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Estimating the burden of rubella virus infection and congenital rubella syndrome through a rubella immunity assessment among pregnant women in the Democratic Republic of the Congo: Potential impact on vaccination policy

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ABSTRACT

Background: Rubella-containing vaccines (RCV) are not yet part of the Democratic Republic of the Congo's (DRC) vaccination program; however RCV introduction is planned before 2020. Because documentation of DRC's historical burden of rubella virus infection and congenital rubella syndrome (CRS) has been minimal, estimates of the burden of rubella virus infection and of CRS would help inform the country's strategy for RCV introduction.

Methods: A rubella antibody seroprevalence assessment was conducted using serum collected during 2008–2009 from 1605 pregnant women aged 15–46 years attending 7 antenatal care sites in 3 of DRC's provinces. Estimates of age- and site-specific rubella antibody seroprevalence, population, and fertility rates were used in catalytic models to estimate the incidence of CRS per 100,000 live births and the number of CRS cases born in 2013 in DRC.

Results: Overall 84% (95% CI 82, 86) of the women tested were estimated to be rubella antibody seropositive. The association between age and estimated antibody seroprevalence, adjusting for study site, was not significant ($p = 0.10$). Differences in overall estimated seroprevalence by study site were observed indicating variation by geographical area ($p \leqslant 0.03$ for all). Estimated seroprevalence was similar for women declaring residence in urban (84%) versus rural (83%) settings ($p = 0.67$). In 2013 for DRC nationally, the estimated incidence of CRS was 69/100,000 live births (95% CI 0, 186), corresponding to 2886 infants (95% CI 342, 6395) born with CRS.

Conclusions: In the 3 provinces, rubella virus transmission is endemic, and most viral exposure and seroconversion occurs before age 15 years. However, approximately 10–20% of the women were susceptible to rubella virus infection and thus at risk for having an infant with CRS. This analysis can guide plans for introduction of RCV in DRC. Per World Health Organization recommendations, introduction of RCV should be accompanied by a campaign targeting all children 9 months to 14 years of age as well as vaccination of women of child bearing age through routine services.

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1. Introduction

Rubella is a vaccine-preventable disease with safe and effective vaccines available since 1969. In the absence of vaccination, infection with the rubella virus usually occurs in childhood and causes a

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mild, self-limited illness characterized by rash and fever. However, if rubella virus infection occurs in a susceptible woman during the first trimester of pregnancy, miscarriage, fetal death, or congenital rubella syndrome (CRS) in the surviving infant often occurs. CRS can result in hearing impairment, blindness, congenital heart disease, mental retardation, and/or other manifestations [1,2].

A single dose of the most common rubella vaccine, RA27/3, is highly efficacious in providing lifelong protection against disease. Prevention of congenital rubella virus infection, including CRS, is the primary goal of rubella vaccination. The preferred approach for prevention of rubella and CRS is for countries to introduce a rubella-containing vaccine (RCV) through a wide-age range campaign and then incorporate it into the national childhood vaccination schedule [2].

In recent years, several World Health Organization (WHO) regions have established rubella/CRS elimination or accelerated control goals [2–6]. In 2003 the WHO region of the Americas set a rubella/CRS elimination goal, achieved the goal in 2009, and in April 2015, was declared free of endemic rubella and CRS [2–5,7]. The WHO European region set a 2015 rubella elimination goal [3,4,8]. In October 2014, a regional rubella elimination goal for the WHO Western Pacific Region was endorsed by its Regional Committee [6]. The WHO African region has not yet established a rubella elimination goal but recommends that countries document the burden of rubella virus infection/CRS and, when feasible, introduce RCVs [9].

RCVs have not been widely administered in the Democratic Republic of the Congo (DRC) nor introduced into the country's national vaccination program [10]. However, there are tentative plans for introduction into the childhood vaccination schedule before 2020 [10]. Documentation of DRC's historical burden of rubella virus infection and CRS has been minimal [1,11,12]. Moreover, DRC has no surveillance system for either disease, but rubella virus transmission within the country has been documented by a rubella antibody seroprevalence assessment conducted in Kinshasa city in 1987–1988 and by measles case-based surveillance since 2005, with serological testing for rubella-specific immunoglobulin type M (IgM) when suspected measles cases are negative for measles IgM [1,11,12]. Considering the interest in rubella control/elimination in the WHO African region, estimates of the burden of rubella virus infection/CRS in DRC are urgently needed [8,9]. We describe analyses of sera from 1605 pregnant women aged 15–46 years from 3 provinces in DRC which were available from a human immunodeficiency virus (HIV) sentinel survey among women attending antenatal care (ANC) sites [13–15]. Estimates of age- and site-specific rubella antibody seroprevalence, population, and fertility rates were used in catalytic models to estimate the incidence of CRS per 100,000 live births and the number of CRS cases born in 2013 in DRC. These estimates will be valuable to DRC's Ministry of Public Health (MOPH) in planning for RCV introduction [10].

