available virus-specific IgG EIA kits.

Results: In total, 297 people participated in the study and 278 samples with sufficient volume, relevant information, and age inclusion criteria were analyzed. The overall IgG prevalence rates were 62.6% for measles and 82.0% for rubella. The age groups targeted in the 2019 SIAs had a higher IgG prevalence than those targeted in the 2015 SIAs for both the infectious diseases. Moreover, the IgG prevalence for rubella was higher than measles in these groups.

Conclusions: The anti-measles and anti-rubella IgG prevalence in the target groups were lower than those required for herd immunity. The immunization program should be emphasized to eliminate measles and rubella. Further population-based studies are warranted.

Introduction

Measles and rubella are vaccine-preventable diseases that may cause significant morbidity and mortality, and they remain endemic in several areas in Papua New Guinea (PNG) (Gowin et al., 2021; Kamac et al., 2017; Senn et al., 2010; International Federation of Red Cross and Red Crescent Societies, 2017). Measles-containing vaccine (MCV) was introduced nationwide via the Expanded Program on Immunization (EPI) in PNG in 1982 (Manning et al., 2011). In addition, rubella-containing vaccine was launched in 2015 as measles–rubella (MR) vaccine (National Department of Health, 2019a). However, it has been challenging to maintain high MCV or MR vaccine coverage in

routine immunization in PNG. In fact, it decreased to 37% in 2018 and 2019 after reaching 66% in 1990 (Kurubi et al., 2009; World Health Organization, 2020a, 2020b; Samiak and Emeto, 2017). PNG also had a major measles outbreak in 2014 (Morgan et al., 2020). Therefore, supplementary immunization activities (SIAs) were added after several years. Nationwide SIAs were recently conducted in 2015 and 2019; the 2015 SIA using MR vaccine targeted children aged 9 months to 14 years, with a coverage of 63%, and the 2019 SIA also used MR vaccine, targeting infants aged 6 to 59 months, with a coverage of 101% (World Health Organization, 2020c). On the other hand, the effectiveness of the SIA in promoting serological immunity has not been evaluated. Considering these factors, it is important to determine the

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prevalence of measles and rubella immunity in the targeted age groups to eliminate these infectious diseases.

Hence, the current research aimed to estimate immunity based on anti-measles immunoglobulin G (IgG) and anti-rubella IgG prevalence among selected pediatric and adult populations in East Sepik province, PNG, and evaluate the effectiveness of the SIAs by comparing the antibody positivity rates of the SIA target age groups in 2015 with those in 2019.

Methods

Study population

This cross-sectional seroprevalence study was conducted in the Wewak District of East Sepik Province, where routine immunization coverage (41.5% for the first dose of measles and rubella vaccine and 30.3% for the second) is lower than the national average of 58.7% and 40.1%, respectively, in the demographic and health surveys conducted during 2016–2018 (National Statistical Office, 2019). We recruited patients from two clinics (Wirui and Town clinics) in the Wewak District in January and February 2020 in cooperation with a study on symptomatic patients infected with *Plasmodium falciparum* malaria in a malaria-endemic area (Yoshida et al., 2021). The inclusion criteria were as follows: 1) patients who visited the clinic due to fever, 2) patients or parents/caregivers of patients aged <16 years who were willing to participate and who provided informed consent after receiving explanation on the study, and 3) those aged >1 year. Participants had to meet all three inclusion criteria. Because this study was conducted in collaboration with the aforementioned study on malaria in symptomatic outpatients, we included febrile patients in our inclusion criteria.

We calculated the sample size using the World Health Organization (WHO) sample size calculator (World Health Organization, n.d.) by applying a 5% level of significance, precision of ± 0.05 , and expected measles and rubella IgG-positive rates of 80%. The required sample size was calculated to be 289 samples in total. Therefore, the target total number of participants was set at approximately 300, which was considered operationally feasible. Patients visiting the two clinics who met the age and symptom criteria were consecutively invited to participate in the study.

