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Prevalence of Seronegativity for Rubella IgG Antibodies in Women Between 15-25 Years of Age: Prospective Observational Study

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ABSTRACT

Rubella being a mild infection, rarely causes any complications in childhood, will cause adverse effects during pregnancy ranging from miscarriage to a child born with congenital rubella syndrome. Prevalence of seronegativity for rubella IgG antibodies in women between 15-25 years of age-a prospective observational study. A prospective study was conducted in the department of obstetrics and gynecology at PGIMER, Chandigarh. A total of 200 women of between 15-25 years who attended gynecology OPD for other reasons selected for the study. After obtaining informed consent, their blood samples were collected. The IgG antibody in the serum was estimated by ELISA. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 22.0. Based on the test results, 166(83%) were immune 33 (16.5%) were not immune and 1 (0.5%) had indeterminate result. Evaluation of susceptibility of women in reproductive age to rubella infection is important to setup a strategy for preventing antenatal rubella through vaccination of non-immune women throughout the country. Through the present study, it can be concluded that screening and vaccination should be targeted at population groups who are at risk including adolescents and women of childbearing age.

INTRODUCTION

Rubella is usually a mild self-limiting illness in adults and children, presenting with low grade fever, maculopapular rash and lymphadenopathy^[1]. It spreads through acquired and vertical transmission. The infectious period is from 7 days prior to 5-7 days after the onset of rash. It is of high public health importance due to teratogenic effects of congenital rubella syndrome(CRS). In pregnant women, Infection during the first 16 weeks of pregnancy can result in miscarriage, Fetal growth restriction, fetal death or an infant born with congenital birth defects known as congenital rubella syndrome^[2]. Immunity is developed as a result of either exposure to infection or by vaccination. A substantial number of women reach childbearing age without acquiring natural immunity to rubella and constitute the vulnerable group(>5%)^[3]. In case of maternal infection before 11 weeks, the risk of congenital defects is reported to be 90%, 33% at 11-12 weeks, 11% at 13-14 weeks, 0% after 16 weeks^[4]. Up to 60% of rubella cases may not present with a rash and hence many cases are not detected or reported because of subclinical nature (50%). Serological surveillance is an important tool for the evaluation of vaccination programmes as it monitors immunity in the population, thus providing information with which further control measures can be done and avoids the limitations of passive disease reporting systems^[5]. This is one of the entry points for CRS surveillance, whose gaps limit the ability to monitor progress towards elimination of CRS in future^[6]. Seroprvalence surveys have documented widespread circulation of the rubella virus in all parts of the world. In 2008, infants born with CRS exceeded 110 000, with the highest CRS burden in South East Asia (48%) and African (38%) Regions^[7]. In 2011, the World Health Organization (WHO) updated guidance on the preferred strategy for introduction of rubella-containing vaccine (RCV) into national routine immunization schedules, including an initial vaccination campaign usually targeting children aged 9 months-15 years. The Global Vaccine Action Plan endorsed by the World Health Assembly in 2012 and the Global Measles and Rubella Strategic Plan (2012-2020) published by Measles and Rubella Initiative partners in 2012 both include goals to eliminate rubella and CRS in at least two WHO regions by 2015 and at least five WHO regions by 2020. This report updates a previous report and summarizes global progress toward rubella and CRS control and elimination during 2000-2014^[8].

Aims and Objectives:

Aims: Prevalence of seronegativity for rubella IgG antibodies in women between 15-25 years of age-a prospective observational study.

Objectives:

Primary Objective: To assess serum anti-rubella antibody positivity and immunity level in age groups between 15-25 years attending gynae outpatient clinic.

Secondary Objectives: Acceptance of vaccination in seronegative women who are eligible for immunization against rubella.

MATERIALS AND METHODS

Study Type: Prospective observational study.

Study Period: 18 months.

Study Place: Nehru Hospital Gynaecology outpatient clinic.

Sample Size: Women between 15-25 years of age was enrolled for the study, during the study period. As per hospital records, 200 women between 15-25 years who attended Gynecology OPD for other reasons will be selected for the study. The proposed sample size will be approximately 200.

Inclusion Criteria:

- Age between 15-25 years.
- Willing to participate and providing written informed consent.

Exclusion Criteria:

- Patients not willing to give informed consent.
- Pregnant women.

Sample Collection

Blood Sample: Approximately 3-4ml of venous blood was collected from each subject aseptically by trained health personnel in a sterile vacutainer.

Rubella IgG Detection: The serum samples after centrifugation were stored in -20 C deep freezer. The kit used in our study was Dialab ELISA kit (Neudorf Austria) for rubella IgG detection. The sensitivity and specificity of this test were 96.4% (87.7-99.6%) and >99.9% (90.5-100%) respectively.

