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Epidemiology of rubella infection in Cameroon: a 7-year experience of measles and rubella case-based surveillance, 2008–2014

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ABSTRACT

Objective The aim of this study was to estimate the proportion of rubella disease in a measles case-based surveillance in Cameroon prior to rubella vaccine introduction into the national immunisation programme.

Design This was a cross-sectional study for rubella infection in Cameroon for the period 2008 to 2014.

Setting Patients suspected with measles from the 10 regions of Cameroon were recruited according to the WHO measles case definition and were tested for rubella IgM antibodies accompanied with the case report/investigation forms.

Participants All persons with rash and fever within 14 days of onset of rash according to the standard WHO African Regional Office (WHO/AFRO) case definition for a suspected measles case.

Outcome measures Descriptive analyses and simple logistic regressions were performed. OR were estimated.

Results A total of 9907 serum samples from people with fever and rash were received in the laboratory from 2008 to 2014. A total of 7489 (75.59%) measles-negative samples were tested for rubella; 699 (9.3%) were positive for rubella IgM antibodies. Logistic regression analysis was done using IgM antibodies detection as the outcome variable. Age, sex and setting were explanatory variables. Logistic regression analysis revealed that, comparing the proportion of rubella IgM seropositivity status by age, the association to a positive rubella IgM increased with age from 1 to 4 years (OR 7.11; 95% CI 4.35 to 12.41; p<0.0001), through 5 to 9 years (OR 13.07; 95% CI 7.93 to 22.93; p<0.001), to 10 to 14 years of age (OR 13.86; 95% CI 8.06 to 25.12; p<0.001). Persons aged ≥15 years were also more likely to have rubella infection than children under one (OR 3.69; 95% CI 1.85 to 7.48; p=0.0001). There were also significant associations with sex, with males being less associated to a positive rubella serology than females (OR 1.33; 95% CI 1.14 to 1.56; p=0.0001). No statistically significant difference in proportion of rubella cases was observed between urban and rural populations (OR 1.11; 95% CI 0.94 to 1.31; p=0.208).

Conclusions This study reveals that rubella virus circulates in Cameroon, with important number of cases in children under 15 years. This finding supports the planned introduction of rubella-containing vaccines into the Expanded Program on Immunization.

INTRODUCTION

Rubella is an acute, contagious viral disease caused by a Togavirus of the genus *Rubivirus* and is characterised by a mild maculopapular rash.[1] The illness is often mild in children but has serious consequences in pregnant women. Arthralgia or arthritis may occur in up to 70% of adult women infected with rubella with rare complications including thrombocytopenic purpura and encephalitis.[2 3] The infection in women during the first trimester of pregnancy can severely affect the fetus, resulting in miscarriage, fetal death or the combination of disabling conditions collectively called congenital rubella syndrome (CRS). Common birth defects are ocular (retinitis, microphthalmia, glaucoma and cataracts), hearing impairment, hearing defects, pulmonary stenosis, persistent ductus arteriosus, microcephaly, developmental delay, mental retardation, bone alterations and damage to the liver and spleen.[4] Global estimates of the burden of rubella suggest that 100 000 infants are born with CRS each year which makes rubella a leading cause of preventable

congenital defects.[5][6] The estimates for 2008 suggest that the highest CRS burden is in South-East Asia (48%) and Africa (38%). Economic analysis for rubella and CRS control suggest that incorporation of rubella-containing vaccine (RCV) into national childhood immunisation schedules is both cost-beneficial and cost-effective.[7] Estimates suggest a wide range for the lifetime cost of treating a single CRS case from US$4200 (inflation-adjusted 2012), in a middle-income country such as Brazil, to over US$200 000 (inflation-adjusted 2012), in a high-income country such as the USA.[8] At least five of six WHO regions have set rubella control or elimination targets by the year 2020, since the Measles and Rubella Initiative was launched in 2001.[7]

In Cameroon, the national Expanded Program on Immunization (EPI) was established in 1976 and includes provision of the first dose of measles-containing vaccine (MCV1) at 9 months of age. Measles case-based surveillance has been integrated to the acute flaccid paralysis surveillance system to monitor the progress with measles control. Rubella vaccination has not yet been introduced into the infant vaccination schedule in Cameroon, and furthermore, surveillance of rubella per se or CRS does not exist. However, the measles case-based surveillance system, established in 2004, includes laboratory testing for the detection of measles-specific and rubella-specific IgM antibodies. Cameroon planned to introduce the (RCV) into the EPI in 2016 starting by a national measles and rubella mass vaccination campaign for children under 15 years. WHO recommends that epidemiological analysis should be carried out in the process of rubella vaccine introduction to evaluate the burden of the disease.[9] However, very limited studies have been conducted in the country to determine the epidemiology of the disease and gather baseline evidence prior to this introduction.

