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Rubella Seromarkers and Determinants of Infection among Tanzanian Children and Adolescents in Prevaccination Era: Are We in the Right Track?

Mariam M. Mirambo, Said Aboud[1], Uwe Groß[2], Mtebe Majigo[1], Martha F. Mushi, Stephen E. Mshana

Department of Microbiology and Immunology, Weill Bugando School of Medicine, Mwanza, Tanzania, [1]Department of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania, [2]Institute of Medical Microbiology, University Medical Centre Gottingen, Gottingen, Germany

Correspondence to:
Dr. Mariam M. Mirambo, Department of Microbiology and Immunology, Weill Bugando School of Medicine, P.O. Box 1464, Mwanza, Tanzania.
E-mail: mmmirambo@gmail.com

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ABSTRACT

Background: The World health organization advocates assessment of the burden of rubella and congenital rubella syndrome (CRS) by seroepidemiological surveys and surveillance programs in all countries without vaccination programs. Due to scarcity of data in developing countries, this study was conducted to assess the seromakers for natural rubella infection in Tanzania during prevaccination era so as to ascertain the gaps for future research and prevention strategies.

Methods: A cross-sectional study was conducted between September and October 2014. Indirect enzyme-linked immunosorbent assay was used to detect rubella IgG and IgM antibodies. STATA version 11 was used to perform data analysis.

Results: Of 723 enrolled participants, 368 (50.8%) and 94 (13%) were positive for specific IgG and IgM rubella antibodies, respectively. On multivariable logistic regression analysis, significant determinants of rubella IgG seropositivity were increase in age (odds ratios [OR]: 1.24, 95% confidence interval [CI]: 1.18–1.29, $P < 0.001$), low socioeconomic status (SES) (OR: 2.38, 95% CI: 1.1.23–4.50, $P = 0.010$), and absence of rash (OR: 4.34, 95% CI: 1.1.17–15.3, $P = 0.027$), while only the presence of rashes was significant determinant of rubella IgM seropositivity (OR: 2.5, 95%; 1.07–5.98, $P = 0.034$). Significantly higher mean IgG titers were observed in population ≥10 years ($P < 0.001$), those residing in urban and peri-urban areas ($P < 0.001$), those from employed mothers ($P = 0.018$), and those with no current history of fever ($P = 0.018$).

Conclusions: The prevalence of specific rubella IgG antibodies in Tanzania is high and is associated with increase in age, absence of rash, and low SES. Results suggest a need to reconsider upper age limit for vaccination campaigns in developing countries. Screening and vaccinating women may be cost-effective campaign to prevent CRS in developing countries.

Keywords: IgG, IgM, rubella, seromarkers

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INTRODUCTION

Rubella infection which is caused by rubella virus in the family *Togaviridae* may present as mild acute illness or asymptomatic illness. The symptomatic illness usually is characterized by mild fever, swollen, tender lymph nodes, and rash. The disease affects nonimmune individuals, mainly children and young adults.[1] Rubella virus often causes self-limiting diseases; however, infection during the first 13 weeks of the pregnancy may result in congenital rubella syndrome (CRS). The prevalence of acute rubella infection and CRS in developed countries has significantly declined due to vaccination programs.[1] In Africa, Asia, and South America, rubella remains a problem whereby more than 100,000 of children are still born with CRS each year because of lack of vaccination programs.[2,3] In pregnant women, the prevalence of specific rubella IgG antibodies in different countries varies from 54.1% to 95.2%.[4-9] A recent report in Tanzania showed that 92.6% of pregnant women were seropositive for IgG rubella antibodies.[8] As there are no screening programs and seroepidemiological surveys for rubella among pregnant women and other susceptible groups in Tanzania, the national prevalence of rubella infection and the natural protective immunity are unknown.

Considering the fact that rubella vaccine has been recently introduced in Tanzania, by the time this study was conducted, there was no vaccination in private or public sector. This study for the first time in Tanzania shows the trend of natural infections of rubella from infants to adolescents. The information is useful for policy makers in the efforts to control the disease by introducing immunization program and implementing new strategies to control CRS.

