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# Rubella virus infections and immune status among pregnant women before the introduction of rubella vaccine in Amhara Regional State, Ethiopia

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ABSTRACT

*Background:* Rubella and its associated congenital anomalies have been greatly reduced in most developed countries through use of the rubella vaccine. However, the magnitude of the problem is underestimated and there are no well-established rubella/congenital rubella syndrome prevention and control strategies in many developing countries, including Ethiopia. The aim of this study was to determine the prevalence of rubella virus infections among pregnant women and their immune status before the introduction of rubella vaccine in Amhara Regional State, Ethiopia.

*Methods:* A prospective cross-sectional study was conducted among pregnant women in Dessie, Felege-Hiwot, and University of Gondar referral hospitals, from December 2015 to February 2017. After obtaining written informed consent, socio-demographic data, reproductive history, clinical manifestations, and the possible risk factors for rubella virus infections were collected using a structured questionnaire. The laboratory analysis of rubella-specific antibodies was done using an enzyme-linked immunoassay method on venous blood samples. Data were entered and analyzed using IBM SPSS Statistics version 20. Binary logistic regression was used to determine the strength of association between the dependent variables and covariates.

*Results:* A total of 600 pregnant women were included in the study. Their mean age was 26.4 ± 5 years (range 16–40 years). The overall seroprevalence of rubella infection was 89%. Of the total study participants, 9.5% were positive for rubella-specific IgM antibody, which indicates acute/recent rubella virus infection. In contrast, 79.5% of them had protective levels of rubella-specific IgG antibody and were immune as a result of previous wild-type rubella infection. However, 11% of the pregnant women were negative for both rubella-specific antibodies; these women represent the susceptible group.

*Conclusions:* A large number of pregnant women had acute/recent rubella virus infections at the time of data collection, indicating that the virus is endemic in the study area. More than a tenth of pregnant women were found to be susceptible to acquiring the infection in future pregnancies, with the possible risk of rubella-associated congenital anomalies. Hence screening of all women of child-bearing age before conception and during pregnancy might reduce the devastating effects of the virus on the developing fetus.



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## Introduction

Rubella virus is an important human pathogen that causes an acute and contagious disease known as rubella, little red, 3-day measles, or German measles (Fokunang et al., 2010). Humans are the only reservoir for this virus (Mounerou et al., 2015). The virus has an incubation period of 2–3 weeks. The route of transmission is air-borne in postnatal cases and transplacental during pregnancy (Kolawole et al., 2014). The disease caused by this virus commonly occurs in childhood and is characterized by a maculopapular rash associated with a low-grade fever, lymphadenopathy, and malaise (Al-Rubai et al., 2010). It can also cause joint pains, headache, and conjunctivitis in adults (Lezan, 2015). Transient arthralgia or arthritis may also occur (Heggie and Robbins, 1969). It is also a rare cause of thrombocytopenic purpura and encephalitis (Sherman et al., 1965). However, up to 50% of rubella cases are subclinical (Horstmann et al., 1965).

Rubella infection is considered relatively benign, and in the absence of pregnancy, the infection is usually mild and self-limiting (CDC, 2001). However, during pregnancy, it has a devastating effect on the developing fetus (Adam et al., 2013; Cradock-Watson et al., 1981) and this represents a major health concern worldwide (Mirambo et al., 2015). Currently, there is no specific treatment for the virus (Olajide et al., 2015). However, its burden can be minimized through use of the live attenuated rubella vaccine (Alleman et al., 2016; Demicheli et al., 2012; WHO, 2014). The control of rubella and congenital rubella syndrome (CRS) relies on a high population level of immunity (Gilbert et al., 2017).