This study aims to determine the epidemiology of rubella disease in Cameroon based on the national measles case-based surveillance system from 2008 to 2014. The outcome of this analysis provides baseline data for future monitoring of the impact of rubella vaccines in the national EPI programme.

METHODS
Sampling and laboratory procedure
We carried out a cross-sectional study on the national rubella case-based surveillance activities for the period 2008 to 2014 in Cameroon. Cameroon is located in Central Africa within the WHO African Region with a projected population of 22 179 707 habitants in 2015. It was estimated that children under 5 years account for about 16.6% and about 51% of the population were female.[10] Life expectancy at birth is estimated to be 58 years, and the total fertility rate is six children per woman of childbearing age.[11]

During the study period, blood samples were collected by nurses from persons with rash and fever within 14 days of onset of rash according to the standard WHO African Regional Office (WHO/AFRO) case definition for a suspected measles case (ie, any person with generalised maculopapular rash and fever plus one of the following: cough or coryza (runny nose) or conjunctivitis (red eyes) or any person in whom a clinician suspects measles). This case definition was applied to both children and adults seeking care in health facilities all over the country. According to the WHO guidelines for measles case confirmation, suspected cases were tested for the presence of measles IgM antibodies.[12] However, in the case of a measles outbreak, only five suspected cases are tested for the presence of measles IgM antibodies and if three or more of the cases test measles IgM positive, this is declared as a laboratory-confirmed outbreak. In the confirmed outbreak situation, no further samples are collected in the affected area until 30 days after the initial confirmation of the outbreak.

At first contact with a suspected measles case, about 1–5 mL of blood was collected by venipuncture into a sterile anticoagulant-free tube. The blood was then allowed to clot then centrifuged at 3000 rpm for 5 min to separate the serum. If there was no centrifuge in the health centre, the blood was stored in a refrigerator until the clot was completely retracted from the serum. The serum was transferred aseptically into a phial and stored at 2°C–8°C for at most 3 days before being transported in a cold chain to Pasteur Institute Cameroon, which houses the national measles/rubella surveillance laboratory, accredited by the WHO Global Measles and Rubella Laboratory Network (Labnet).

In the testing laboratory, sera were stored at −20°C and tested within 7 days. ELISA for rubella-specific IgM antibodies was carried out according to the manufacturer's instructions (Enzygnost Anti-Rubella Virus/IgM kit; Siemens, Erlangen, Germany). Patients with rubella IgM-positive serum samples were classified as laboratory-confirmed rubella cases. Due to limited resources, all samples were tested once and those producing equivocal results were not retested.

Data management and analysis
The laboratory results and completed individual case investigation forms were sent to the EPI programme. Forms collected from the laboratory were reviewed and entered into the WHO electronic database. The case-based surveillance data were reported on a weekly basis by the EPI programme to the WHO country office.

Statistical analyses were performed using the SPSS statistical package (V.16). Data were cleaned and analysis of rubella cases done by year, age, age group, sex, setting/region and months. Descriptive analysis was completed with bivariate analyses using x^2 or Fisher's exact tests for categorical variables to find key determinant of rubella infection in Cameroon. A 95% CI was calculated for the OR, and values of $p<0.05$ were considered statistically significant. Logistic regression analysis was used to estimate OR of IgM seropositivity

Table 1 Proportion of rubella cases in Cameroon by year (2008–2014)

Year	Number tested for rubella IgM	Outcome of tests	
		Positive (%)	Indeterminate (%)
2008	646	78 (12.1%)	20 (3.1%)
2009	688	32 (4.7%)	1 (0.1%)
2010	655	42 (6.4%)	6 (0.9%)
2011	1107	105 (9.5%)	30 (2.7%)
2012	1185	147 (12.4%)	43 (3.6%)
2013	1342	147 (11.0%)	44 (3.3%)
2014	1866	148 (7.9%)	58 (3.1%)
Total	7489	699 (9.3%)	202 (2.7%)

as outcome variable with age, sex and setting as explanatory variable.

RESULTS

Proportion of rubella diseases

A total of 9907 samples from suspected measles cases were received in the laboratory from 2008 to 2014 among which 7489 (75.59%) measles-negative samples were tested for rubella; 699 (9.3%) were positive for rubella IgM antibodies. The proportion of rubella IgM antibodies varied from 4.7% in 2009 to 12.4% in 2012 (table 1). Also, results of 202 (2.7%) cases were indeterminate and were treated as negative.