Principle of the Test: The rubella IgG ELISA test kit was based on quantitative and qualitative detection of IgG antibodies to rubella in the test serum. The micro well plate was coated with rubella antigen. The specimens were added to the micro wells and incubated. The samples containing anti rubella Ig antibodies bound to antigen coated on micro wells and form immobile Ab-Ag complexes. Substrate was then added and incubated to produce blue colour. Following this a stop solution containing sulphuric acid is added to stop the reaction producing colour change. The colour intensity corresponded to the amount of rubella antibodies present in the specimen which is read by micro plate reader at 450nm.

Interpretation of Results Quantitative Analysis: For equivocal results, the specimen were retested with the same serum and kit. In case of samples giving equivocal results, the specimen were retested in duplicate and interrelated according to the results obtained.

Results	Quantitative(concentration)
Negative	<8 IU/ml
Positive	≥11 IU/ml
Equivocal	≥8-<11IU/ml

Statistical Analysis Plan: Data was analyzed using SPSS software version 22.0. Normalcy of the data was checked by applying Kolmogorov-Simrnov Test. For continuous parametric variables, if required was analyzed by applying student T test/analysis of variance (ANOVA) test. Categorical data like socioeconomic class, no of abortions, history of CRS, h/o immunization with rubella vaccine, fetal complications etc. Rubella seronegativity/seropositivity was analyzed by regression applied to calculate Odds Ratio(OR) of having rubella seronegativity if a patient is selected independent variable by controlling other independent variables i.e. prior rubella infection. Data will be expressed in frequency, percentage and median as per variability of data. Data will also be depicted graphically using bar diagrams, pie charts, box plots as well as in tabulation. Two tailed P value 0.05 is considered statistically significant with 95% confidence interval.

Ethical Justification: According to the guidelines set by Indian council of medical Research (ICMR) [1994] and Helsinki declaration(modified 2000),the followings was adhered in all patients enrolled in the study: As it is an observational study, it won't alter the basic treatment plan or management steps of the patient at all, during the study period. The study was done strictly as per ICMR guidelines. The patients involved in the project was informed participants. Each patient (or and relatives) was adequately informed of the aims, methods and the anticipated benefits. Every precaution was taken to respect the privacy of the patient and the confidentiality of the patient's information. The patient was given the right to abstain from participation in the study or to withdraw consent to participate at any time of the study without reprisal. Total integrity and impartiality was maintained throughout the study. Due care and caution was taken at all stages of the research to ensure that the patient is put to minimum risk, suffer from no irreversible adverse effects and, generally, benefit from and by the research and the principle of non exploitation shall be followed. The study was conducted in an accountable and transparent manner. An informed written consent was obtained from all women participating in this study or their relatives and clearance will be obtained from ethics committee of this institute before starting the study. Women with seronegative status got additional benefit of vaccination.

RESULTS AND DISCUSSIONS

In this study 200 non pregnant women who attended gynecology OPD at PGIMER, Chandigarh for any complaints were screened for rubella IgG antibodies using ELISA Kits from July 2018 to December 2019.The main aim of our study was to find out the prevalence of susceptible women in these age group. The collected blood samples were processed in the department of virology, PGIMER Chandigarh using commercially available IgG ELISA kits (Euroimmun) as per the manufacturer instructions.

Table 1: Distribution of Women Based on Test Results of Rubella IgG Antibodies

Total(n)	Seropositive(n)	Seronegative(n)	Equivocal(n)
200	166(83%)	33(16.5%)	1(0.5%)

Prevalence of Rubella IgG in the Study Population:

Out of the 200 women screened, rubella IgG seronegativity was found in 33/200 women. Only one sample remained equivocal i.e.9.9 IU/ml. This sample was tested again and each time equivocal results were obtained. The equivocal sample result has been excluded from statistical analysis.