The staff at both clinics underwent a 1-day training before the study in collaboration with Wewak General Hospital. The training included ethical considerations, study methodology, and blood sampling practices.

Ethical considerations

All study protocols were approved by the Medical Research Advisory Committee (MRAC) of the National Department of Health (MRAC No:19.37., Rabaul, PNG) and National Center for Global Health and Medicine (NCGM-G-001644-00, Tokyo, Japan). The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Written informed consent was obtained from participants aged 16 years and older before enrollment. Since the participants included children, we provided sufficient explanations using age-appropriate terms. For participants aged below 16 years, written informed consent was obtained from parents or legal guardians.

Blood sample collection

In total, 400 μ l of blood sample was obtained via finger prick and was transferred onto a Whatman® 903 protein saver card (Whatman, Maidstone, Kent, UK). After drying at room temperature for at least 4 hours, the samples were placed individually in a sealed plastic bag, stored at

4°C, and transported to the laboratory at Juntendo University within two weeks.

Anti-measles and anti-rubella IgG assessment

Blood samples were extracted from the dried blood spots by punching one circle (diameter, 3 mm) and eluting overnight in 120 μ L of phosphate buffer saline containing 0.5% Tween-20 and 5% skimmed milk (Hachiya et al., 2018). The enzyme immunoassays (EIAs) for measles and rubella-specific IgG were performed with virus-specific IgG EIA kits (SEIKEN measles IgG (II)-EIA and SEIKEN Rubella IgG (II)-EIA; Denka Seiken, Tokyo, Japan), considering the commercial availability of the kits at the time of the present study. SEIKEN IgG EIA kits for measles and rubella were considered as standard assays in laboratory manuals for pathogen detection in Japan (National Institute of Infectious Diseases, 2017, 2021). Denka Seiken reported that the test kit results are accurate within $\pm 10\%$ of the known antibody titers. Optical density values were indexed following the manufacturer's instructions, and the correlation between the EIA titer and international units (IUs) indicates that IU [mIU/mL] = $45 \times$ EIA titer for measles and IU = $2.3 \times$ EIA titer for rubella (company data, Denka Co., Ltd.). An EIA titer of 4.0 or higher was considered as positive, and an EIA titer of less than 2.0 was considered as negative for both measles and rubella, following the manufacturer's instructions.

Data entry and statistical analysis

All collected data were double-entered and cleaned in an Excel 2016 spreadsheet (Microsoft, Redmond, WA, the USA). Of the 282 people that participated in the study, we excluded participants with missing data on age ($n = 2$) and those with missing serological samples ($n = 2$). Data on the remaining 278 participants (98.6%) were used for further analysis. The IgG levels with 95% confidence interval (CI) were calculated and stratified between age groups. The chi-square test was used to evaluate differences between age groups and IgG prevalence for measles and rubella. Statistical analysis was performed using Stata Statistical Software: Release 15 and 16 (StataCorp LP, College Station, TX, the USA). A p value of <0.05 is regarded as significant.

Results

The mean age of the 278 participants included in the data analysis was 18.2 (range: 1–78) years, and women accounted for 54.0% of all participants. The overall IgG prevalence rates were 62.6% (95% CI: 56.6–68.3) for measles and 82.0% (95% CI: 77.0–86.3) for rubella. About 84.1% (95% CI: 74.8–93.4) of women of reproductive age (15–49 years) tested positive for rubella. The age-specific anti-measles IgG prevalence fluctuated among children aged 1–19 years. Moreover, it steadily increased among adults and reached more than 90% among those aged over 40 years. The age-specific anti-rubella IgG prevalence fluctuated among children aged 1–19 years old, and it reached more than 85% among adults (Table 1).

