

Seroprevalence of Rubella IgG in Women of Reproductive Age Group in a Tertiary Care Teaching Hospital

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Abstract

Rubella is a highly contagious infection caused by the rubella virus. Mothers who develop rubella early in pregnancy have a 90% chance of transmitting the infection to their unborn babies. Adverse effects on the fetus include stillbirth and congenital rubella syndrome. Pregnant women are not regularly screened for rubella antibodies in government hospitals in Kerala. Therefore, to raise awareness of healthcare providers, it is necessary to collect epidemiological data on the seroprevalence of rubella in this vulnerable group. Several sociodemographic variables as potential predictors of immunity to rubella were also analyzed. A cross-sectional descriptive study was conducted at Govt TD Medical College in Alappuzha, Kerala, of 604 women of childbearing potential who attended the Out patient department of the Obstetrics and gynecology division for the year from June 2016 to June 2017. Rubella-specific IgG (Quantitative) ELISA was done on patients after obtaining informed consent and filling out a questionnaire through direct interview. The test sera were considered seropositive (>15 IU/ml), seronegative (<13 IU/ml), or intermediate (13 -15 IU/ml) as per the manufacturer's instructions. Rubella seroprevalence in the study group was found to be 73.3%. Around 26.65% were nonimmune to rubella infection. About 27.4% of antenatal cases in the present study were susceptible to rubella. The primigravidae had lower seroprevalence(28.5%) than multigravidae. The percentage of seropositivity was found to increase with age. Our observations show that women of childbearing age are highly susceptible to rubella. High seroprevalence without regular childhood vaccination indicates continued infection transmission of the rubella virus in the community. Hence there is a need for proper sero surveillance in this group who has not been vaccinated, before conception to eradicate CRS and Rubella.

Keywords: Rubella, Congenital Rubella Syndrome, Seroprevalence, ELISA

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INTRODUCTION

Rubella, first reported in the mid-1700s, is a mild self-limiting disease in children characterized by low-grade fever, lymphadenopathy, and measles-like rash. Friedrich Hoffmann made the first clinical description of rubella in 1740, confirmed by de Bergen in 1752 and Orlow in 1758.¹ The rubella virus received little attention after its recognition in 1881 until its association with birth defects was recognized in 1941 by the Australian ophthalmologist, N McAlister Gregg. In pregnant women, infection during the first 16 weeks of pregnancy can lead to miscarriage, stillbirth, or a baby born with a birth defect known as congenital rubella syndrome (CRS).²⁻⁴ The highest risk of CRS is found in countries with high rates of rubella susceptibility in women of childbearing age and globally where approximately 110,000 babies are born with CRS each year.⁴ In a study conducted by the World Health Organization (WHO), in developing countries, 10-25% of women tested seronegative.⁵ Since up to 60% of rubella infections are subclinical, susceptibility or immunity to rubella can only be determined by serological testing^{6,7}. Data from Vellore showed that 9.8% of children in India with the suspected congenital disease had congenital rubella. Therefore, it is important to know the proportion of the adolescent population susceptible to rubella to know the risk of adverse pregnancy outcomes.⁸

Serological testing such as ELISA is an important tool to measure rubella-specific IgG and IgM, it is considered a convenient, sensitive, and accurate diagnostic method. Since it is a preventable disease by vaccines, preventing congenital rubella is the ultimate goal of any country in the forefront of rubella immunization.

The Aim of the Study was

1. To determine the seroprevalence of rubella antibodies in the childbearing age group
2. To identify various sociodemographic variables as potential predictors of rubella immunity

MATERIALS AND METHODS

This descriptive cross-sectional study included healthy pregnant and non-pregnant women enrolled in the Department of Obstetrics

and Gynecology and was conducted at Govt TD Medical College, Alappuzha, Kerala from June 2016 to June 2017. The study commenced after approval by the ethical committee and state board research committee of our institute.

After informed consent was received, a questionnaire form was completed for each participant through a face-to-face interview. Data collected included age, marital status, education level, occupation, place of residence, income, pregnancy status, trimester, birth, history of birth defects, abortion, etc. Approximately 5 ml of blood was obtained by venipuncture under aseptic precautions, serum was separated and stored in two aliquots, one at 4°C and the other at 20°C. Solid ELISA Kit Rubella IgG (Quantitative) was purchased from Chemux BioScience, Inc., CA with relative sensitivity and specificity of 100%. IgG quantitation results are expressed in International Units (IU), with calibration performed against the reference standards of 0, 15, 30, and 100 IU/ml according to the manufacturer's instructions given in the leaflet, using standard procedures performed by a qualified technician under the supervision of a microbiologist. Manufacturer reference values for seropositive results were given as >15 IU/ml, seronegative if the concentration was <13 IU/ml. An IgG value between 13 -15 IU/ml was considered equivocal. Internal positive controls for rubella IgG antibodies were included in each ELISA plate in addition to the controls provided by the manufacturer to monitor test performance. To obtain valid results, the following validation requirements must be met: Absorbance of blank 0.25. Test results are considered invalid if the above validation requirements are not met and the tests are repeated.