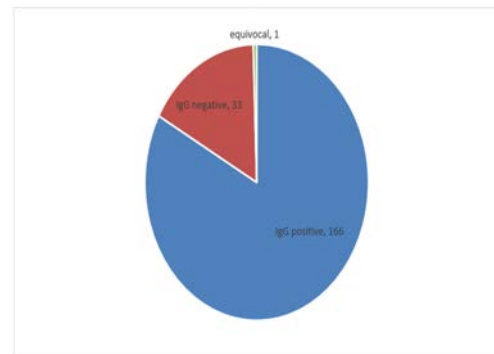


Fig. 1: Seroprvalence of Rubella According to the Test Results

Table 2: Distribution of Women Based on State of Residency

Address	Total(n=200)	IgG positive	IgG negative	P value
Chandigarh	45(22.6%)	36/45(80%)	9/45(20%)	0.53
Punjab	81(40.7%)	64/81(79%)	17/81(20.9%)	
Haryana	32(16.1%)	30/32(93.7%)	2/32(6.4%)	
Himachal	19(9.5%)	15/19(78.9%)	4/19(21%)	
Jammu and Kashmir	4(2%)	4/4(100%)	0/4(0%)	
Uttarpradesh	17(8.5%)	16/17(94.1%)	1/17(5.8%)	
Others	2(1%)	1/2(50%)	0/2(0%)	

Rubella seroprvalence in Reference to a State of Residency:

Among the subjects recruited for the study highest were from Punjab 81(40.7%) followed by Chandigarh 45(22.6%) with seronegativity of 17 (20.9%) and 9(20%) respectively. The highest susceptible group were from Huamachil(21%) followed by Punjab (20.9%) and Chandigarh (20%). All subjects from Jammu and Kashmir were seropositive. The difference is not statistically significant (p value-0.53).

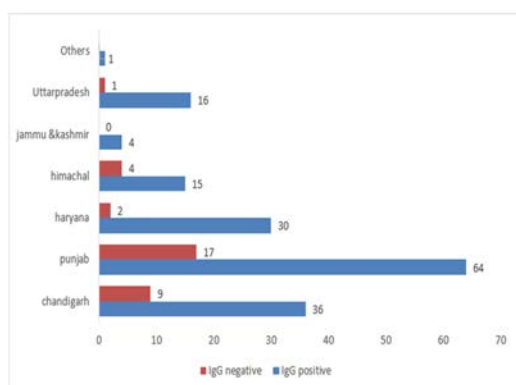


Fig. 2: Distribution of Women Based on State of Residency

Rubella Seronegativity in Reference to Area of Residency(Urban/Rural): >half of the total study population 113 (56.8%) belonged to the rural areas. Rubella IgG seronegativity was higher in women belonging to urban area 18 (54.5%) as compared to those from rural areas 15 (45.5%) though the result was not statistically significant(p=0.22).

Age Related Distribution of Rubella Seronegativity: Majority of women belonged to age of 21-25 years is 133 (66.3%). The median age of study population was 19 years. The prevalence of rubella IgG seronegativity in women of 15-20 years was 8/67 (11.9%) while 25/133 (18.9%) seronegative women belonged to 21-25 years. The seroprvalence of rubella was not statistically significant between the groups (p value=0.14)

Rubella Seroprvalence Based on Chief Complaints: Majority of the women who came to gynae opd presented with the chief complaints of irregular cycles (46.7%) out of which 20.2% were seronegative. Among the women with complaints of infertility (12.6%) and preconception counselling(4.5%) where seronegative respectively. Hence, these people who are the potential candidate for pregnancy in near future and susceptible to rubella infection.

Rubella Seronegativity Based on Parity and Obstetric History: Out of 200 women 83.5% were nulligravida with seronegativity of 16.1%. of 6% of recurrent abortion group 16.6% were seronegative and susceptible. Among 10.5% of primi/multi, 19% were seronegative. Hence, from the study not much significance between parity was found and it was not statistically significant. Only 6% of seronegativity is being contributed by recurrent abortion group. The women grouped in primipara/multipara also includes previous one abortions or with previous normal term deliveries or preterm deliveries.

Table 3: Distribution as Per Socio Economic Status

Socio economic status	Total(n=200)	IgG positive	IgG negative	P Value
Higher	13(6%)	12(92.3%)	0(0%)	0.223
Lower	187(94%)	154(82.35%)	33(17.6%)	

Rubella Seronegativity Based on Socioeconomic Status: Socio economic status was assigned based on the kuppuswamy scale which included educational qualification, occupation and family income. They were given scores and grouped accordingly. The upper and upper middle were grouped as higher socio economic group and the rest from lower middle to lower groups were listed under lower socio economic group. The seroprvalence of rubella IgG positivity in lower socioeconomic status was found to be 154/187 (82.35%) and higher socioeconomic status was (92.3%). Rubella seronegativity was higher in women belonged to lower socio economic status as compared to higher socio economic status (17.64% vs 0%). the difference was not statistically significant(p value=0.1).