To evaluate the effectiveness of SIAs in 2015 and 2019, the measles and rubella IgG prevalence was compared among targeted birth cohorts to validate the SIA coverage. As children aged 5–6 years received both SIAs, the prevalence among children aged 1–4 years (targeted only in the 2019 SIA) and those aged 7–19 years (targeted only in the 2015 SIA) were evaluated. The seroprevalence rates of the relevant birth cohort in the 2019 SIA (1–4 years old) were 67.8% (95% CI: 55.5–80.1) for measles (indicated as “a” in Table 2) and 89.8% (95% CI: 79.2–95.6) for rubella (indicated as “c” in Table 2). Similarly, the seroprevalence rates of relevant birth cohorts in the 2015 SIA (7–19 years) were 49.5% (95% CI: 39.6–59.4) for measles (indicated as “b” in Table 2) and 68.3% (95% CI: 58.7%–76.6%) for rubella (indicated as “d” in Table 2).

Moreover, the measles and rubella IgG prevalence among the age groups targeted by the SIAs were compared. For measles, the IgG preva-

Table 1
Age-specific seroprevalence results of measles and rubella IgG among individuals in East Sepik province, Papua New Guinea, in 2020

Age during the study (years)	Birth year	Number of participants	Measles IgG	Rubella IgG
1	2018	8	75%	88%
2	2017	17	71%	94%
3	2016	18	83%	94%
4	2015	16	44%	81%
5	2014	9	78%	78%
6	2013	9	33%	78%
7	2012	15	60%	40%
8	2011	2	50%	50%
9	2010	14	50%	71%
10	2009	10	70%	60%
11	2008	5	20%	60%
12	2007	8	63%	75%
13	2006	10	20%	90%
14	2005	6	67%	100%
15	2004	10	30%	50%
16	2003	5	80%	80%
17	2002	7	57%	71%
18	2001	4	25%	100%
19	2000	5	40%	80%
20–24	1995–99	26	50%	88%
25–29	1990–94	14	57%	93%
30–34	1985–89	19	79%	89%
35–39	1980–84	9	89%	100%
+40	-1979	32	94%	94%
Overall		278	62.6 % (56.6–68.3)	82.0% (77.0–86.3)

Table 2
Comparison of anti-measles and anti-rubella IgG prevalence among targeted birth cohorts according to the SIAs in 2015 and 2019 (without overlapping birth cohorts)

Age during the study (years)	Birth year	Targeted SIA	Anti-measles IgG prevalence		Anti-rubella IgG prevalence	
			Average	95% Confidence interval	Average	95% Confidence interval
1–4	2015–8	2019	67.8% ^a	55.5–80.1	89.8% ^c	79.2–95.6
5–6	2013–4	2015 & 2019				
7–19	2000–12	2015	49.5% ^b	39.6–59.4	68.3% ^d	58.7–76.6

*SIA: supplementary immunization activity

Prevalence was significantly higher among children aged 1–4 years than in those aged 7–19 years (“a” vs. “b” in Table 2, $p < 0.05$). For rubella, children aged 1–4 years had a significantly higher IgG prevalence than those aged 7–19 years (“c” vs. “d” in Table 2) ($p < 0.05$).

Discussion

To the best of our knowledge, this is the first study about anti-measles and anti-rubella IgG prevalence in children and adults after introducing the MR vaccine in PNG. The current study had three main findings. First, the IgG prevalence was significantly lower than the population immunity required to eliminate measles and rubella. Second, the target age group of the 2019 SIA had a higher IgG prevalence than the target age group of the 2015 SIA for both measles and rubella. Third, the anti-measles IgG prevalence was lower than the anti-rubella IgG prevalence in both the target age groups in the 2015 and 2019 SIAs.

The WHO stated that to eliminate measles, the coverage of two-dose MCV should be 95% or higher (World Health Organization, 2017a). However, the IgG prevalence of measles in this study was 62.6% (95% CI: 56.6–68.3), which is significantly lower than the required herd protection threshold to interrupt measles virus transmission. Based on a cross-sectional study in Madang province, PNG, conducted between 2007 and 2008, the anti-measles IgG prevalence rate was 77% (95% CI: 73–81), which was higher than that of the current study, even though the nationwide SIAs using MCV or MR vaccine were conducted in sub-