Distribution of rubella cases by age

Among the 699 positive cases, the median age was 5 years, range 5 months to 68 years. Figure 1 shows that 2.43% of rubella-positive cases were children below 1 year of age (representing the targeted age in the routine EPI programme) and 96.85% of cases were below 15 years (marking the entrance to childbearing age for young girls).

Rubella distribution by age group

The proportion by age group shows that the age groups between 5–9 years and 10–14 years had highest proportions of rubella infection (figure 1 and table 2).

Distribution of rubella cases by sex

The sex was available for 698 cases (99.85%) out of 699. More than half (380/698, 54.44%) of positive rubella cases were females. Females were 1.3 times more associated to a positive rubella IgM than males (OR 1.33; 95% CI 1.14 to 1.56; p=0.0001) (table 2).

Rubella in women of childbearing age (15–49 years)

There were 242 females of childbearing age who were tested, 11 (4.55%) were positive for rubella IgM antibodies. The proportion of positive rubella cases within this high-risk group varied from one year to another, with the lowest of 0.0% in 2008 and the highest of 15.8% in 2012.

Rubella case distribution by setting/region

The setting was specified for 7466 suspected rubella cases (99.7%) out of 7489. There was no statistically significant difference in proportion of rubella cases between urban and rural populations (OR 1.11; 95% CI 0.94 to 1.31; p=0.208) (table 2). The proportion of rubella-positive cases by regions in Cameroon between 2008 and 2014 shows that, the East, North-West and the South-West regions had higher proportions of rubella cases (figure 2).
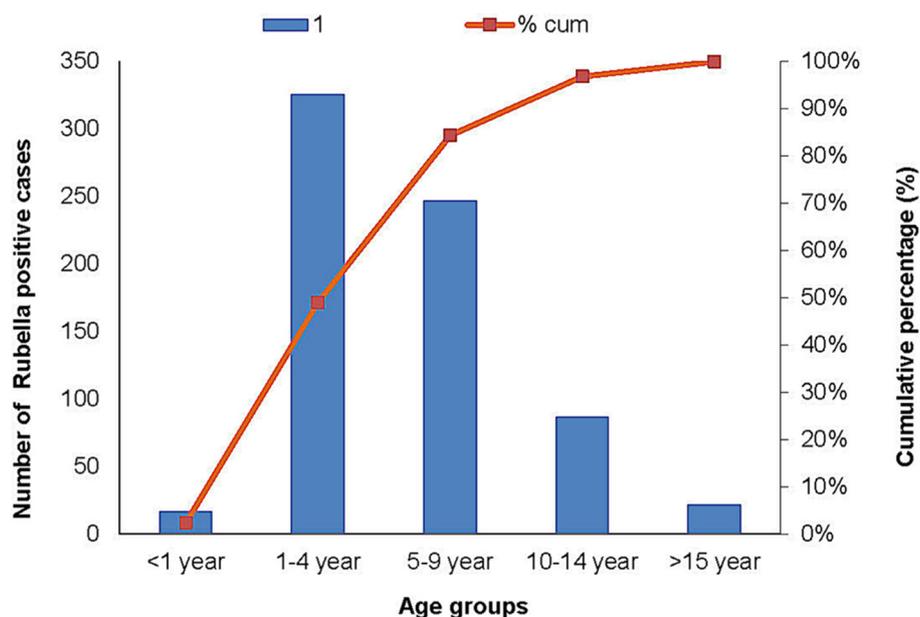

Figure 1 Rubella case distribution by age in Cameroon, 2008–2014.

Table 2 Distribution of rubella cases by some sociodemographic characteristics in Cameroon, 2008–2014

	Number tested for rubella	Number tested positive (%)	OR	95% CI	P value
Age group					
<1 year	1244	17 (1.37)	1		0.0001
1–4 years	3635	326 (8.97)	7.11	4.35 to 12.41	
5–9 years	1610	247 (15.34)	13.07	7.93 to 22.93	
10–14 years	540	87 (16.11)	13.86	8.06 to 25.12	
≥15 years	452	22 (4.87)	3.69	1.85 to 7.48	
Total	7481	699 (9.3)			
Sex					
Male	3904	318 (8.2)	1		0.0001
Female	3584	380 (10.6)	1.33	1.14 to 1.56	
Total	7488	698 (9.3)			
Setting					
Rural	4815	435 (9.0)	1		0.208
Urban	2651	264 (9.9)	1.11	0.94 to 1.31	
Total	7466	699 (9.3)			

Seasonal distribution of rubella cases from 2008 to 2014

The analysis of the number of rubella cases during the study period 2008 to 2014 revealed an apparent seasonality in Cameroon. Monthly variation showed that the number of rubella cases during the months of February to April was highest, which represents the end of the dry season and beginning of the raining season in most parts of Cameroon with a sharp decline in numbers in the months of July through September (figure 3).