METHODS

The cross-sectional study was carried out between September and October 2014 in Mwanza city. The study involved urban and rural settings of Ilemela and Nyamagana districts with a total population about 706,453 with 388,902 (55%) ≥20 years.[10] Mwanza city, which has 1.5% of Tanzania population, is the second largest city in Tanzania located on the shore of the Lake Victoria.

These data were collected before the national rubella vaccination campaign commenced. The sample size was calculated using Kish formula[11] using the prevalence of 80% from Kenya among school-aged children. A 95% confidence interval (CI) with a tolerable error of 5% was used. The minimum sample size obtained was 307, but 723 participants were enrolled to increase the power of the study. Participants aged between 6 months and 21 years were included while all participants with a prior history of rubella vaccination were excluded.

Multistage sampling was used to obtain representative antenatal clinics and schools followed by convenient sampling to enroll participants until the desired sample size of each age group was reached. To obtain under-fives, three busy clinics in the city were conveniently selected, and for the population aged 6–14 years, 7 primary schools were randomly selected, and finally, for the age 15 years and above, 5 secondary schools were randomly selected. The sample size from each age group was determined based on the proportion of the age group to the total population of the same age group residing in Mwanza city as per 2012 census [Table 1].[10] The recruitment was serially done until the sample size was reached.

After obtaining parent/guardian written informed consent, 2–5 ml of blood samples was collected using plain vacutainer tubes (Becton, Dickinson and Company, Nairobi, Kenya). Blood samples were transported to the laboratory, whereby sera were stored at − 40°C freezer until the time for batch testing.

Structured data collection tool was used to collect sociodemographic data. The presence or absence of rashes (within 1 month) was inquired by investigators, and in case of under-fives, confirmation was obtained from the parents/guardians. History of fever within a week was also noted. In addition, number of siblings, education of the parents, employment status of the parents, and any other income-generating activity such as fishing, carpentry, and petty trades were also noted. High socioeconomic status (SES) was defined as parents having secondary education and above, employed, or having any other income generating activity.[12]

Laboratory investigations

Sera were tested for specific IgG and IgM using commercially indirect enzyme-linked immunosorbent assay (ELISA) (ChemWell® 2910-Awareness Technology Inc., USA) according to manufacturer's instructions. Based on manufacturer and the WHO standard, rubella IgG titers of ≥10 IU/ml was considered as positive and presumed immune to rubella infection. While based on the manufacturer, the index value of ≥ 1.1 was considered rubella IgM-positive signifying recent infection. The sensitivity and specificity of IgG ELISA used in this study was >99%.[13,14] For IgM, sensitivity was 97.6% with a specificity of 99.3%.[15]

Table 1: Mwanza city population by age group studied in relation to sample size

Age group	Total population, *n* (%)	Sample size, *n* (%)	Sampling frame
0-5	124,479 (32)	230 (31.8)	RCH clinics*
6-14	155,714 (40)	285 (39.4)	Primary school
15-21	108,906 (28)	208 (28.8)	Secondary school
Total	389,099	723	

*Reproductive and child health clinics

Data management

Data were analyzed using the STATA version 11 (College Station, Texas, USA). Categorical variables were presented as proportions and analyzed using the Pearson's Chi-square test to observe the significance of proportion differences. Continuous variables (age, IgG titers, IgM index values, number of siblings, etc.) were summarized as mean ± standard deviation, and independent *t*-test was performed to determine the statistical difference. Factors associated with rubella IgG and IgM seropositivity were defined using multivariable logistic regression models. Age was used as continuous in determining predictors of IgG and IgM seropositivity, while for titers, comparison age was categorized into two groups below 10 years and above or equal 10 years. The associated factors tested were age in years, sex, location, number of siblings, presence of rashes, and SES. For establishing determinants of IgG and IgM seropositivity, all factors with $P < 0.05$ were fitted into the multivariable logistic regression analysis. Odds ratios (OR) and their 95% CI were noted. The seroprevalence of IgG for each age was calculated, and the results were used to determine the general increase in seroprevalence by unit increase in age using scatter diagram with line fit generated by STATA program.