Statistical Analysis

Data were imported into Microsoft Excel and statistical analysis was performed using SPSS20.0. Qualitative variables are expressed as

Table 1. Rubella IgG seroprevalence in the study group

	IgG positive	IgG negative	Total
Pregnant	419 (72.6%)	158(27.4%)	577
Nonpregnant	24 (88.9%)	3 (11.1%)	27
Total	443(73.3%)	161(26.6%)	604

Table 2. Seroprevalence of rubella according to their reproductive characteristics

Variables		Titre Category		P-value
		Susceptible	Protective	
		(<15 IU/ml)	(>15 IU/ml)	
Age in years	18-28 (n=442)	27.1%	72.9%	0.906
	29-38 (n=142)	25.4%	74.6%	
	39-48 (n=20)	25%	75%	
History of Rubella	Yes (n=43)	0%	100%	<0.0001
	No (n=561)	28.7%	71.3%	
Abortion	Yes (n=90)	24.9%	75.1%	0.02
	No (n=514)	36.7%	63.3%	
Trimester	1 st (n=249)	29.3%	70.7%	0.657
	2 nd (n=191)	26.2%	73.8%	
	3 rd (n=137)	25.5%	74.5%	
Congenital anomalies	Yes (n=4)	50%	50%	0.289
	No (n=600)	26.5%	73.5%	
Infertility	Yes (n=6)	50%	50%	0.194
	No (n= 598)	26.4%	73.6%	
Primi gravida	n = 239	28.5%	71.5%	0.628
Multi gravida	n = 338	26.6%	73.4%	

frequency and percentage. Quantitative variables were expressed as mean and standard deviation and compared using the chi-square test. P-value < 0.05 was considered to be statistically significant.

RESULTS

The study recruited 604 women aged 18 – 48 years. The mean age of the study group was 26.2 ± 5.27 years old. The overall rate of rubella seropositivity was 73.3%. The serum sensitivities to Rubella IgG in pregnant (n = 577) and nonpregnant women (n = 27) were 419 (69.37%) and 24 (3.97%) respectively (Table 1) Accordingly, 26.6% of the study population was found to be negative for rubella indicating high susceptibility and the need for vaccination. Various patient factors such as age, marital status, education, occupation, place of residence, income, pregnancy status, trimester, childbirth, history of rubella, immunization, birth defects, and abortion were queried based on immunity to rubella.

Although the titer has no significant relation with age, the highest seropositivity was seen among the age group 39-48 years. The mean titer value was 37.57±16.06. The antibody level in age-wise data shows no change, indicating that rubella is endemic in the community (Table 2).

Among the antenatal cases 58.57%

were multigravida and 41.2% were primigravida. Susceptibility to rubella was found to be 26.6% and 28.5% in multi and primigravida groups respectively. No significant relation was seen between rubella IgG titer value with gravidity and parity (p=>0.05), while the risk of contracting rubella was slightly more in the first trimester than in others. This also was not found to be statistically significant. Nearly half of the infertile group (n=6) in the study were seronegative. Four women gave a history of children born with congenital anomalies(minor) not related to congenital rubella. Two among them were seropositive (Table 2).

No significant relation was seen between seropositivity and any of the variables studied except the history of rubella and abortion. There was a significant association (P<0.0001) between IgG seropositivity and the history of rubella (Table 2). Similarly, the association between abortion and seropositivity was also found to be statistically significant (Table 2).

Various sociodemographic variables were studied as a function of immunity to rubella (Table 3). The seropositivity was higher in the unemployed (74.2%) than in the employed group (67.1%). Impaired immune status in the lower socioeconomic group was also observed (69.4%). But these differences were not significant. Three

Table 3. Socio-demographic characteristics of enrolled participants in the study (n=604)

Variables		IgG sero-positivity	P-value
Residency	Rural	336[73.7%]	0.74
	Urban	107[72.3%]	
Education	Primary	151[71.6%]	0.468
	Higher	292[74.3%]	
Occupation	Employed	47[67.1%]	0.212
	Unemployed	396[74.2%]	
Income	Low	184[69.4%]	0.055
	Middle	259[76.4%]	
Marriage	Yes	442[73.3%]	0.546
	No	1[100%]	
Crowding index	>3	382[73.3%]	0.974
	<3	61[73.5%]	
Immunization	Unknown	440[73.2%]	0.295
	Known	3[100%]	

women in the infertile category who gave a history of immunization against rubella as a part of infertility workup had significant titers.

