Prevalence of Rubella Antibodies Among Children in the Democratic Republic of the Congo

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Background: While generally mild in children, rubella infection in early pregnancy can lead to miscarriage, fetal death or congenital rubella syndrome. Rubella vaccination is not yet available as a part of routine immunization in the Democratic Republic of the Congo (DRC), and the burden of infection is unknown.

Methods: In collaboration with the 2013–2014 DRC Demographic and Health Survey, a serosurvey was carried out to assess population immunity to vaccine-preventable diseases. Dry blood spot samples collected from children 6–59 months of age were processed using the Dynex Technologies Multiplier FLEX chemiluminescent immunoassay platform (Dynex Technologies, Chantilly, VA).

Results: Among the 7195 6- to 59-month-old children, 33% were positive and <1% indeterminate for rubella antibodies in weighted analyses. Seroprevalence was positively associated with age of the child and province, with seropositivity highest in Bandundu (53%) and lowest in Kasai-Oriental (20%). In multivariate analyses, serologic evidence of infection was associated with age of the mother and child, socioeconomic status and geographic location.

Conclusions: Rubella infection is prevalent among children in the DRC, and while most seroconversion occurs in young children, a significant proportion of children remain at risk and may enter reproductive age susceptible to rubella infection. While not currently in place, implementation of a surveillance program will provide improved estimates of both rubella virus circulation and the burden of congenital rubella syndrome. Such information will play an important role in future policy decisions, vaccine delivery strategies and may provide a basis upon which the effectiveness of rubella antigen introduction may be assessed.

Key Words: rubella, congenital rubella syndrome, immunization, vaccine-preventable diseases, Democratic Republic of the Congo

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Rubella is a vaccine-preventable infection caused by the rubella virus and is predominantly spread through direct contact or inhalation of aerosolized droplets.[1] In childhood, the disease is generally mild, characterized by fever and rash[2]; however, as many as 50% of infections are asymptomatic or without exanthema.[3] During pregnancy, infection of the mother may lead to fetal infection that, particularly during the first trimester, may result in miscarriage, fetal death or an infant born with birth defects known as congenital rubella syndrome (CRS).[2,4–7] A leading cause of preventable congenital defects in offspring,[8] CRS may lead to deafness, blindness, mental retardation and congenital heart disease.[4,6,7] However, the severity of effects on the fetus may depend on the period of gestation at which the infection occurs.[9] Despite limitations because of under-reporting, 2010 estimates suggest that approximately 116 new cases of CRS per 100,000 live births occur per year in Africa; with an estimated 38,000 cases (range: 18,000–80,000), the burden of CRS in Africa is among the highest globally.[10] In the Democratic Republic of the Congo (DRC), a recent study estimated that the number of CRS cases in 2013 was 2253 (95% confidence interval: 267–4991), with cases higher in rural than urban areas.[11]

Morbidity and mortality associated with rubella infection are preventable as safe and effective rubella-containing vaccines (RCVs) have been available since 1969; these are generally offered in combination with measles (measles-rubella) or both measles and mumps (measles-mumps-rubella). Successful implementation of widespread RCV immunization has resulted in substantial reductions in rubella incidence throughout the world. In outbreak situations, the effectiveness of different RCVs has been estimated to be ≥90% effective at interrupting transmission events, and vaccine-induced immunity is assumed to be lifelong.[12,13] While the primary goal of rubella vaccination is to prevent CRS,[14] elimination of rubella virus transmission in the World Health Organization (WHO) Region of the Americas in 2015 indicates that worldwide rubella eradication may be possible.[12,15]

At present, only 10 of 46 member states include the rubella antigen in their routine immunization (RI) program.[12,16] Introduction of RCV has been limited; the WHO recommends the inclusion of the rubella antigen into RI in countries that have well-established, effective childhood immunization programs with the capacity to maintain high levels (≥80%) of measles vaccination (measles-containing vaccine, first dose) coverage or provide 2 doses of measles vaccine using RI or supplementary immunization activity (SIA).[12] While introduction of RCV may hinder the natural spread of rubella in small children, inadequate childhood coverage may result in an increased number of individuals lacking natural immunity, which may ultimately lead to epidemics in adulthood. This paradoxical shift of susceptibility to older ages, particularly among women of child bearing age, may then increase the prevalence of CRS in the population more than without vaccine introduction[12] as experienced in both Costa Rica and Greece after periods of inadequate rubella coverage in children.[17,18]

