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Research Article

Rubella Specific IgG and IgM Antibodies among Infants before Rubella Vaccination in Dar es Salaam, Tanzania: A Cross-Sectional Study

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#Equal contribution

Abstract

Background: Prevention of Rubella virus infection using rubella vaccine has been widely used in high-income countries contributing to the declining of congenital rubella syndrome. Before introduction of rubella vaccine in Tanzania October 2014, status of rubella specific antibodies in the infant was limited. This study was conducted to assess the rubella specific IgG and IgM antibodies among infants before receiving the vaccine.

Methods: A cross-sectional study was conducted in March 2015, at Ilala Municipality Dar es Salaam Tanzania among infants aged 9 months. A structured questionnaire was used for data collection. Dried blood spots were collected and tested for the presence of Rubella specific IgG and IgM antibodies using enzyme-linked immunosorbent Assay. The sero positivity of rubella antibodies was expressed as proportions.

Results: A total of 150 infants were recruited in the study, the majority 79 (52.7%) were males. A total of 104 (69.3%) were positive to IgG antibodies while 7 (4.7%) were positive IgM antibodies. Around 21 (20. 2%) of infants had a strong immunity to rubella with IgG titres ≥ 15 IU/ml. There were a significantly different proportion of IgG antibodies with infant location

Conclusion: There is substantial preclinical rubella infection in Dar es Salaam, before the age of rubella vaccination.

Keywords: Rubella; Infants; IgM; IgG; Antibodies

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Abbreviations

CRS: Congenital Rubella Syndrome;
DBS: Dry Blood Spot;
ELISA: Enzyme-Linked Immunosorbent Assay;
IgG: Immunoglobulin G;
IgM: Immunoglobulin M;
MUHAS: Muhimbili University of Health and Allied Sciences;
OD: Optical Density;
RCV: Rubella Contained Vaccine.

Introduction

Rubella infection is an acute, mild viral disease mainly affecting susceptible children and young adults worldwide. In most cases, the disease is self-limiting but may lead to congenital rubella infection with complications of Congenital Rubella Syndrome (CRS) [1,2]. When infection occurs in the first trimester, 90% of infants may present with CRS [3]. Rubella infection in some African countries is common among under-five years old children, suggesting the possibility of infection at a younger age [4,5]. Some studies have reported Rubella virus-specific IgM and IgG seroprevalence to increase with the increase of age [4,5]. A study done in Mwanza Tanzania reported seroprevalence of rubella specific IgG of 92.6%, among pregnant women signifying natural immunity [6].

In rubella, passive immunity results from the acquisition of specific IgG antibodies from a previously infected pregnant mother across the placenta or through breastfeeding which may persist for 4-6 months after birth [7]. Following rubella infection or immunization, IgM antibodies develop within 2 weeks and do not persist beyond 6 weeks. On the other hand, specific IgG antibodies develop and usually persist for life [8].

Prevention of Rubella virus infection using Rubella Containing Vaccine (RCV) has been widely used in high-income countries with a considerable decline of CRS [9-12]. The main aim of vaccination is to ensure women of childbearing age have protective immunity to Rubella virus. There is some variation among countries in terms of the concentration of IgG antibodies considered to be protective. However, the presence of rubella IgG antibodies ≥ 10 IU/ml is commonly considered to provide evidence of protection [13].

There was no routine rubella vaccination in Tanzania before October 2014, when the rubella vaccine was introduced country-wide.

The status of rubella specific antibodies in infant prior vaccination was not known. This study was conducted to assess the seroprevalence of rubella specific antibodies among infants at 9 months of age just before receiving routine immunization with RCV.

Materials and Methods

Study design, setting, and population

A descriptive cross-sectional study was conducted in March 2015 in Dar es Salaam, the largest city in Tanzania with an estimated population of around six million inhabitants. The study was conducted at three reproductive and child health clinics located at Bugruni, Ukonga and Tabata suburbs in Ilala District. The study population was infants at nine months of age attending reproductive and child health clinics clinic for routine immunization with RCV. The sample size was estimated using Kish Leslie formula at 95 % confidence interval (CI) considering 10% seroprevalence of rubella specific IgM antibody among under five in Mwanza Tanzania [14] and 5% margin of error.

Data and specimen collection

A structured questionnaire for socio-demographic information of each infant and mother pair was completed by the clinic Nurse. Dried Blood Spot (DBS) specimens were collected from a heel or finger prick by sterile single-use self-launching pediatric lancet onto each of the four 13-mm diameter circles on Schleicher & Schuell #903 filter paper. The DBS samples were dried on racks at room temperature, wrapped in clean wax paper and then placed in plastic zip-lock bags. Up to 15 wrapped filter paper samples were placed in a single bag, along with sachets of 1g silica gel desiccant (Minipax sorbent Packets; Technologies, Ink) then transported to the Immunology laboratory at Muhimbili University of Health and Allied Sciences (MUHAS) in Dar es Salaam for storage at -20oC until the time of testing.

