# Epidemiological evaluation of rubella virus infection among pregnant women in Ibadan, Nigeria

Olubusuyi M Adewumi, Adebowale O. Olayinka, Adebiyi B. Olusola, Temitope O.C. Faleye, Folorunso W. Sule, Olubukola Adesina

**Abstract:** Rubella is a vaccine-preventable, mild rash-inducing viral disease with complications that include a spectrum of birth defects in the developing foetus, especially if the infection is acquired in the early months of pregnancy. Consequently, the primary objective of global rubella control programmes is prevention of congenital rubella infection and associated birth defects often collectively referred to as congenital rubella syndrome.Despite the availability of safe and effective vaccines, and elimination of rubella virus in many developed countries substantial commitment to rubella control has not been demonstrated in the developing countries. This study appraises immunity to rubella, and consequently makes appropriate recommendations aimed at facilitating effective control. A cross-sectional sero-surveillance study was carried out among 272 consenting ante-natal clinic attendees in south-western, Nigeria. Prevalence rates of 91.54% and 1.84% were recorded for anti-rubella virus (anti-RV) IgG and IgM respectively. Also, 90.7% and 92.3% of the women aged ≤30 years and ›30 years respectively had detectable anti-RV IgG. No significant association (p=0.94) was recorded between anti-RV IgG detection and age of the women. Previous exposure and susceptibility of significant fraction of the population to rubella infection were confirmed. Considerable political commitment and promotion of free rubella immunization specifically for women with childbearing potential were recommended.

Olubusuyi M. Adewumi[1], Adebowale O. Olayinka[1], Babatunde A.Olusola[1], Temitope O.C. Faleye[1, 3], Waidi F. Sule[4], Olubukola Adesina[2]

1. Department of Virology, College of Medicine, University College Hospital,University of Ibadan, Ibadan, Nigeria

2. Department of Obstetrics and Gynaecology, College of Medicine, University College Hospital,University of Ibadan, Ibadan, Nigeria

3. Department of Microbiology, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria

4. Department of Biological Sciences, Osun State University, PMB 4494, Osogbo, Nigeria

Corresponding author

Olubusuyi Moses **Adewumi**

Department of Virology,

College of Medicine,

University College Hospital,

University of Ibadan, Ibadan, Nigeria

Mobile Phone: +234 806 022 6655

## Introduction

Rubella virus is a member of the *Rubivirus* genus inthe family *Togaviridae* [1]. Itis a cubical, medium-sized (60 to 70 nm), lipid-enveloped virus with a positive-sense, single-stranded RNA genome. It is the only non-arthropod borne virus in the family and the aetiologic agent of rubella.

Rubella is a vaccine-preventable, mild rash-inducing viral disease with complications [2, 3] that include a spectrum of birth defects in the developing foetus, especially if the viral infection is acquired in the early months (first trimester) of pregnancy [3-6]. Birth defects associated with rubella virus infection range from blindness, deafness, and congenital heart disease, to mental retardation and central nervous system (CNS) complications which are often collectively referred to as congenital rubella syndrome (CRS) [4, 7, 8]. Furthermore, in extreme cases, *in-utero* infection of a foetus with rubella virus can cause fetal demise [9]. Consequently, the primary objective of rubella-control programmes is prevention of congenital rubella virus infection, and by association CRS [10].

Despite the development and administration of effective vaccines for prevention and control of rubella virus infection since the late 1960s, and prevention as well as feasibility of or elimination of the causative agent in many developed countries [11, 12], the infection is still endemic in Nigeria. In fact, it has been shown that a significant number of non-immunized women of childbearing age remain susceptible to rubella virus infection in the country [13]. Also, subclinical or clinical infections as well as continuous circulation of rubella virus have previously been reported in Nigeria [13-18].

Efforts to realize significant political commitment and investment in rubella control and possible virus elimination in Nigeria has not yielded significant result. For example, to date rubella

vaccine is only accessible at a cost to the informed few in the population. Also, most vaccinees receive monovalent measles rather than rubella-containing vaccines (RCVs) like trivalent measles-mumps-rubella (MMR) vaccine. Though, the later is advertised on the platform of National Immunization Programme (NIP).