In the DRC, rubella antigen is not currently a part of RI, and the true burden of rubella is unknown. However, the country does have an established measles case-based surveillance (CBS) system in which laboratory testing for rubella IgM is conducted on specimens found to be negative or indeterminate for measles IgM antibody. Between 2010 and 2012, measles outbreaks occurred in all 11 provinces, and among children <5 years of age, >9% of

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measles-negative cases were confirmed rubella IgM positive.[19] A study using the measles CBS system identified 258 rubella IgM positive individuals among the 1013 available samples from 2010 to 2012 in Kinshasa, DRC, with 35% of the rubella cases among 0–4 year olds.[20] Furthermore, a study of 2004–2013 data from the measles CBS system found that 24% of the 11,733 samples analyzed for the presence of rubella IgM were positive, with 35% of the rubella cases among the 0–4 year olds.[21] Furthermore, the percentage of rubella IgM positive cases identified through this system rose from 20% in 2005 to 46% in 2013, with circulating DRC rubella viruses belonging to genotypes 1B, 1E, 1G and 2B.

Given the limitations of the measles CBS system for estimating the burden of rubella (only those presenting with measles-like illness may be captured, and only a subset of these suspected measles cases are tested), these studies suggest that rubella is circulating in DRC, and an increasing number of cases have been identified over time, with a significant proportion among young children. Therefore, in collaboration with the 2013–2014 Demographic and Health Survey (DHS), we assessed the prevalence of serologic response against rubella in children 6–59 months of age to obtain nationally representative and age-specific estimates of rubella infection in the DRC.

MATERIALS AND METHODS

Study Population and Design

The DRC is the fourth most populous nation in Africa with an estimated 77.8 million inhabitants and 11.9 million children under the age of 5 years.[22] From November 2013 to February 2014, the second DHS was conducted in the DRC. Using a 2-stage stratified cluster design, the survey generates nationally representative data on population health and social indices. Details on the sampling design and data collection procedures are described elsewhere.[23] Data were collected from a nationally representative sample of 9000 households; only children 6–59 months of age in households from which men were selected to participate were eligible for the survey.

Data obtained from children included, but was not limited to, demographics, anthropometric measures, health outcomes and vaccination history. After parental consent, dried blood spots (DBS) were collected from participating children. All survey data were double entered from paper questionnaires to an electronic format using the Census and Survey Processing System (US Census Bureau, ICF Macro, Rockville, MD) and verified by comparison. Ethical approval was obtained at UCLA Fielding School of Public Health, the Kinshasa School of Public Health and the Centers for Disease Control and Prevention.

Laboratory Analysis

DBS samples were extracted using a modified extraction protocol[24] and processed at the UCLA-DRC laboratory housed at National Laboratory for Biomedical Research in Kinshasa, DRC. A 0.25" DBS punch was extracted, shaking at room temperature, in 1 mL phosphate buffered saline, 0.05% Tween-20 and 5% dried milk, which represents a 1:143-fold dilution assuming 7 µL of serum per punch. The Dynex Technologies Multiplier FLEX chemiluminescent immunoassay platform with a research use only M^2 multiplex kit for measles, mumps, rubella, varicella zoster virus and tetanus was used to test samples for IgG antibody response. Polystyrene beads coated separately with antigen to measles, mumps, rubella, varicella zoster and tetanus were immobilized within 54-well M^2 assay strips with 10 beads per well and processed using a modified Dynex DS2 automated enzyme-linked immunosorbent assay system for IgG antibody detection. Based upon epidemiologic studies,[25,26] cutoffs for serologic results were as follows: <8.2 IU/mL as negative; 8.2 to <10 IU/mL as indeterminant; ≥10 IU/mL as positive. For analyses, the positive/negative cutoff for rubella IgG antibody detection was set at 10 IU/mL.