2. Methods

2.1. Rubella antibody seroprevalence assessment

HIV sentinel surveys among pregnant women attending ANC sites are based on a convenience sample of sentinel sites chosen to capture women from a variety of geographical and socioeconomic backgrounds. Details on how sites are selected can be found here [16]. The 2008–2009 HIV sentinel surveys in DRC included 30 sentinel ANC sites [13,14]. This study focuses on a subset of 7 ANC sites in 3 provinces.

Sera prepared from venous blood collected during 2008–2009, per WHO guidelines from 6615 pregnant women aged 15–47 years from 7 ANC sites in Bandundu, Kinshasa, and Kasaï Occidental provinces for national HIV sentinel serosurveys in DRC, had been used for a polio serosurvey in adults and were available for additional testing [13–16]. Specifically, the 7 ANC sites were (1) Kikwit (urban) and (2) Vanga (rural) in Bandundu, (3) Binza-Meteo, (4) Boyambi, and 5) Kingasani (all urban) in Kinshasa, and 6) Mikalayi (rural), and (7) Tshikapa (urban) in Kasaï Occidental (Fig. 1). The Demographic and Health Survey II (DHS II) conducted in 2013–2014 in DRC reported that, nationally, 88% of women aged 15–49 years participating in the survey who had a live birth in the 5 years preceding the survey had sought antenatal care during their pregnancy for their most recent live birth; the results were 90%, 89%, and 96% for women declaring residence in Bandundu, Kasai Occidental, and Kinshasa provinces, respectively, and were 94% and 86% for those declaring residence in urban and rural areas, respectively [17]. A survey conducted in 2009 in Kinshasa province among women at least 18 years of age who had been pregnant within the prior 3 years reported that 98% of women surveyed had attended ANC during their most recent pregnancy [18].

Sera from a randomly-sampled subset of the above-mentioned 6615 women were quantitatively analyzed for rubella-specific immunoglobulin type G (IgG). Prior to random sampling of the women for the rubella antibody serosurvey described in this report, HIV-positive women were excluded since HIV infection may negatively impact serum IgG levels; HIV prevalence in the 7 above-mentioned ANC sites ranged from 1.8% to 5.1% in 2008–2009 [13,14,19]. Also prior to random sampling for the rubella serosurvey, women attending the 3 ANC sites in the densely populated urban area of Kinshasa city (Binza-Meteo, Boyambi, and Kingasani) were pooled. Kinshasa was thereafter considered a single study site (referred to as the "Kinshasa" study site); thus, there were 5 study sites for the serosurvey (Table 1). From 5829 HIV-negative women from the original 6615, 1650 women (66 serum samples from each of 25 strata, i.e., 5 age groups from each of the 5 study sites) were randomly chosen. The sample size was determined based on the estimation of rubella antibody seroprevalence with a precision of ±10% assuming true prevalence of $\geqslant$80% and 5% unusable serum samples. Of the 1650 sera, 45 (3%) had insufficient volume for IgG assessment: 16, 7, 8, 10, and 4 from the Kikwit, Kinshasa, Mikalayi, Tshikapa, and Vanga study sites, respectively. Demographic attributes (e.g., age at blood collection, age at first pregnancy, number of pregnancies, rural or urban residence, level of education, occupation, and civil status) were analyzed for associations with rubella antibody seropositivity [13,14].

Sera were shipped by air from DRC to the Centers for Disease Control and Prevention (CDC-Atlanta) on dry ice and stored at −20 °C prior to rubella IgG assessments performed at CDC-Atlanta's Measles, Mumps, Rubella, and Herpesvirus Branch laboratory. Rubella-specific IgG antibody concentrations, expressed as International Units/millimeter (IU/ml), were determined using the Rubella IgG enzyme-linked immunosorbent assay (ELISA) II system according to the manufacturer's instructions (Wampole Laboratories, Princeton, New Jersey). The optical density (OD) ratio was calculated by dividing the specimen OD by the cutoff value supplied by the manufacturer. Specimens with OD ratios >2.2 were diluted with kit dilution buffer, and rubella-specific IgG antibody concentrations were determined from the diluted serum. Sera with titers of $\geqslant$10 IU/ml were considered seropositive for rubella antibody, whereas those with an equivocal determination (8.19–9.99 IU/ml) or with titers of <8.19 IU/ml were considered seronegative [2]. The 14 women with equivocal determination were distributed among 4 study sites as follows: Mikalayi (n = 6, ages in years = 17, 19, 22, 23, 37, 38), Vanga (n = 1, age in years = 34), Tshikapa (n = 4, ages in years = 17, 29, 34, 35), and Kinshasa (n = 3, ages in years = 17, 17, 18). Immune individuals with ELISA-determined IgG < 10 IU/ml should be too small in number to affect the results presented in this report [20].