Though previous studies have documented rubella infection among selected populations in different regions of the country [13-18], this study was designed to specifically appraise rubella infection among symptomatic pregnant women in the population. Findings from the study will further strenghten the drive for effective prevention and elimination of rubella in Nigeria. Therefore, to achieve the aforementioned, this study was designed and conducted to evaluate anti-RV IgM and IgG among ante natal clinic attendees with symptoms suggestive of rubella in the selected facilities.

## Materials and Methods

### Study location

This study was carried out among pregnant women attending ante natal clinics in University College Hospital and Ade-Oyo State Hospital in Ibadan, south-western, Nigeria. University College Hospital is a tertiary health care facility of the University of Ibadan. The hospital is equipped with facilities for teaching of medical students, research and provision of clinical services to the community. Attendees in the hospital are majorly residents of average economic and educational status. On the other hand, Ade-Oyo State Hospital is a secondary health care facility located in the aboriginal nerve of the city, densely populated by indigenes and serving wide range of people with spectra of social, economic and educational background. The hospital serves pregnant women of varied economic and educational status from different parts of the city.

The ante-natal clinic records an average of 380 ± 20 new pregnant women per week. Pregnant women from the University College Hospital and Ade-Oyo State Hospitals were subsequently referred to as RUC (rubella study pregnant women in UCH) and RAD (rubella study pregnant women in Ade-Oyo) study groups respectively. The two hospitals selected for the study attend to pregnant women of varied educational and socio-economic backgrounds.

**Enrolment of pregnant women**

To achieve our aim and objectives, consenting ante-natal clinic attendees were enrolled from the two selected hospitals described above. Pregnant women were enrolled between September 2012 and June, 2013. Consenting antenatal clinic attendees were examined for presence of observable rubella-like rash, fever, lymphadenopathy and arthralgia. Pregnant women presenting with any of the listed clinical presentations were enrolled for the study. Subjects without any of the clinical presentations were excluded from the study. Demographic and other relevant information were obtained using structured questionnaire.

**Research Methodology**

Blood sample was collected from a total of 272{median age = 31 years, age range = 17-43 years (RUC: n = 182; age range = 17-43 years; RAD: n = 90; age range = 19-42 years)} pregnant women who consented verbally, and were subsequently enrolled strictly based on inclusion criteria at the point of registration and routine examination for ante-natal clinic. Ethical approvals for the study were granted by the UI/UCH Ethics Committee (UI/EC/11/0058) and Oyo State Ministry of Health (AD3/479/349).

**Sample collection**

About 5ml of blood sample was collected via venipuncture of each pregnant woman into an appropriately labeled sterile container free of anticoagulants or preservatives. Thereafter, samples were transported to the laboratory immediately in a cold box with frozen ice packs to maintain a condition of about 4-8ºC. Serum samples were separated by low-speed centrifugation at 500g for 5 minutes, or direct removal of the serum using a sterile disposable pipette after retraction of the clot. Then, two aliquots of serum were prepared and transferred into labeled sterile cryovials and stored at -20ºC until ready for analysis, while the coagulated cells were stored at -20ºC in the sterile container.

**Laboratory analysis**

Laboratory analysis was carried out in the Department of Virology, College of Medicine, University College Hospital, Ibadan. The samples were analyzed for qualitative and quantitative detection of anti-rubella IgM and stable memory IgG using DIA.PRO® Diagnostic Bioprobessrl (Sedelegale: Via Lucio Giunio Columella, 31-20128-Milano, Italy) Enzyme Immunoassay in accordance with the manufacturer's description. Results of the anti-IgG assay was interpreted with antibody titer ≥15 IU/ml as the cut-off point. Both test kits used have diagnostic sensitivity and specificity performance of >98%.

**Statistical analysis**

Results of the study were analyzed with t-test and $\chi^2$ statistical tests using Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows. P-value $\leq 0.05$ was used as indicator of statistical significance. Also, demographic features and other relevant information about the study populations were compared (Table 1).