Statistical Analysis

As the DRC does not include RCVs as part of RI, it is presumed that a positive serologic test is the result of infection. The χ^2 analyses were performed on the weighted sample to assess the sociodemographic differences by serologic test results (positive and negative for rubella antibody). Univariate logistic regression models were used to identify independent predictors of seropositivity among variables included in Table 1. Multivariable regression models were initially run with all variables; using backward selection, only significant predictors (alpha ≤ 0.05) were retained. Children for whom test results were indeterminate (n = 6) were categorized as positive, and in sensitivity analyses, these subjects were removed to assess the impact of their inclusion on findings.

To assess spatial distribution of serologic response in children, maps of the prevalence of rubella seropositivity by province were created for all children (6–59 months), those <1 and 4 years of age, separately. A smoothed map of the spatial pattern was also created using inverse distance weighting spatial interpolation, which uses nearby values to predict prevalence in unmeasured locations. The prevalence values of the 12 closest clusters to an unmeasured location were used to interpolate its prevalence of seropositive children, with closer communities having a greater influence than those farther away. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC), and maps were generated using ArcGIS software version 9.3 (ESRI, Redlands, CA).

RESULTS

Among the 7195 children 6–59 month of age included in analyses, 2279 (32%) were positive, 4910 (68%) were negative and 6 (<1%) were indeterminant for rubella antibody (Fig. 1). To account for population sampling methods, application of DHS sampling weights resulted in 7250 children among whom 2408 (33%) were positive, 4834 (67%) were negative and 8 (<1%) were indeterminant.

Overall, children born to highly educated, high socioeconomic status, older mothers (>26 years of age) were more likely to test positive for rubella IgG compared with their younger, lower socioeconomic status counterparts (Table 1). Assessment of the assay response reveals an increase in seropositivity with increasing age, with a positive linear relationship: from 12% of 6 month olds to 37% of 59 month olds (range: 12%–54%; Fig. 2).

Among all children in weighted, age-adjusted analyses, those living in Bandundu and Bas-Congo had the highest prevalence of seropositive children (53% and 44%, respectively) whereas Kasai-Oriental had the lowest (20%; Fig. 3). In addition, among children 6–11 months of age, seropositivity was highest in Bandundu (28%) and lowest in Kinshasa (11%), while among the oldest children (those 4 years of age), seropositivity was highest in Bandundu (65%) and lowest in Kasai-Oriental (24%).

Overall, place of residence was associated with serology as those living in an urban environment were more likely to be seropositive than rural residents (Table 1). Assessment within provinces revealed this association held for Equateur, Kasai-Occidental, Katanga and Maniema while in Bandundu the opposite was found: seropositive outcomes were more likely to be found in rural than urban settings (Fig. 4).

In multivariate analyses, the odds of seropositivity increased with increasing age (compared with 6–12 month olds, children 4 years of age had 3.78 times the odds of a positive test result for rubella antibodies), mother's age (children of mothers ≤20 years

TABLE 1. Weighed Demographic Characteristics of 2013–2014 DRC-DHS Respondents 6–59 Months of Age by Rubella Serosurvey Result