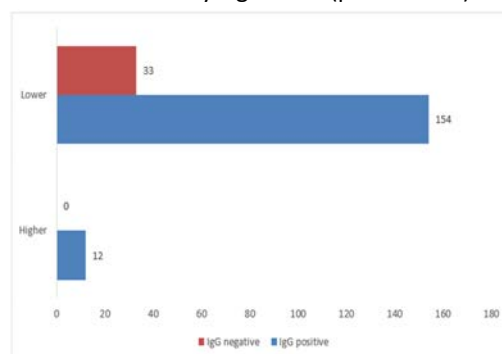


Fig. 3: Distribution as Per Socio-Economic Status

Table 4: Distribution as Per Previous CMF Babies in Married Women

Previous CMF babies	Total(n=81)	IgG positive	IgG negative	P Value
YES	3(3.7%)	3(100%)	0(0%)	0.7
NO	76(93.82%)	62(81.5%)	14(17.72%)	
Stillbirth	2(2.46%)	2(100%)	0(0%)	

Rubella Seronegativity and Previous History of Congenital Malformation: In the study, a total of 3 women had previous history of a congenitally malformed fetus. Out of these, all three were found to be seropositive. Among 3 CMF two were of congenital heart disease and one neural tube defect. The difference is not statistically significant.

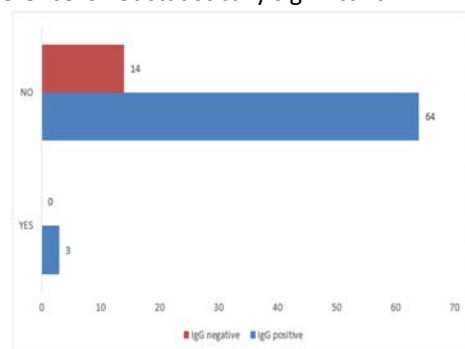


Fig. 4: Distribution Based on Previous History of CMF in Married Women

Rubella Seronegativity and Prior TORCH Screening:

Only 4 out of 81 women were screened for TORCH infection for previous history of recurrent abortions. Out of this 4 women, one was found to be seronegative. Among the 95% of married women who never underwent screening, 16.8% were susceptible. The results of this study matched 80% (3/4) with the previous screening reports.

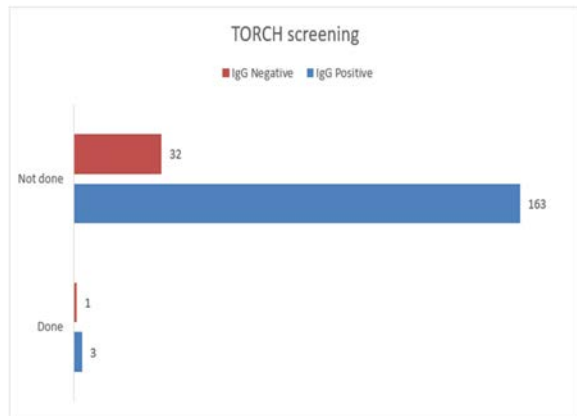


Fig. 5: Distribution as Per Screening by TORCH Test

Rubella seronegativity in reference to H/O vaccination Among 200 women 85.4% gives proper history of vaccination, of which 16.4% were susceptible. Among 16.9% of women who does not gave proper H/O vaccination, 17.8% were seronegative and it was not statistically significant.

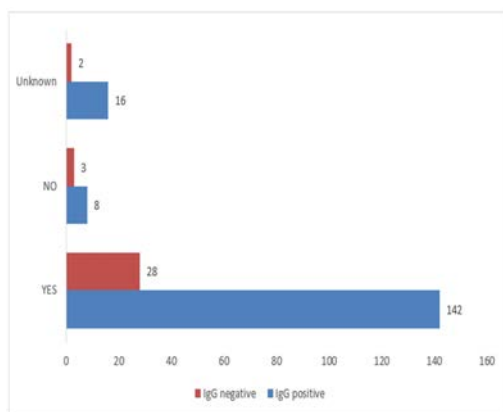


Fig. 6: Distribution of Women Based on H/S Vaccination

Rubella Seronegativity in Reference to Awareness and its Impact on Pregnancy:

Among 200 women, only 4/200 (2%) of the study population were aware of rubella and its impacts in pregnancy out of which one individual is susceptible. Among the 98% of the subjects who were unaware of rubella, 16.3% turns out to be susceptible.