Ethical clearance

The ethical clearance to conduct this study was obtained from the Joint Catholic University of Health and Allied Sciences/Bugando Medical Centre Ethical Review Committee. In addition, permission was obtained from hospitals, clinics, and school administrations.

RESULTS

Sociodemographic characteristics

A total of 723 participants were enrolled in the study. The mean age was 8.9 (±6) years. The age ranged from 0.8 to 21 years. Of 723 participants, 230 (31.8%) were under-fives, 285 aged between 6 and 14 years, and 208 aged above 15 years [Table 1]. Females, 437/723 (60.4%) constituted the majority of participants. Of total participants, 358/723 (49.5%), 330/723 (45.6%), and 35/723 (4.9%) were from peri-urban, rural, and urban areas, respectively. The mean number of siblings per household was 4.2 ± 2.2.

Prevalence of rubella-specific IgG and IgM antibodies

A total of 368 (50.8%), 261 (36.9%), and 94 (13%) were found to be IgG-seropositive (IgG+, IgM−), susceptible (IgG−, IgM−), and IgM-seropositive (IgM+), respectively. IgG seropositivity rates for population with no acute infection were 28.6% (58/203), 32.8% (39/119), 90.2% (147/163), and 86.1% (124/144) for the age groups of <5, 5 to <10, 10 to <15, and ≥15 years old, respectively [Figure 1]. Based on the sampling frame, IgG seropositivity was 26.1% for those from reproductive and child health clinics, 75.1% for those from primary school, and 71.6% for those from secondary school.

Factors associated with IgG and IgM seropositivity

The mean age of IgG seropositive participants was 11.8 ± 5.1 years compared to 5.0 ± 4.7 of IgG-seronegative participants, $P < 0.001$. Furthermore, it was observed that when age increases by 1 year, the IgG seroprevalence increased by 4.5% reaching 81.3% at the age of 15 years [Figure 2]. Of 87 participants with low SES, 66 (75.9%) were IgG-seropositive compared to 357 (56.1%) of 636 participants with high SES, $P < 0.001$ [Table 2].

On multivariable, the IgG seropositivity was significantly found to increase as the age increases (OR 1.24, 95% CI; 1.18–1.29, $P < 0.001$). Other significant determinants on multivariable analysis for IgG seropositivity were low SES (OR: 2.38, 95% CI, 1.23–4.50, $P = 0.010$) and absence of rashes (OR: 4.34, 95% CI, 1.17–15.3, $P = 0.027$).

Regarding determinants associated with IgM seropositivity [Table 3], only the presence of rashes was significantly associated with rubella IgM seropositivity (OR: 2.5, 95%; 1.07–5.98, $P = 0.034$).

Mean IgG titers and associated factors

The mean IgG titer in population with positive IgG rubella antibodies was 46.7 ± 13.8 IU/ml. Population ≥10 years had mean IgG titers of 48.8 ± 11.26 compared to 40.9 ± 18.24 in population below 10 years ($P < 0.001$). Other factors found to influence mean titers of rubella IgG antibodies were population residing in urban and peri-urban ($P < 0.001$), population from employed mothers ($P = 0.018$), and those with no fever ($P = 0.018$) [Table 4].

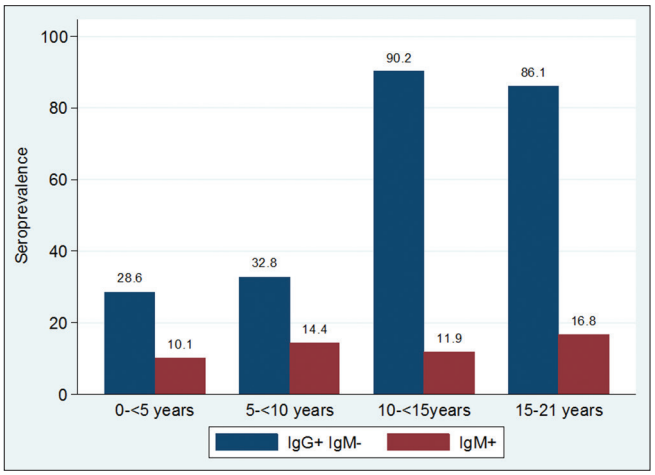

Figure 1: Seroprevalence in different age groups (0–<5 years, 5–<10 years, 10–<15 years, and 15–21 years) for IgG and IgM. IgM−: Negative IgM status, IgG + and IgM+: Positive status for IgG and IgM, respectively. The population > 10 years had significantly higher IgG seropositivity than population < 10 years ($P < 0.001$)