**Results**

Overall, prevalence rate of 91.54% (249/272) and 1.84% (5/272) were recorded for anti-rubella virus (anti-RV) IgG and IgM respectively. Further analysis of the results showed that 83 (92.2%) and 1 (1.1%) of the women in RAD had anti-RV IgG and IgM respectively (Table 2). Also, 166 (91.2%) and 4 (2.2%) of the women in RUC had anti-RV IgG and IgM respectively (Table 2). Overall, 90.7% (117/129) of women aged ≤30 years and 92.3% (132/143) of those aged ˃30 years respectively had detectable anti-RV IgG. Further analysis of the results for RAD showed that 46 (90.2%) of the women aged ≤30 years and 37 (94.4%) of those aged ˃30 years respectively had detectable anti-RV IgG, these rates were statistically comparable (Table 2). Also, results for RUC showed that 71 (91.0%) of the women aged ≤30 years and 95 (91.3%) of those aged ˃30 years had detectable anti-RV IgG (Table 2). No significant association (p=0.94) was recorded between the presence of anti-RV IgG and age of pregnant women (Table 2). Significant difference (p=0.0005) was recorded in educational status of the women by location (woman with tertiary education were more likely to be in RUC); however, similar anti-RV IgG prevalence rates were observed in both locations. Pregnant women enrolled for the study had comparable presentations of fever, lymphadenopathy and rash (Table 1). Also, Chi square analysis showed no association (p=0.78) between location and previous exposure to RV (presence of anti-RV IgG) (Table 2).

## Discussion

A high anti-RV IgG prevalence rate was observed in the study. This suggests previous exposure to rubella virus because the women were rubella vaccine inexperienced. It also implies previous subclinical or clinical infections with rubella virus. Anti-RV IgM was not detectable in most of the women despite the enrolment technique (based on presentations of clinical symptoms suggestive of rubella). Thus, it implies that the clinical presentations though suggestive of rubella infection might have resulted from other infections. However, detection of anti-RV IgM in a fraction of the study population confirms recent infection and continuous circulation of the virus. Specifically, the presence of serologically naive pregnant women (8.46%) in the population demonstrates susceptibility of a significant fraction of the population to rubella virus infection.

In previous studies [14-18], varied anti-RV IgG prevalence rates have been reported among women of childbearing age and pregnant women in different regions of Nigeria. It is however, pertinent to note that findings from this study corroborate previous reports of subclinical or clinical infection as well as continuous circulation of rubella virus in Nigeria [13-18]. It is also in congruence with preliminary report [13] of high prevalence rate (89.4%) of anti-RV IgG among vaccine naïve pregnant women attending ante-natal clinic in one (Ade-Oyo State Hospital) of the study locations. Previously, anti-RV IgG prevalence rate of 54.1% was reported among rubella vaccine naïve pregnant women in a study conducted in the north-eastern, Nigeria [16].

Specifically, detection of anti-RV IgM and record of rubella antibody naivety among a fraction of the study population depict CRS situation in the country. Cutts and Vynnycky [19] in a review of the literature on the prevalence of anti-rubella antibodies from developing countries concluded that CRS is an under-recognized public health problem and that appropriate data need to be collected to estimate the cost-effectiveness of a potential global rubella control program.

Furthermore, it had been shown that determination of incidence of rubella and CRS remain important steps to achieve effective prevention and control programme [11].

Comparable prevalence rates of anti-RV IgG were recorded despite varied age, age at first marriage, and mean parity (Table 1) of the studied pregnant women. This observation might imply that women in the community possibly become exposed and infected with rubella virus early in life; before reaching childbearing age. However, there is the need for more extensive study on specific variables to facilitate appropriate conclusion. Similar anti-RV IgG prevalence rates were recorded among the women irrespective of their educational status or location of residence (Table 1). Also, comparable rates of presentations of probable symptoms of rubella infection including fever, lymphadenopathy, arthralgia and rash were observed among the studied population. These observations might also suggest comparable risks of infection irrespective of persons' educational and economic status in the region. Nevertheless, it confirms continuous and consistent circulation of rubella virus in the population. Rubella vaccine is not included in the childhood immunization programme neither is there provision for selective immunization of women of childbearing age in Nigeria. However, it is only available to informed few at a cost, thus high prevalence of anti-RV IgG detection in the population confirms previous exposure and infection by the virus.

It is pertinent to note that the World Health Organization (WHO) recommended the use of rubella-containing vaccine (RCV) in all countries with national childhood immunization schedules to prevent congenital rubella infection, including CRS in 2000 [20]. The number of WHO member states using RCV increased from 83 (43%) in 1996 to 130 (67%) in 2009.

Consequently, the number of rubella cases reported dramatically decreased from 670,894 in 2000 to 121,344 in 2009 [21]. However, despite the WHO recommendation and subsequent accomplishments in different parts of the world, rubella vaccine is still available to Nigerians at a cost.