	Negative (n = 4834)		Positive (n = 2416)		
	n	%	n	%	χ^2 *P* Vaue
Children's information					
Child age					
6–11 mo*	702	15	148	6	<0.0001
1 yr	1245	26	442	18	
2 yr	1116	23	545	23	
3 yr	970	20	577	24	
4 yr	798	17	703	29	
Child sex					
Male	2459	51	1175	49	0.0759
Female	2375	49	1240	51	
Children in household†					
1	793	16	265	11	<0.0001
2	991	21	481	20	
3	927	19	458	19	
4	762	16	442	18	
5 or more	1361	28	770	32	
Mother's information					
Mother's age at birth (yr)					
≤20	885	18	339	14	<0.0001
21–25	1301	27	663	27	
26–30	1211	25	680	28	
31–35	792	16	408	17	
>35	644	13	325	13	
Mother's highest level of education					
No education	1023	21	438	18	0.0015
Primary	2115	44	1044	43	
Secondary/higher	1696	35	933	39	
Wealth index‡					
Poorest	1159	24	473	20	<0.0001
Poorer	1067	22	623	26	
Middle	1010	21	460	19	
Richer	939	19	417	17	
Richest	659	14	443	18	
Province					
Kinshasa	291	6	188	8	<0.0001
Bandundu	580	12	651	27	
Bas-Congo	179	4	137	6	
Equateur	769	16	310	13	
Kasai-Occidental	396	8	165	7	
Kasai-Oriental	655	14	140	6	
Katanga	499	10	249	10	
Maniema	182	4	73	3	
Nord-Kivu	418	9	194	8	
Orientale	443	9	179	7	
Sud-Kivu	421	9	130	5	
Residence					
Urban	1373	28	794	33	<0.0001
Rural	3462	72	1622	67	

*Only children 6 months of age and older were invited to participate in the serosurvey.

†Children in household is the sum of boys and girls that currently live in the household.

‡Wealth index is a composite measure of a household's cumulative living standard, calculated from household ownership of selected assets (such as televisions and bicycles), materials used for housing construction and types of water access and sanitation facilities. Using principal components analysis, the DHS separates all interviewed households into 5 wealth quintiles.

of age had the lowest odds of rubella seropositivity compared with all other age groups), wealth index (richest compared with poorest) and province (Bandundu and Bas-Congo with the highest odds of positive test result and Kasai-Oriental with the lowest compared with Kinshasa; Table 2). Exclusion of indeterminant serologic results did not impact findings (data not shown).

DISCUSSION

In this nationally representative sample, we found that rubella virus is circulating throughout DRC, and approximately one third of children 6–59 months of age show serologic evidence of infection. Seroprevalence of rubella-specific IgG antibodies was associated with both age of the child and province: 11%–28% of 6–11 month olds and 24%–65% of 4 year olds were seropositive for rubella, with the highest prevalence in Bandundu.

Our finding of increased rubella seropositivity with increasing age is consistent with childhood serosurveys in other African countries conducted before RCV introduction.[27,28] A study conducted in the Central African Republic found that 32% of children 6 to <12 months of age and 38% of children 1–4 years of age had evidence of rubella-specific IgG antibody.[27] In study of Nigerian

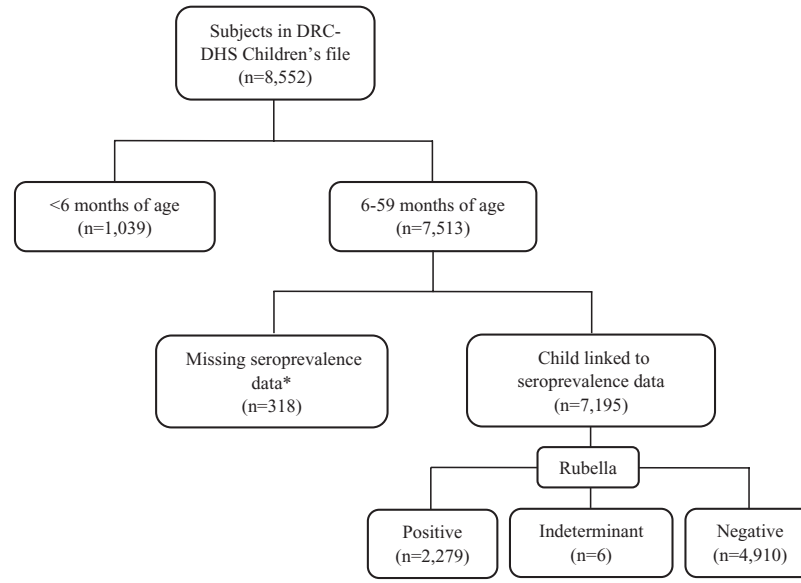

FIGURE 1. Study inclusion for assessment of rubella seroprevalence among 6- to 59-month-old 2013–2014 DRC-DHS respondents (unweighted). *Those with missing seroprevalence data include 18 who were not present, 129 who refused participation, 120 for whom the DBS sample was not found in the database, 20 for whom the barcode to match DBS sample was not known and 31 "others."