sequent years (Senn et al., 2010). This finding could have several explanations. First, the routine immunization coverage in East Sepik is lower than in Madang (National Department of Health, 2019b). Considering the years in which both studies were conducted, the measles immunization coverage rates for children aged below 1 year in Madang province were 60% in 2006 and 52% in 2007. Meanwhile, they were 11% in 2018 and 14% in 2019 in East Sepik. Second, East Sepik has a lower population density than Madang. Thus, it has a less chance of human-to-human contact and exposure to wild measles viruses. Wewak urban, where the current study was conducted, has a lower population density than other areas within East Sepik province. That is, its population density is 15 people per square kilometer of land area (National Statistical Office, n.d.; World Bank, 2010). Third, the Denka Seiken ELISA kit, which was used in the current study, may have a lower sensitivity than the Dade Behring Enzygnost kit used in Madang (Senn et al., 2010). Moreover, direct comparison results of measles IgG were not available.

The two-dose rubella-containing vaccine administered at 9 and 18 months was introduced in the routine immunization schedule as MR vaccine in 2016 (National Department of Health, 2019a). Participants aged 5–19 and 1–6 years at the time of the study might have received MR vaccine in the SIAs conducted in 2015 and 2019, respectively. The participants aged ≥ 20 years could have acquired rubella immunity via natural infection because they had no public opportunities for vaccination with rubella-containing vaccines (Hagan et al., 2018). The findings of the current and previous study in Maprik, East Sepik province, showed a

wide circulation of rubella in this area like Caribbean and African countries (Dowdle et al., 1970; Mirambo et al., 2015; Riddell et al., 2012; Vynnycky and White, 2010).

CRS surveillance is one of the key factors for rubella elimination, however, this is not fully implemented in PNG as there are a few challenges (Riddell et al., 2012; Toda et al., 2015). Thus, serological assessments such as those in the current study using cross-sectional data for both children and adults, particularly women of childbearing age, are useful in assessing rubella immunity.

The other challenges correlated with routine immunization are as follows: disparities in health care resources between urban and rural areas, poor access to health care services, socioeconomic conditions, lack of skilled human resources, lack of understanding of immunization in the population, and inadequate immunization records (Gowin et al., 2021; Kurubi et al., 2009; Manning et al., 2011; Samiak and Emeto, 2017; United Nations Children's Fund, 2015). PNG introduced the Special Integrated Routine EPI Strengthening Program (SIREP) strategy in 2015 with the support of the WHO and UNICEF to improve its immunization program (World Health Organization, 2017b). Notably, improved population-based local planning and stronger community engagement are effective in improving immunization coverage and quality, and it is suggested that SIREP can help strengthen routine immunization programs (Morgan et al., 2020). Besides, the integrated package of services is suggested to contribute to the success in SIAs, and SIAs for measles and rubella can enhance and reinforce routine immunization via a synergistic effect (Morgan et al., 2020; World Health Organization, 2016; Wallace et al., 2017). Because the measles IgG prevalence in the present study was found to be insufficient to eliminate measles, routine immunization needs to be emphasized along with the implementation of SIREP and SIAs with high coverage.

There are two possible reasons for the higher IgG prevalence of both measles and rubella in the 2019 SIA target population than that in 2015: higher vaccination coverage in 2019 and differences in time since each SIA was conducted. First, the 2019 SIA recorded a higher immunization coverage compared to that in 2015 (World Health Organization, 2020; World Health Organization, 2019). The nationwide major vaccination campaign against the polio outbreak in PNG was conducted in 2018, and it was reported that the following were accomplished during this campaign: health community volunteer network, immunization outreach across the country, social mobilization, community engagement, and rapid convenience monitoring. These activities were strongly supported by more than 130 international polio experts, mainly from the WHO, and more than 30 were deployed as long-term experts at the provincial level (World Health Organization, 2019). Such experiences and initiatives undertaken in the previous year could have contributed to the high immunization coverage of the 2019 SIA and higher IgG prevalence in the target population. Second, although large-scale SIAs are effective in boosting herd immunity, the effect is not long-lasting and has been reported to decline over time without high routine immunization coverage (Chong et al., 2020). With regard to low routine immunization coverage in PNG, the effectiveness of SIAs in 2015 may have declined over time.