DISCUSSION

Rubella is the mildest of common viral exanthems. Many cases go undetected and unreported, as up to 60% of rubella cases may have no typical symptoms and therefore go undetected. Seroprevalence surveys play a decisive role in documenting the widespread circulation of the rubella virus.⁴

There are no large pan-Indian studies assessing the susceptibility of women of childbearing age to rubella infection. Most published studies focus on small heterogeneous groups of target groups.^{9,11} After the introduction of the MMR vaccine, the disease moved from children to young adults.

In our study among the reproductive age group, 73.3% have protective levels of rubella IgG; thus making 26.6% susceptible to rubella infection. The antenatal population formed 95% of the study group. About 27.4% of antenatal cases in the present study are nonimmune to rubella. This shows that they may acquire the infection anytime during the antenatal period. Another study by Tripathy SR et al. show that 29.46% of antenatal cases were susceptible to infection.¹⁰

The prevalence of rubella IgG in our study was relatively lower than that seen in Kerala and other Indian states.¹¹⁻¹⁴ There is considerable variation in the susceptibility to rubella in antenatal cases in different geographical regions in India (Table 4). Most of the studies mentioned here were done before the availability of rubella vaccines in children in India. Global studies also show a seropositivity rate of 83.3% by Meng Q et al.¹⁵ 84.7% by Zahir H et al.¹⁶

This study found that age-related seropositivity for rubella increase with age. (Table 2). Studies conducted in Gujarat, Amritsar, and Puducherry also brought out similar results. The incidence of rubella increases with age in our study suggesting that rubella is endemic. Similar studies in Sri Lanka and Iraq also showed an increase in seropositivity in the age group of 25-29 years.^{17,18} The higher seroprevalence in multigravida is consistent with the fact that the risk of acquiring rubella decreases with increasing age and parity.¹⁹

No relationship was observed between rubella immunity and parity in our study. The IgG titers among different trimesters also don't show a significant difference. These findings corroborate with a similar study done in North Kerala and Tirupathi.^{11,20}

Another important finding in our study was the lower seroprevalence of rubella in primigravida (Table 2). This low prevalence makes infants more susceptible to infections and thus at risk for CRS, which is consistent with research that shows a higher incidence of congenital rubella in neonates.²¹

The prevalence of rubella seroprevalence was slightly higher in women from lower socioeconomic classes (73.7%), although not statistically significant. Similar trends were reported by Yadav and Jubaida^{7,22} One of the likely reasons for the higher seroprevalence in this group could be the close contact and crowded living conditions.

In the study by Gandhoke et al.²³ in Delhi, 5022 samples from pregnant women were evaluated; The seroprevalence of rubella was higher in women with a poor obstetric history (87%) than in those with a normal pregnancy outcome (83%). In our study, a higher rate of seropositivity (63.3%) was observed in women

Table 4. Data on non-immune rubella status in pregnant women from different geographical regions of India

No.	Author(Year of publication)	Place	No. of pregnant women	Sero-negativity
1.	Singla et al. (2004)	Amritsar	233	32.8%
2.	Padmaja et al. (2010)	Kerala	485	34.3%
3.	Vinod Raveendran et al. (2012)	Puducherry	182	12%
4.	Gupta et al. (2015)	Lucknow	152	11.8%
5.	Shilpi Gupta et al. (2015)	Bijapur	75	74.7%
6.	Thayyil J et al. (2016)	Kerala(Kozhikode)	70	5.7%
7.	Priyanka D et al. (2016)	Tamil Nadu	100	10%
8.	Kori et al. (2017)	Jabalpur	369	38.2%
9.	Saibal Adhya et al. (2019)	Delhi, Pune	600	10%
10.	Dr Nita Fazil et al. (2020)	Kerala (kochi)	200	19.5%
11.	Shahapur et al. (2020)	Vijayapur	125	60.8%
12.	Himani Bharadwaj Pandya et al. (2021)	Gujarat	90	11.1%
13.	Present study	Kerala (Alappuzha)	577	27.4%

with an adverse pregnancy outcome suggesting that rubella may be the cause of recurrent miscarriage in women. Similar findings were reported from North Kerala (100%), Punjab (73.2%), and Bangladesh (86.8%).^{11,24,25}

The majority of our participants were not aware of the nature of the disease. Forty-three among them who gave a history of acquiring the disease in early adulthood had protective IgG titers (100%) and hence the association was statistically significant ($p < 0.0001$).