Laboratory investigations and analysis

Rubella specific IgG and IgM antibodies were determined using commercially available enzyme-linked immunosorbent assay (ELISA) (virion/serion D-97076 Würzburg, Germany) according to the manufacturer's instructions. Briefly, the blood spots were punctured and put into microplate wells for overnight elution using sample buffer. The materials were pre-treated with rheumatoid factor-absorbent before IgM detection to remove the possibility of false positives.

The standard curve for both IgG and IgM established by the manufacturer was supplied with the ELISA kit having optical density (OD) readings of calibrators on the vertical (Y) axis and respective concentration in IU/ml on the horizontal (X) axis. The concentration of Rubella Specific IgG and IgM antibodies in a sample was determined by comparison of OD of each sample to the concentration of the calibrators of the standard curve. The intra-assay variations of OD were corrected by multiplying with the correction factor, calculated as the ratio of OD reference value to mean of standards of each reading plate according to the manufacturer's instructions.

Data analysis

Data were entered in excel software and analysed using Statistical Package for Social Sciences version 20.0. Continuous variables are presented as means and Standard deviation and categorical variables as numbers and proportions. Group differences were examined by using Student's t-test for continuous variables and chi2 tests for categorical variables. The antibody titre ≥10 IU/ml specific for rubella were considered positive and infants with IgG antibody levels of ≥10 IU/ml were considered to have rubella virus seroprotective titres [15].

Results

Social demographic and clinical characteristics

The study recruited 150, the majority 79 (52.7%) were males and 71(47.3%) were residents of Buguruni. The mean weight of infants was 8.29 ± 2.24 kg, great count (51.3%) weighted the mean. Only 6 (4.0%) reported a history of hospital admission (Table 1). No infant had neither history of blood transfusion nor clinical features associated with rubella infections, including CRS.A large proportion of the infants' mothers reported being married 112 (86.3%), unemployed 97(64.7%) and lower education level. The HIV serostatus was revealed in 140 of mothers, among them, 9 (6.4%) were HIV seropositive (Table 1).

Characteristic	Frequencies	Percent (%)
Sex of Infant		
Male	79	52.7
Female	71	47.3
Location		
Buguruni	73	48.7
Ukonga	30	20.0
Tabata	47	31.3
Weight of Infant (Kg)		
Mean ± SD	8.29 ±1.25	
Below mean (0 - 8.2)	77	51.3
Above mean (>8.29)	73	48.7
History of Hospitalization		
No	144	96.0
Yes	6	4.0
Mothers' marital status		
Married	125	83.3
Not married	25	16.7
Mothers' Education Level		
Lower Level	104	69.3
Higher Level	46	30.9
Mothers' Occupation		
Employed/Business	53	35.3
Unemployed	97	64.7
HIV-Mothers(n=140)		
Negative	131	93.6
Positive	9	6.4

Table 1: Characteristics of infants at nine months old and their mothers attending reproductive and child health clinic in Dar es Salaam, Tanzania.

Seroprevalence of rubella-specific IgG and IgM antibodies

A total of 104 (69.3%), 46(30.7%) and 7(4.7%) were found to be immune (IgG positive), non-immune (IgG-- negative and recently infection (IgM positive) respectively. Out of the 104 found immune with IgG titres ≥ 10 IU/ml, 21(20.2 %) had strong immunity with IgG titres ≥ 15 IU/ml (Table 2). The mean IgG titer was 11.47 ± 5.82; the majority of infants (52%) had IgG antibodies titres below the mean.

Results of sero-markers	Frequency (%)
IgG antibodies	
Positive	104 (69.3)
Negative	46 (30.7)
IgM antibodies	
Positive	7 (4.7)
Negative	143(95.3)
IgG Titres (IU/ml)	
Mean ± SE	11.47± 5.82
<10	46 (30.7)
10 - <15	83 (55.3)
≥ 15	21 (14.0)

Table 2: Rubella specific IgG and IgM among nine months aged infants before vaccination in Ilala Municipality, Dar es Salaam, Tanzania.

Characteristics of participants and Rubella Specific IgG antibodies

The proportion of positive IgG antibodies were significantly higher among infants from Tabata (89.4%) and Ukonga (80.0%) than Bugurni (52.1%) ($p<0.001$). The proportion differences of IgG antibodies observed among infant's sex mean weight, history of hospitalization and mothers' characteristics were not statistically significant (>0.05) (Table 3).