It has been recognized [22] with confirmations [23-25] that high childhood immunization rates is essential to achieving effective prevention of CRS [22]. Accordingly, WHO advises a minimum target rate of 80 percent for childhood immunization programs [20]. However, considering the practicability of achieving 80 percent success rates in childhood immunization in Nigeria, *vis-à-vis* documented success in prevention of CRS with selective immunization of all women of childbearing age [2] we recommend selective vaccination of women with childbearing potential in the country.

## Conclusions

Specifically, the study shows serologic evidence of previous exposure and/or recent infection by rubella virus among the studied women. It also shows that a proportion of the pregnant women were newly infected, even as some of them remained susceptible to the virus. Findings from the study corroborate reports of previous studies in the country and further approve that elimination of rubella virus in Nigeria is feasible since the definite susceptible population is defined. Therefore, to facilitate effective rubella control in Nigeria we recommend substantial political commitment and institution of health policy that promotes awareness and free rubella virus immunization programme especially for women of childbearing age.

## Acknowledgements

209 The authors would like to acknowledge the support of the Head, Department of Obstetrics and
210 Gynaecology, University of Ibadan, the Medical Director, Ade-Oyo State Hospital, the entire staff
211 of both ante-natal clinics and study participants. Also, the authors would like to appreciate
212 Mr.Oyewole S.O. and his team for their cooperation.

213

214 **Author's contributions**

215 AMO conceptualized and designed the study. AMO, OOA, OBA, FTOC and AO were involved
216 in sample and data collection, and laboratory analysis. SWF and AMO were involved in data
217 analysis and interpretation of results. AMO prepared the first draft of the manuscript and all
218 authors read, revised and approved the final manuscript.

219

220 **Conflicts of interests**:

221 No conflict of interest was reported by the authors.

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## Table 1(on next page)

Profile of the RAD and RUC ante-natal clinics attendees enrolled for the rubella epidemiology study in Ibadan, Nigeria

**Table 1: Profile of the RAD and RUC ante-natal clinics attendees enrolled for the rubella epidemiology study in Ibadan, Nigeria**

| Parameters | RAD (%) | RUC (%) | Remarks |
|---|---|---|---|
| Mean Age (Year) | 30.07 | 31.57 | Significantly different (p=0.02). |
| Age at first marriage (Year) | 25.1 | 27.67 | Significantly different (p=0.0005). |
| Mean parity | 1.36 | 0.97 | Significantly different (p=0.03). |
| Vaccination record | 23 (25.6) | 56 (30.8) | No association between location and vaccination record (p=0.37). |
| Education | | | Significant association between |
| Primary | 8(8.9) | 1(0.6) | location and educational status |
| Secondary | 39(43.3) | 19(10.5) | (p=0.0005), that is a woman with |
| Tertiary | 43 (47.82) | 162(89.0) | tertiary education was likely to be in RUC. |
| Fever | 44.4% | 51.1% | Fever not associated with location (p=0.3). |
| Lymphadenopathy | 9 (10) | 27 (14.8) | Lymphadenopathy not associated with location (p=0.27). |
| Ever had rash | 18 (20) | 46 (25.3) | Ever had rash not associated with location (p=0.34). |
| Rash (2 weeks before enrolment) | 15 (16.7) | 40 (22.0) | Rash not associated with location (p=0.31). |

**Key**: - RAD: Rubella study subjects in Ade-Oyo Maternity Hospital, RUC: Rubella study subjects in University College Hospital.

## Table 2(on next page)

Relationship between anti-rubella virus antibody prevalence rates and variables of RAD and RUC ante-natal clinic attendees in Ibadan, Nigeria

**Table 2. Relationship between anti-rubella virus antibody prevalence rates and variables of RAD and RUC ante-natal clinic attendees in Ibadan, Nigeria**

| Variables | No. tested among RAD (% positive) | p value | No. tested among RUC (% positive) | p value |
|---|---|---|---|---|
| Anti-RV IgG by age | | | | |
| ≤ 30 years | 51 (90.2) | | 78 (91.0) | |
| ˃ 30 years | 39 (94.4) | Not valid | 104 (91.3) | 0.94 |
| Overall anti-RV IgG by location | 90 (92.2) | | 182 (91.2) | 0.78 |
| Overall anti-RV IgM by location | 90 (1.1) | | 182 (2.2) | Not valid |