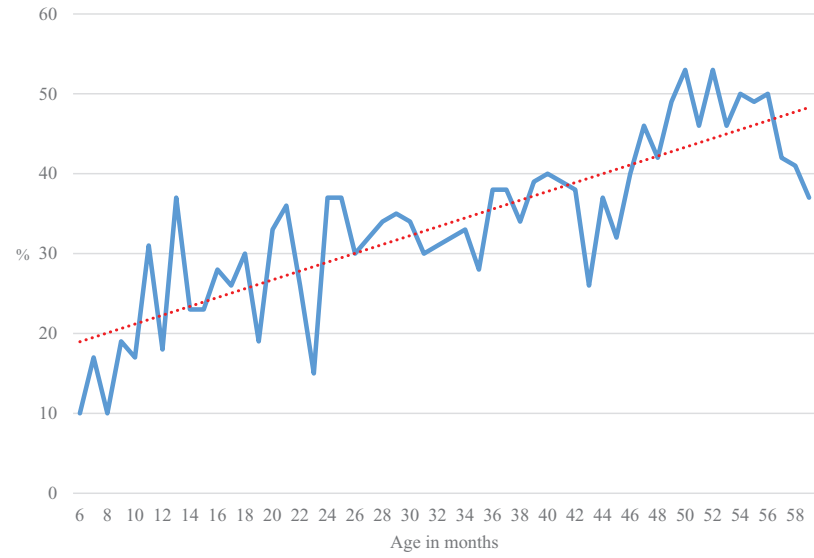

FIGURE 2. Percent of positive rubella antibody test results according to age among 2013–2014 DRC-DHS child respondents (with linear trend line in red). full color online

children, 36% of children <1 year, 40% of those between 1 and 4 years and 52% of children between 5 and 10 years of age were positive for rubella IgM antibody.[28] However, it is worth noting that these studies are limited in scope because of small sample sizes and assessment of serology in only Bangui, Central African Republic and Jos, Nigeria.

Currently in the DRC, the only opportunity for laboratory identification of rubella infection is through measles CBS. Based on this limited system, among identified rubella cases, 2% were in children ≤6 months of age, which may be because of maternal IgG protection, and 17% in children ≥10 years of age.[29] It should be noted that these estimates are not representative of the true burden of infection as only suspected measles cases (those identified and presenting with measles-like illness) that are negative or indeterminate are then tested against rubella. While we were limited by the age range of children included in the study population (6 months to <5 years), we found 48% of female 4 year olds were seropositive, leaving 52% at risk of rubella infection (similar to males). As no population-based estimates of the burden of rubella exist, these data suggest that a significant proportion of young women may enter reproductive age susceptible to rubella infection. While most viral exposure and seroconversion occurs before 15 years of age, a study of pregnant women in 3 DRC provinces found that 16% (95% confidence interval: 14–18) were serologically negative and at risk of rubella infection between 2008 and 2009.[11] Furthermore, as serologic data from 14 African countries indicate a significant range in the susceptibility of women of childbearing age[30,31] and differences in serology within DRC vary significantly by geographic area,[11] surveillance and information on rubella seroprevalence among adolescent women and adults are necessary.

We also found that 15% of 6 month olds had serologic evidence of rubella infection. While maternal antibodies are likely waning at this age,[27] it is not possible to distinguish whether seropositivity was the result of persistent maternal antibodies, CRS as a result of maternal infection during pregnancy or infection with rubella in early infancy.[32] Previous research suggests that retrospective determination of CRS is possible through a comparison of antibody profiles of the child and mother[33–35]; however,