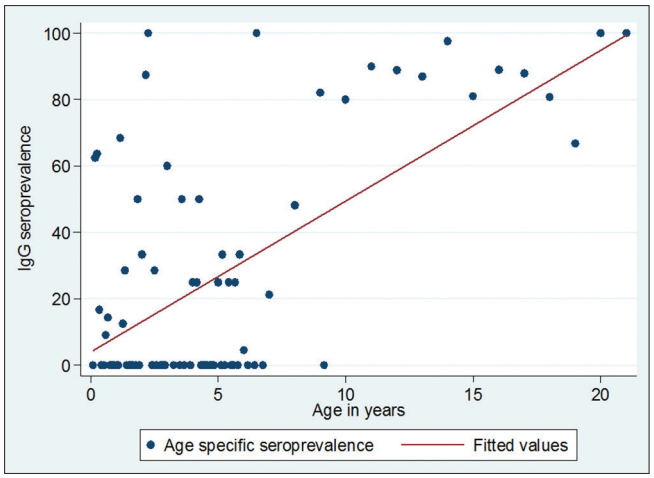

Figure 2: As age increases by 1 year, the seroprevalence increased by 4.5% (*P* < 0.001) while the risk of acquiring rubella infection is 24% higher per 1 year increase in age

Semi-quantitative median IgM index values

The index value for IgM ELISA assay of ≥1.1 was considered positive. The highest index value observed was 9.6. Of the 94 participants with positive specific IgM antibodies, the median index value was 1.6 (IQR: 1.2–2.4).

DISCUSSION

To the best of our knowledge, this is the first large study in Tanzania that has investigated on rubella infections in different age groups in the unvaccinated population. The population studied might not represent the children and adolescent general population in Mwanza city because school and under-fives clinic attendance is not 100% but the results give baseline data regarding rubella infections in unvaccinated population in developing countries.

Table 2: Univariable and multivariable analyses of factors associated with IgG seropositivity in 723 participants

Characteristics	IgG serostatus			Multivariable	
	Seropositive (%)	Seronegative (%)	*P*	OR (95% CI)	*P*
Age (years)*	11.8±5.1	5.0±4.7	<0.001	1.24 (1.18-1.29)	<0.001
Number of siblings*	4.98±4.7	3.2±1.9	<0.001	1.09 (0.97-1.22)	0.149
Sex					
Male	157 (54.9)	129 (45.1)	0.111		
Female	266 (60.8)	171 (39.1)			
Residence					
Urban	13 (37.1)	22 (62.9)	0.010		
Rural	187 (56.7)	143 (43.3)		0.64 (0.24-1.64)	0.350
Peri-urban	223 (62.3)	135 (37.7)		0.62 (0.24-1.59)	0.317
Rash					
Yes	4 (14.3)	24 (85.7)	<0.001		0.027
No	419 (60.3)	276 (39.7)		4.34 (1.17-15.3)	
SES					
High	357 (56.1)	279 (43.9)	<0.001		0.01
Low	66 (75.9)	21 (24.1)		2.38 (1.23-4.5)	

*Mean age and number of siblings. SES=Socioeconomic status, OR=Odds ratio, CI=Confidence interval

Table 3: Univariable and multivariable analyses of factors associated with IgM seropositivity in 723 participants