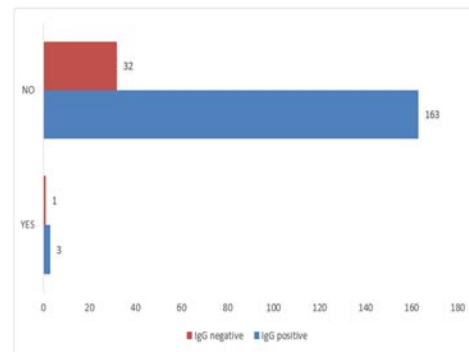


Fig. 7: Distribution of Women Based on Awareness of Rubella and its Impact on Pregnancy

Follow Up After the Test Results: 33 seronegative women were informed telephonically about the results and the need for rubella vaccination. They have been advised to get the vaccination from their nearest hospital. At the same time, they were also advised not to conceive for at least 2 months after getting vaccination. 2 of the women could not be reached due to non availability of contact numbers. Almost none of the women were aware of rubella and its impact on pregnancy. A total of 25 are vaccinated till now and 6 were willing to get the vaccination before conception. This prospective cross-sectional study was conducted in 200 subjects between the age group of 15-25 years who attended Gynecology OPD of PGIMER, Chandigarh for any complaints. The study was conducted to detect the rubella susceptible women by screening them for rubella IgG status and counsel them for vaccination before the pregnancy to decrease the possibility of CRS in the fetus. Infection with rubella in early pregnancy can have multiple complications in the fetus manifested by somatic, developmental, neurological, sensory, auditory and cardiac defects^[9]. This study was aimed at identifying the rubella IgG seronegative among the women between 15-25 age group and tests performed as described in materials and methods. Quantitatively concentration <8IU were taken as negative, >11IU/ml were taken as seropositive and between 8-11 IU/ml were reported as equivocal.

Prevalence of Seronegativity for Rubella in the Study Population:

The prevalence of IgG seronegative for rubella is 16.5% in this study. This is in concordance with the study done in New Delhi among adolescent girls aged 15-18 years reported that overall Rubella IgG seronegativity was 17.8%^[10].

Prevalence of Rubella Seronegativity Based on State and Area of Residency:

Among the subjects recruited for the study highest were from Punjab 81(40.7%) followed by Chandigarh 45(22.6%) with seronegativity of 17 (20.9%) and 9 (20%) respectively. The highest susceptible group were from Huamachil (21%) followed

by Punjab (20.9%) and Chandigarh (20%). The difference in the seroprevalence is explained based on the difference in the vaccination campaign and coverage in these states^[11].

Age Related Distribution of Rubella Seronegativity: Majority of women belonged to age of 21-25 years is 133 (66.3%). The median age of study population was 19 years. The prevalence of rubella IgG seronegativity in women of 15-20 years was 8/67(11.9%) while 25/133 (18.9%) seronegative women belonged to 21-25 years. The prevalence of seronegativity higher among the age group of 21-25 can be due to missing of catch up vaccination campaign recently started in many states which covers age <15 years^[12].

Rubella Seronegativity Based on Socioeconomic Status: The seroprevalence of rubella IgG positivity in lower socioeconomic status was found to be 154/187 (82.35%) and higher socioeconomic status was (92.3)^[13].

Rubella Seronegativity and Previous History of Congenital Malformation and Stillbirth: In the study, a total of 3 women had previous history of a congenitally malformed fetus. Out of these, all three were found to be seropositive. Among 3 CMF two were of congenital heart disease and one neural tube defect. 2% of women with H/O stillbirth were found to be seropositive. CRS accounted for 10-15% of all cases of pediatric cataract and as many as 10-50% of all children with congenital anomalies were found to have laboratory evidence of CRS^[14].

Limitations: There are certain limitations in this study. The study population is not representative of total population. They are recruited by a convenient sample technique which may limit the generalization of the results. At present, facilities are still lacking to provide vaccination to susceptible group before conception.

CONCLUSION

This prospective observational study was performed to identify the susceptibility to rubella in childbearing age. The following observations were made:

- Out of the total 200 women screened, 33 (16.6%) were found to be susceptible for rubella infection as interpreted from ELISA test.
- The women enrolled were from 15-25 years of age. The median age of the study population was 19.5 years.
- The prevalence of rubella IgG seronegativity in reference to state of residency was similar and it was not statistically significant.
- The susceptible women in both rural (13.27%) and urban areas (20.9%) were comparable but it was not statistically significant (0.1).

- The susceptible women in both higher economic group (0/12) and lower economic group (33/187) were comparable but it was statistically not significant (0.2).
- No statistical significance was found in rubella seroprevalence among women with history of CMF babies and stillbirth in previous pregnancy (p=0.7). National wide surveillance of the susceptible population may highlight the existing burden of CRS in the country and might help the policy makers for implementation of new programmes to reduce the CRS in future. There should be a provision for implementation of rubella vaccine in national immunization programme among the childbearing age group. Catch up vaccination programmes in the community should be considered to cover up the susceptible group.

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