Anti-measles IgG prevalence was lower than anti-rubella IgG prevalence compared between the same target age groups in each SIA. The exact reason of this difference is not known. Meanwhile, similar findings were observed in other countries, including Lao PDR and Bhutan (Hachiya et al., 2018; Wangchuk et al., 2019; Zahraei et al., 2020). In Lao PDR, the stability testing showed that the measles vaccine component was more sensitive to heat than that of rubella, and this was assumed to be the reason for the low measles antibody prevalence (Hachiya et al., 2018). In Bhutan, it was hypothesized that immunity to measles following vaccination declined over time, whereas immunity to rubella did not (Wangchuk et al., 2019). Although direct evidence is lacking, difficulties in maintaining a cold chain have been reported in PNG; this might affect the difference between anti-measles and anti-

rubella IgG prevalence (Kamac et al., 2017; Manning et al., 2011). Further studies with large, population-representative participants and individual immunization records must be conducted to validate the exact reason why IgG prevalence varies even when both measles and rubella components are administered simultaneously.

The current study had several limitations. First, the sampling design and the number of participants were insufficient to estimate population immunity against measles and rubella. Non-probability convenience sampling at febrile clinics was performed in a limited number of locations and with a limited number of subjects, considering local conditions, including security, which may have led to bias, and the sample size is small and unrepresentative. Therefore, to estimate the current population immunity, large samples from wider geographical areas using cluster sampling are required. Second, it is not possible to distinguish between vaccine acquired and naturally acquired immunity to measles and rubella. Written immunization records are valuable information on whether each individual was actually administered the vaccine as routine and SIA. However, SIAs were not usually recorded on individual cards or certificates in the country, and routine immunization records were not available during participant recruitment at the fever clinics. Measles and rubella immunity might have been obtained by natural infection rather than routine immunization or SIAs. Nevertheless, we could not determine the mechanism for acquiring immunity in each participant. Although the results of this study do not allow us to distinguish between the pathways of immunity acquisition, they can serve as an indirect assessment of the effects of vaccination and are useful for estimating herd immunity. Third, the cutoff values for IgG levels measured using numerous commercially available EIA kits have not been standardized (Hachiya et al., 2018). The current study followed the manufacturer's instruction, and the Denka-Seiken test is one of standard tests for measles and rubella EIAs (National Institute of Infectious Diseases, 2017; Ogawa et al., 2020; Phengxay et al., 2011; Saito-Abe et al., 2021) and is correlated with EIA values obtained using Enzygnost (National Institute of Infectious Diseases, 2021; Terada et al., 2009). The sensitivity and specificity of the kit were reported as 89.2%–96.6% and 66.7%–95.2%, respectively, for measles and 81.0%–95.7% and 63.2%–89.5%, respectively, for rubella (Takayama et al., 2009; National Institute of Infectious Diseases, 2019). To better assess sero-epidemiological data, the cutoff values and methods used for comparison using different test kits should be standardized. Hence, considering the abovementioned limitations, the results of this study should be cautiously interpreted.

In conclusion, the anti-measles and anti-rubella IgG prevalence in selected target groups studied in East Sepik province, PNG, was lower than the required herd immunity, and the target age group of the 2019 SIA had a higher IgG prevalence than that of the 2015 SIA for both measles and rubella. Based on the results, conducting SIAs with high coverage is crucial for eliminating measles and rubella from the country. In addition, a population-based evaluation of anti-measles and anti-rubella IgG antibodies must be conducted to accurately estimate the prevalence of immunity for vaccine-preventable diseases.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YI and MH supervised the entire study process, including study design, training of researchers, and collection and interpretation of the data. MY contributed to the training provided to surveyors and data collection. MY and NY performed immunological evaluation and interpreted the results. SM, KK, and MMT developed the tables, analyzed the data, and revised the manuscript. ST, TM, and FWH supported the study design. MT and YM advised the laboratory procedures. All authors read and approved the final manuscript.

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