CRS is a common cause of birth defects in countries where rubella is endemic and vaccination against the disease is not common. The exact epidemiology or actual burden of rubella and CRS in India is insufficient due to limited data on disease surveillance and reporting system. The risk of congenital malformations is 90% if infection occurs before 11 weeks, 33% at 11-12 weeks, 11% at 13-14 weeks, 24% at 15-16 weeks, and 0% after 16 weeks.²⁶

Rubella is the leading cause of vaccine-preventable birth defects.²⁷ It is estimated that in 2010 about 103,000 children with CRS were born worldwide, of which around 47,000 children, i.e. 46% were in the South-East Asia region (SEAR).²⁸ The World Health Organization (WHO) has set a goal of improving the seroprevalence of rubella-specific IgG antibodies to 95% and limiting the seroprevalence of pregnant women worldwide

to 5% or less by 2020.²⁹ A recent meta-analysis of the global prevalence of rubella-specific IgG seroprevalence among women of childbearing age (WCBA) covering five different WHO regions (Europe, Africa, and Africa). , Americas, Middle East and Asia Southeast Asia) shows that all studies from Southeast Asia show a sound level of >10%.³⁰ Measles, mumps, and rubella vaccine (MMR) has been in India since 2000 but is managed only by the private sector where, as few as 11% of children receive their immunisations.³¹ Nearly 16% of children in the state of Kerala received the vaccine from private sector. Various mathematical and epidemiological models have examined childhood rubella vaccination programs and have recommended that at least 80% coverage is required to prevent a long-term increase in the incidence of CRS. Analysis by Winter et al showed that low vaccination rates increase the incidence of CRS by about 5% compared with no vaccination.³²

India has the largest burden, with an estimated 40000 CRS cases.³³ The facility-based surveillance for CRS revealed that about one-fifth of the suspected CRS patients during 2016-18 had evidence of laboratory confirmed rubella infection indicating continued transmission of rubella in India.³⁴ Another study conducted in Cameroon had hypothesized that the increased seroprevalence in the absence of adequate immunization could be attributed to the circulating wild strain of the Rubella virus.³⁵

Therefore India has set a target of eliminating Measles and Rubella / Congenital Rubella Syndrome (CRS) by 2023. To achieve this goal, India conducted a phased national SIA from 2017 to 2019, using MRCVs targeting children aged 9 months to less than 15 years old in each district through routine and/or supplementary immunization activities (SIAs).^{36,37} These SIAs were implemented in all Indian states except Delhi and West Bengal with high coverage reported.³⁸ In accordance with the National Strategic Plan for Achieving and Sustaining Measles and Rubella Elimination in India, nearly 324 million children in India received the MR immunisation between 2017 and 2020.³⁹ Following these SIAs, MRCV was introduced in the routine childhood immunization, with the primary dose given at the age of 9-12 months and second dose at the age of 16-24 months.⁴⁰

CONCLUSION

To our knowledge, this is the first study in South Kerala to provide data on the seroprevalence of rubella in women of reproductive age. Our hospital is the only tertiary referral care institute in Alappuzha, Kerala. We cater to all classes of the population since the number of private hospitals is much less than that compared to other districts. So we believe that the study group is a good representative of the population of Alappuzha. A serological study conducted at six sentinel sites in India in 2019-20 found that more than 80% of pregnant women were seropositive for rubella and about 17% were susceptible to rubella infections. In our study, a significant proportion of the study population is at risk of developing rubella, which may increase the incidence of CRS in children. IgG seroprevalence can be used as an indicator of rubella elimination in the country. Hence the recommendation is to include screening for rubella susceptibility by serology for all women of childbearing age at their first preconception counseling visit to reduce incidence of congenital rubella syndrome. Vaccination of seronegative women with MR vaccine and use of MMR in national immunization programme will help in elimination of the disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

AM and LK conceived and planned the project. AM, SD and AA conducted interviews and filled the questionnaire. AJ conducted statistical analyses. AM and AJ analyzed the data. AM wrote the manuscript. All authors read and approved the final manuscript for publication.

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DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study was approved by the Institutional Ethical Committee and the State Board of Medical Research (SBMR) with reference number EC01/2016.

INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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