Characteristics	IgM status			Multivariate	
	Seropositive (%)	Seronegative (%)	*P*	OR (95% CI)	*P*
Age (years)*	10.04±5.58	8.8±6.0	0.061		
Number of siblings*	4.1±2.2	4.2±2.2	0.293		
Sex					
Male	32 (11.2)	254 (88.8)	0.242		
Female	62 (14.2)	375 (85.8)			
Residence					
Urban	6 (17.14)	29 (82.9)	0.021		
Rural	54 (16.4)	276 (83.6)		0.95 (0.37-2.40)	0.911
Peri-urban	34 (9.5)	394 (90.5)		0.53 (0.20-1.37)	0.188
Rash					
Yes	8 (28.5)	20 (71.4)	0.012		0.034
No	86 (12.37)	609 (77.6)		2.5 (1.07-5.98)	

*Mean age and number of siblings. OR=Odds ratio, CI=Confidence interval

Table 4: Comparison of IgG titer mean by different factors

Variables	IgG mean titers (IU/ml)	95% CI	*P*
Age (years)			
<10 (109)	40.9±18.24	37.44-44.37	<0.001
≥10 (314)	48.8±11.26	47.55-50.05	
Acute Infection			
IgM-positive (368)	46.63±14.04	45.19-48.07	0.615
IgM-negative (55)	47.64±12.33	44.31-50.97	
Sex			
Males (157)	46.84±14.97	44.48-49.12	0.934
Females (266)	46.73±13.14	45.14-48.31	
Residence			
Urban and peri-urban (236)	49.21±13.92	47.42-50.99	<0.001
Rural (187)	43.68±13.10	41.79-45.57	
Mother's occupation			
Not employed (172)	44.86±13.79	42.78-46.93	0.018
Employed (251)	48.07±13.72	46.37-49.77	
Fever			
Yes (10)	36.62±11.78	28.19-45.06	0.018
No (413)	47.01±13.79	45.67-48.34	
Number of siblings			
<4 (120)	45.71±16.35	42.76-48.67	0.1636
≥4 (303)	47.18±12.69	45.74-48.62	

CI=Confidence interval

As in previous studies in Sub-Saharan Africa[16-19] and Turkey,[20] the prevalence of natural IgG seropositivity in this study was found to be high. The IgG seropositivity was found to increase by 4.5% per a year increase in age. Our results indicate that there is no advantage of vaccinating population >10 years in Mwanza or Tanzania in general. These findings reinforce the WHO recommendations[3] of establishing local data of rubella natural immunity before introducing vaccination program. Vaccinating people who are presumed immune is too costly for developing countries such as Tanzania and other countries in Sub-Saharan Africa. As in previous studies,[8,20-22] increase in age, absence of rashes, and low SES have been found to predict rubella IgG seropositivity indicating high transmission rates of rubella virus in developing countries.

Despite the fact that the ELISA test used in this study was not μ capture ELISA and positive samples were not confirmed by avidity test, the overall rate of acute rubella infection as defined by the presence of specific IgM antibodies was lower than 37% which was recently observed in Zimbabwe.[23] However, similar findings have been observed in previous studies in Africa.[18,24] Compared to the previous study conducted among pregnant women in the same setting by Mwambe *et al.*,[8] the observed IgM seropositivity rate in the present study is significantly high ($P < 0.001$). This could be explained by the fact that the population in Mwambe's study aged 16 years and above whereby in this study about one-third of the participants were under-fives. This suggests that protective immunity against rubella virus increases with age as observed in this study. Based on these data, there is high rubella transmission during childhood (<10 years) underscoring the significance of vaccination in this age group.

Acute rubella infection can be indicated by the presence of skin rashes. Although a nonspecific sign in developing countries, in this study, participants with rashes had 2.5 times higher risk of being IgM seropositive compared to those with no history of rashes.

CONCLUSIONS

There is high transmission rate of rubella virus infection in Mwanza, Tanzania. IgG seropositivity which is presumed immune is significantly associated with increase in age. There is no significant difference in IgG seropositivity between population aged between 10 and 15 years and those >15 years. There is a need for the vaccination campaign to target children up to 10 years of age coupled by screening and vaccinating all susceptible women >15 years of age as cost-effective campaign to prevent CRS in Tanzania.

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Conflicts of interest

There are no conflicts of interest.

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