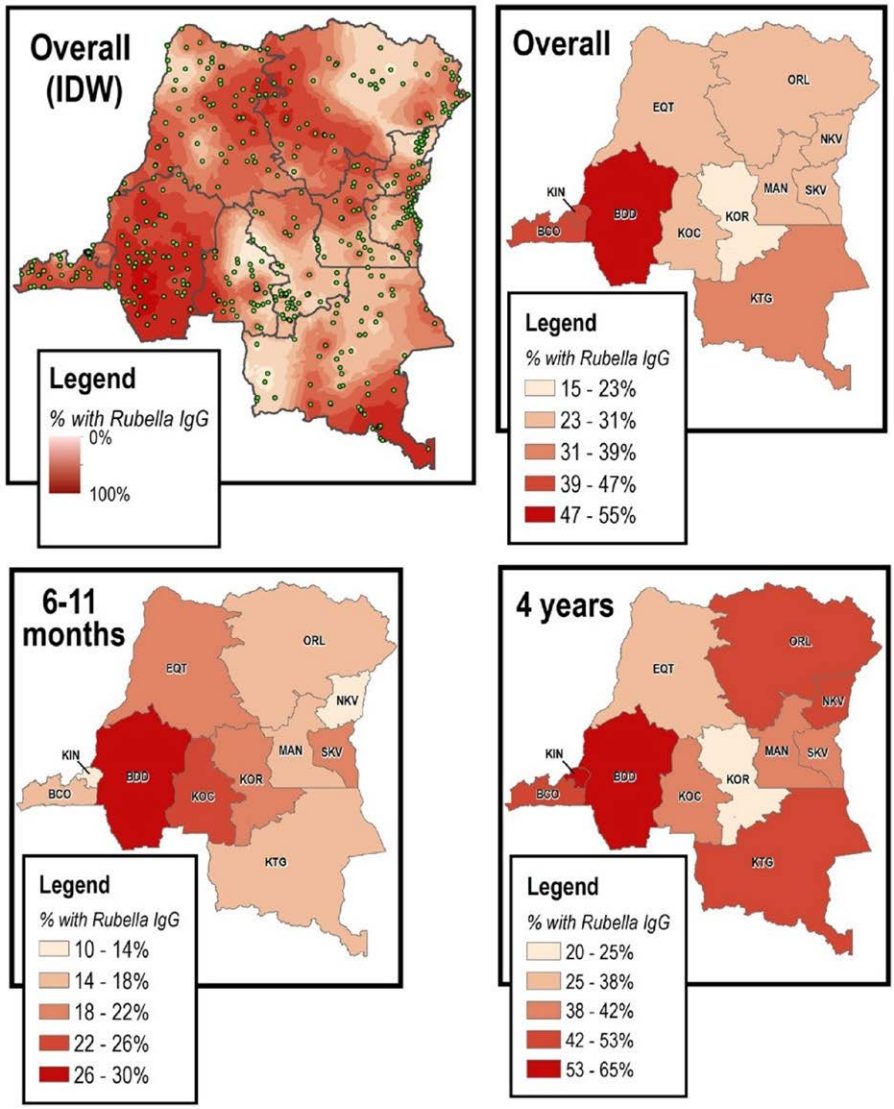

FIGURE 3. Geographic distribution of rubella seropositivity for 2013–2014 DRC-DHS by province among all children 6–59 months of age with and without inverse distance weighting (IDW),* children 6–11 months of age and children 4 years of age. The 2013–2014 sampling clusters are indicated in green. *A smoothed map of the spatial distribution of rubella seropositivity prevalence was created using IDW spatial interpolation, using prevalence of the 12 closest clusters to predict prevalence of an unmeasured location. full color online