The World Health Organization (WHO) proposed the introduction of rubella vaccine in each country in the year 2000 (Robertson et al., 2003) and different efforts are undergoing in different WHO regions (Martínez-Quintana et al., 2015; CDC, 2010; WHO, 2008). As a result, the burden has declined, although mostly in industrialized countries (Adewumi et al., 2014). However, rubella vaccine is still not available in many developing countries (Njeru et al., 2015) and it is not included in their immunization programs (WHO, 2012). Rubella is an under-recognized public health problem (Cutts and Vynnycky, 1999; Mamvura et al., 2015). In Africa, few countries have included rubella vaccine in their national immunization programs and data on the seroprevalence of the virus are very limited (Martínez-Quintana et al., 2015).

Although Ethiopia has planned to introduce the rubella vaccine (WHO, 2015), it is currently not included in the national immunization program (Getahun et al., 2016). There are only a few reports on rubella in the country (Cutts et al., 2000a; Gebreselassie and Almaz, 1985), with most containing very old information (Gebreselassie and Almaz, 1985; Sandow et al., 1982) or reporting on suspected cases of measles among children (Mitiku et al., 2011; Getahun et al., 2016; Shiferaw et al., 2016). There is only one recently published report on rubella among pregnant women (Tamirat et al., 2017) and one case report on CRS (Mekonnen, 2017) in the country. All of these indicate that there is scarcity of data and that the magnitude of rubella and its consequences is largely unknown. Hence, the aim of this study was to determine rubella virus infections and immune status among pregnant women before the introduction of rubella vaccine in Amhara Regional State, Ethiopia.

## Materials and methods

### *Study design, area, and period*

A prospective cross-sectional study was conducted in three referral hospitals in Amhara Regional State, namely Dessie, Felege-Hiwot, and University of Gondar referral hospitals, from December 2015 to February 2017.

### *Study participants*

The study participants were pregnant women who visited the respective antenatal care clinics of the referral hospitals during the study period and gave informed consent and the required amount of blood sample for laboratory analysis.

### *Sample size and sampling technique*

The study participants were selected using a simple random sampling technique and the sample size was calculated using a single population proportion formula by considering a 95% confidence interval, 4% margin of error, and 50% proportion. The sample size was proportionally allocated to the selected referral hospitals based on the previous flow of pregnant women visiting the antenatal care clinics of the respective referral hospitals. Pregnant women who gave informed consent and the required amount of blood sample were included in the study. Pregnant women who were seriously sick at the time of data collection and those who visited the respective referral hospitals for the second time during the study period were excluded from the study.

### *Data collection*

After obtaining written informed consent from each study participant, socio-demographic data, clinical information, and information on reproductive history and possible risk factors of the pregnant women were collected using a structured and pre-tested questionnaire.

### *Blood collection and handling*

Using a plain tube, 5 ml of venous blood was collected aseptically from each pregnant woman for the determination of rubella antibodies. Blood was allowed to clot for an hour at room temperature, centrifuged at 3500 rpm for 5 min, and then serum was separated and collected in sterile storage vials to be stored at −70 °C until laboratory analysis.

### *Laboratory analysis and interpretation of results*

Rubella IgM and IgG antibodies were determined using an enzyme-linked immunoassay (ELIA) method as per the manufacturer's instructions (Linear Chemicals SL, Spain). The results were read in a micro-well reader at 450 nm and compared in a parallel manner with calibrators and controls. For rubella-specific IgM, the qualitative result was interpreted as positive if the rubella IgM index was >1.1, negative when the index was <0.9, and equivocal when the index was ≥0.9 and ≤1.1. The quantitative rubella IgG result was expressed in international units per milliliter (IU/ml). In accordance with the manufacturer's instructions, the IgG result was interpreted as positive when the IgG index value was >10 IU/ml, as equivocal at 5–10 IU/ml, and as negative at <5 IU/ml.

### *Quality assurance mechanisms*

The rubella test kits (IgM and IgG EIA kits) have their own quality control materials that can be run in parallel with patient samples, and all test procedures were done strictly following the manufacturer's instructions. In addition, standard operational procedures were strictly followed and the questionnaire was pre-tested in non-selected health institutions. Training was given for data collectors and they were also regularly supervised by the research team. In addition, the inclusion and exclusion criteria were given to the data collectors.