Logistic regression analysis

Logistic regression analysis reveals associations of rubella IgM seropositivity with age. Compared with children less than 1 year of age, the association increased with age from 1 to 4 years (OR 7.11; 95% CI 4.35 to 12.41; p<0.0001), through 5 to 9 years (OR 13.07; 95% CI 7.93 to 22.93; p<0.001), to 10 to 14 years of age (OR 13.86; 95% CI 8.06 to 25.12; p<0.001). In addition, people aged 15 years and above captured in the measles case-based surveillance system were also more likely to have rubella infection than children under one (OR 3.69; 95% CI 1.85 to 7.48; p=0.0001). There were also significant associations with sex, with males being less associated to a positive rubella IgM than females (OR 1.33; 95% CI 1.14 to 1.56; p=0.0001).

DISCUSSION

The national measles case-based surveillance system in Cameroon enabled the estimation of the proportion of rubella infections among suspected measles cases. From this study, we observed that during the measles outbreaks between 2008 and 2014, the proportion of rubella cases ranged from 4.7% in 2009 to 12.4% in 2012, with number of cases ranging from 32 to 148 per year. The increase in the proportion of rubella cases during this period could
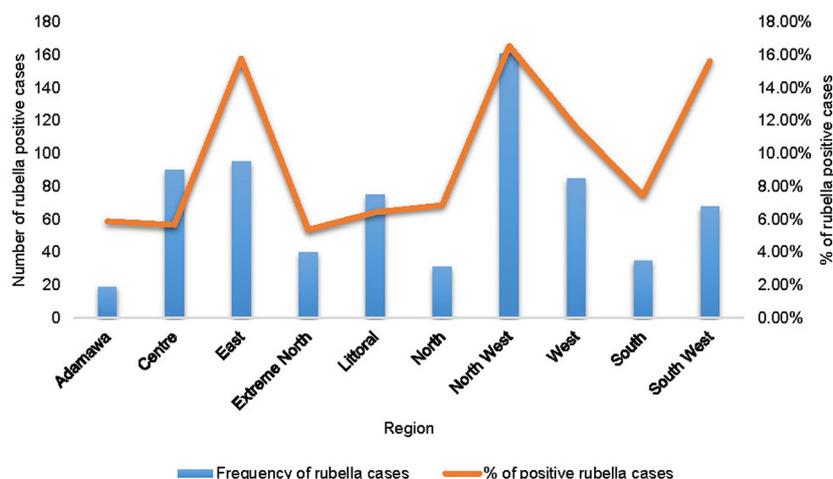
Figure 2 Distribution of rubella-positive cases by region in Cameroon, 2008–2014.
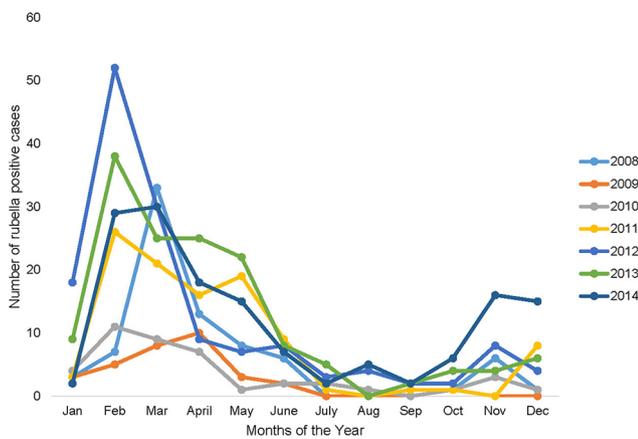
Figure 3 Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008–2014.

actually be indicating a rubella outbreak also, and this type of observation necessitates a clear case definition of rubella infection. Also, the observed increase in rubella cases detected, particularly in 2010 and 2011, could be attributed to the improvements in the sensitivity of the measles case-based surveillance system, through linkage with the strengthened acute flaccid paralysis surveillance system within the context of polio eradication.

Most rubella cases were reported in children below 15 years, indicating that rubella was mainly an illness of young and early-school-age children. This was similar to findings in Ethiopia and Zimbabwe where 94% and 98% of cases, respectively, came from this age group.[13 14] Similarly, the lowest proportion of cases was seen in children below 1 year thereby substantiating the potential benefit if a rubella vaccine is incorporated into the national routine immunisation programme which targets children of this age group. Vaccinating children in the routine immunisation programme at this age will provide protection against rubella in these children through adolescence and adulthood by interrupting virus circulation early in childhood and ideally establishing herd immunity in the population. This will further reduce the risk of acquiring rubella infection during pregnancy and also reduce the burden of CRS.