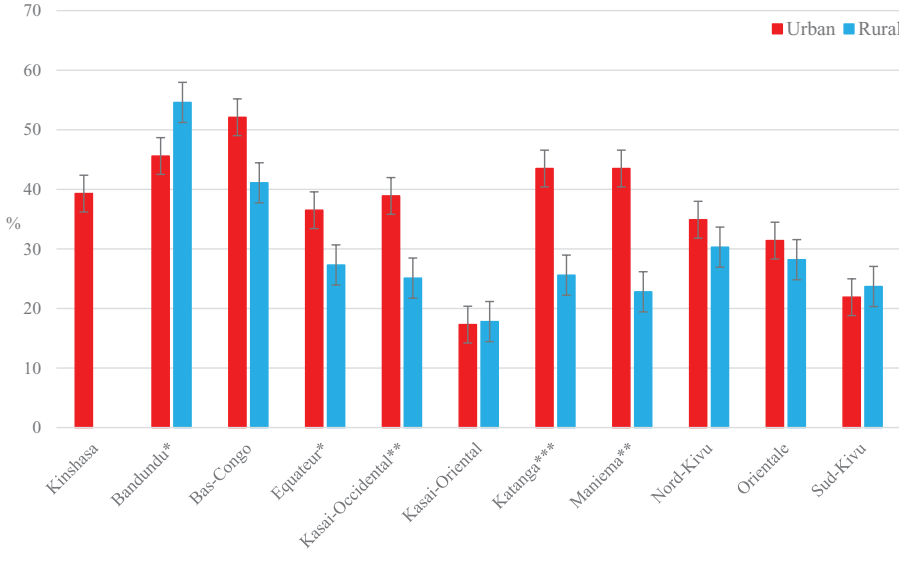

FIGURE 4. Prevalence of seropositive results according to place of residence by province among 6- to 59-month-old 2013–2014 DRC-DHS respondents (with standard error bars). *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$. full color online

TABLE 2. Weighted Logistic Regression of Sociodemographic Factors Associated With Rubella Seropositivity of 6- to 59-Month-Old 2013–2014 DHS Respondents

	OR_{Crude} (95% CI)	$OR_{Adjusted}$* (95% CI)
Children's information		
Child age		
6–11 mo†	ref	ref
1 yr	1.69 (1.37–2.08)	1.73 (1.40–2.14)
2 yr	2.33 (1.90–2.86)	2.46 (1.99–3.03)
3 yr	2.83 (2.31–3.48)	2.96 (2.40–3.66)
4 yr	4.19 (3.42–5.14)	4.37 (3.54–5.40)
Child sex		
Male	ref	-
Female	1.09 (0.99–1.21)	-
Children in household‡		
1	ref	-
2	1.45 (1.22–1.74)	-
3	1.48 (1.24–1.77)	-
4	1.74 (1.45–2.09)	-
5 or more	1.70 (1.44–2.00)	-
Mother's information		
Mother's age at birth (yr)		
≤20	ref	ref
21–25	1.33 (1.14–1.56)	1.15 (0.98–1.36)
26–30	1.47 (1.25–1.71)	1.35 (1.14–1.59)
31–35	1.34 (1.13–1.60)	1.14 (0.95–1.36)
>35	1.32 (1.10–1.58)	1.19 (0.98–1.44)
Mother's highest level of education		
No education	0.78 (0.68–0.89)	-
Primary	0.90 (0.81–1.00)	-
Secondary/higher	ref	-
Wealth index§		
Poorest	ref	ref
Poorer	1.43 (1.24–1.66)	1.28 (1.10–1.50)
Middle	1.12 (0.96–1.30)	1.07 (0.91–1.26)
Richer	1.09 (0.93–1.27)	1.19 (1.00–1.41)
Richest	1.65 (1.40–1.94)	2.02 (1.64–2.49)
Province		
Kinshasa	ref	Ref
Bandundu	1.73 (1.40–2.14)	3.01 (2.27, 3.99)
Bas-Congo	1.18 (0.89–1.58)	1.86 (1.34–2.59)
Equateur	0.62 (0.50–0.78)	1.10 (0.83–1.48)
Kasai-Occidental	0.64 (0.50–0.83)	1.12 (0.82–1.54)
Kasai-Oriental	0.33 (0.25–0.43)	0.52 (0.38–0.70)
Katanga	0.77 (0.61–0.98)	1.15 (0.88–1.52)
Maniema	0.62 (0.44–0.85)	1.04 (0.71–1.52)
Nord-Kivu	0.72 (0.56–0.92)	1.09 (0.81–1.46)
Orientale	0.62 (0.48–0.80)	1.10 (0.81–1.49)
Sud-Kivu	0.48 (0.36–0.62)	0.80 (0.58–1.10)
Residence		
Urban	1.23 (1.11–1.37)	-
Rural	ref	-

*Using backwards selection, only significant predictors (alpha ≤ 0.05) were retained in the final model; predictors in adjusted model include child's age, mother's age, wealth index and province.