Variable	IgG antibodies		P-value
	Positive N (%)	Negative N (%)	
Sex			
Male	57 (72.2)	22 (27.8)	0.430
Female	47 (66.2)	24 (33.8)	0.415
Mean weight	8.35 ± 1.2	8.16 ± 1.3	
Location			
Bugruni	38 (52.1)	35 (47.9)	< 0.001
Ukonga	24 (80.0)	6 (20.0)	
Tabata	42 (89.4)	5 (10.6)	
History of Hospitalization			
No	99 (68.8)	45 (31.2)	0.448
Yes	5 (83.3)	1 (16.7)	
Mothers' education level			
Low	35 (74.5)	12 (25.5)	0.357
High	69 (67.0)	34 (33.0)	
Mothers' marital status			
Not married	20 (80.0)	5 (20.0)	0.205
Married	84 (67.2	41 (32.8)	
Mothers' occupation			
Unemployed	69 (71.1)	28 (28.9)	0.518
Employed/Business	35 (66.0)	18 (34.0)	
Mothers' HIV status			
Negative	89 (67.9)	42 (32.1)	0.188
Positive	8 (88.9)	1 (11.1)	

Table 3: Descriptive characteristic of participants and the status of rubella specific IgG antibodies.

Discussion

To the best of our knowledge, this is the first study in Tanzania to investigate the status of rubella IgM and IgG antibodies at the age of nine months of unvaccinated infants. Determination of IgG and IgM antibodies helps to reveal the proportion of infants with a protective level of immunity, susceptible to infection and those with recent infection. This study observed over two-third of infants having a protective level of natural immunity at nine months of age. Also, the study revealed the 5% of infants with evidence of recent exposure to rubella infection based on rubella specific IgM antibodies.

Existence of rubella IgM antibodies is evidence of natural infection; therefore, our findings suggested that some infants get Rubella virus infection before nine months, the age set for rubella vaccination in Tanzania. However, susceptibility to rubella virus infection before the age of vaccination is associated with the location of residence. We observed that infants from Bugruni were more susceptible than the other two locations based on a non-protective level of immunity, with a risk difference of 28-37%. The IgM seroprevalence found in this study is higher compared to findings from Sudan, where at 12 months of age, 2% of children had rubella IgM antibodies [1]. Likewise, our findings are comparable to the study in Mwanza, Tanzania among children aged 0-5 years, which reported an increase in rubella specific IgM seroprevalence significantly as the age increased [5].

The finding in this study that over two-third of infants were positive to rubella specific IgG antibodies at 9 months, suggests early sub-clinical rubella infection after birth which builds observed high level of natural immunity. Although passively transmitted maternal antibodies to rubella may contribute, the previous report indicates that approximately 5% of infants may still have maternal antibodies at 9 to 12 months [16]. The absence of clinical features of rubella infection among participants in this study increase evidence for the occurrence of subclinical infection among infants before nine months [2].

Routine rubella vaccination was introduced in Tanzania in 2014 for infants at nine months in a combination with Measles vaccine. The findings in our study that over two-third of infants had protective immunity is an indication that at nine-month might not be the appropriate age for the rubella vaccine in our setting. The age for rubella vaccination may be different depending on local established data of rubella natural immunity [17]. in most developed countries, RCV is given to children at 12 months of age because passively acquired maternal antibodies have usually disappeared by that age [8]. Our finding of a significant level of serological markers of rubella infection at the age of 9 months before vaccination is not surprising as rubella infection has been reported being common in many resource-constrained countries without routine vaccination where outbreaks may occur without clinical recognition [2,13]. In most cases, the disease is self-limiting and rarely causes complications in children.

With this evidence of early infection before the age of rubella vaccination in our setting, there is still an increased risk of transmission of the virus to susceptible pregnant women in the community that increases the chance of CRS. These findings warrant more investigation to determine the appropriate age for initiating Rubella vaccination in our setting.

This study was conducted at a reproductive and child health clinic. Normally, sick infants attend hospitals instead of reproductive and

child health clinics. There is a possibility of missing infants with acute rubella infection at nine months old.

Conclusion

There is serological evidence of substantial preclinical rubella infection with two-third of infants having natural immunity at nine months of age. The findings warrant more investigations to determine the most appropriate age for giving the first rubella vaccination

Declarations

Ethics approval and consent to participate

Ethical clearance was obtained from the Senate Research and Publications Committee of the Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania. Administrative permission for the study was granted by the Ilala Municipal Health authorities in Dar es Salaam city. Written informed consent for infants' participation in the study was obtained from parents or guardians before enrolment into the study.

Availability of data and material

All relevant data generated and analyzed during this study are available from the corresponding author on reasonable request.

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Author's Contribution

MI, JM, FM, and FSM participated in the conception and designing of the study. MI participated in data collection while MI and MM performed the serological tests. MI, FM, MM, FSM analyzed, interpreted the data and participated in the writing of the manuscript. All authors read and approved the final version of the manuscript.

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