†Only children 6 months of age and older were invited to participate in the serosurvey.

‡Children in household is the sum of boys and girls who currently live in the household.

§Wealth index is a composite measure of a household's cumulative living standard, calculated from household ownership of selected assets (such as televisions and bicycles), materials used for housing construction and types of water access and sanitation facilities. Using principal components analysis, the DHS separates all interviewed households into 5 wealth quintiles.

CI indicates confidence interval; OR, odds ratio.

we were limited in our ability to perform such analyses. Additional limitations included possible misclassification of serostatus as a result of the chosen testing platform. However, compared with 4 commercially available gold standards, the validity of the M^2 multiplex was high (averaged 89.8% for sensitivity and 98.5% for specificity), thus the impact on results is likely minimal (Higgins SG. Validations of Dynex multiplexed serology panel for measles, mumps, rubella, varicella zoster virus and tetanus, unpublished work, 2016). Moreover, as we were able to evaluate the serology of 4 other vaccine-preventable diseases using the multiplex assay, the cost-effectiveness of this assay outweighed this limitation. In addition, because of the presence of 13 serologically indeterminate results, we initially categorized these children as positive, yet in sensitivity analysis, exclusion of these individuals did not change our results. While we presumed a positive serologic test result was a result of infection, it is possible that a small number of children may have had the opportunity for vaccination; however, the lack of documentation in the DHS on vaccines outside those provided by the government was a limiting factor.

Apart from disease burden, deciding whether to introduce the rubella antigen also requires careful evaluation of the economic impact and costs associated with immunization. Based on 2016 price of 10 doses per vial, the combined Measles-Rubella vaccine only increases the cost per dose by $0.30 USD.[8,36] While this increase in cost can be an obstacle for countries like the DRC, in 2011 the Global Alliance for Vaccines Initiative opened a funding window to which low- and middle-income countries may apply for funding to support rolling out a vaccine against rubella,[37] thus alleviating the financial burden from counties that qualify and apply. Rubella vaccination has been found to be cost effective in resource-limited countries, specifically when the treatment of 1 CRS case over a lifetime can exceed $75,000 USD.[38] Furthermore, as it does not require cold chain considerations and can be combined with the measles vaccine, which is already part of the immunization program, the rubella antigen may be easily adapted into national vaccine programs.

Thus far, a small number of sub-Saharan African countries have introduced rubella vaccine into their RI schedule.[16] However, the WHO recommends the inclusion of the rubella antigen into RI in countries that have well-established, effective childhood immunization programs with the capacity to maintain high levels (≥80%) of measles vaccination (measles-containing vaccine, first dose) coverage or provide 2 doses of measles vaccine using RI or SIA.[12] In the DRC, United Nations Children's Fund/WHO estimate that national measles RI coverage was 77% in 2014[39] and of the 516 health zones, 23% fell below 80% coverage.[40] Large funding shortfalls have led to the delay of SIAs and measles outbreaks continued throughout 2015 in a number of areas where coverage remained low.[8]

In the interim, as the DRC prepares for rubella antigen introduction, it is important to implement strengthen surveillance efforts to better understand the epidemiology of rubella and CRS in the country, which are not in place at the time of writing this article. Nationwide estimates of the burden of CRS among infants, as well as the rubella immunity profile among reproductive-age women, in the DRC will play an important role in policy decisions and vaccine delivery strategies[41] as a combined vaccination strategy focusing on both children and at-risk adults will be necessary to ensure women of childbearing age are adequately protected.[12,42] As the rubella epidemic cycle is estimated to be 6–9 years,[43] monitoring the population and assessment of rubella incidence may not only help to identify epidemic years but also be used to predict when future epidemics are likely. Most importantly, such surveillance will provide the opportunity for the planning and implementation of targeted interventions based upon incidence of CRS and rubella susceptibility by geographic location to improve the health of the population.

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