The proportion of females of reproductive age with positive rubella IgM among captured suspected measles cases was very low (4.55%). It has been documented in other regions that, higher rubella IgM seroprevalence rate was observed in children and adolescent than in adults, with the trend of IgM positivity decreasing with increase in age.[13 15–20] The apparent association of positive rubella IgM results to females should be interpreted with caution as the small differences could be as a result of diagnostic or selection bias in the women than in the men.

There was an apparent seasonal trend in the number of rubella cases where peaks were seen during the end of the dry season (February) and beginning of the raining season (April) in most parts of Cameroon with a sharp decline

in numbers in the month of July through September then gradually begins to increase from October through December. A similar trend was noted by Mitiku *et al*[13] in Ethiopia where a seasonal distribution of cases occurred each year and peaked from March to June. Rubella cases in this study do not show any statistically significant difference between urban and rural populations. Mitiku *et al*[13] noted a significantly higher number of positive cases in the urban areas compared with rural areas.

Occurrence of rubella antibodies in children of 5 months in this study indicates possibility of infection at a younger age although CRS burden is still unknown in Cameroon. In a literature review of CRS and acquired rubella in developing countries, Cutts *et al* reported that data from developing countries suggested that the risk of CRS is at least as high as that in industrialised countries during the prevaccination era.[21] The incidence of CRS per 1000 live births in Cameroon is still unknown. Jivraj *et al*[22] revealed ocular and auditory manifestations of CRS among 320 students from two schools (one for children with hearing impairment and one for children with normal hearing) in Mbingo, Cameroon with 28 (10.2%) probable or clinically confirmed cases according to the WHO case definitions. A probable case of CRS was defined as an individual with two or more of the following conditions: cataract, congenital glaucoma, pigmentary retinopathy or hearing impairment which are clinical major signs of rubella infection. Hearing-impaired children were seven times more likely to have positive serology (48.8%) than children with normal hearing (7.4%; p<0.0001).[22]

These results are subject to some limitations. First, the case definition used to detect the rubella cases was designed for the measles case-based surveillance system. Many individuals with rubella disease may not have rash which occurs in 50%–80% of persons infected with rubella.[9] The sensitivity of the case definition used for measles surveillance is likely not high enough to identify all rubella cases. The system also relies mostly on health facilities and may have missed some community cases. The database also shows existence of missing data for some variables highlighting some issues in the data management and rapid control applications for some key variables.

However, the integration of rubella testing with measles case-based surveillance provides an opportunity to gain understanding about the epidemiology of rubella infection. To better understand the burden and epidemiology of rubella and CRS, Cameroon may consider integration of both surveillances by adopting a more inclusive case definition for measles and rubella, and also conducting well-designed population base studies on rubella burden. The following definition was used by the Pan American Health Organization for rubella surveillance as the region moved towards an elimination target: a suspected case is one in which a health worker suspects rubella.[23] The European Centre for Disease Prevention and Control also adopted a modified definition, namely, any person with sudden onset of generalised maculopapular rash and at

least one of the following: cervical adenopathy, suboccipital adenopathy, postauricular adenopathy, arthralgia or arthritis.[24] As Cameroon and other African countries work toward introducing RCVs and plan elimination goals, a modified case definition will need to be considered so as to improve detection rates.

Another major issue Cameroon should consider when introducing rubella vaccination is that a high vaccination coverage above 80% is required to sustain immunity from childhood to older age groups. A coverage below 80% in children will mean shifting susceptibility to rubella in a good number of unvaccinated children through older age particularly in women of childbearing age, thereby secondarily incrlinkedeasing the risk of CRS. Such a shift in susceptibility to older age groups occurred and was documented in Greece and South Africa.[25 26]

Cameroon should therefore consider establishing a sentinel surveillance for CRS and find additional strategies to fill immunity gaps in older age groups. Information from such studies will be useful in monitoring the impact of introducing a rubella vaccine into the EPI programme.

CONCLUSION

Rubella virus circulates in Cameroon with an important number of children under 15 years being affected. Children under 1 year presented with low proportions indicating a potential benefit of introducing a rubella vaccine into the national routine immunisation programme, as this will mean a good opportunity to interrupt virus circulation and protect many children through adolescence and adulthood.

To better understand the burden and epidemiology of rubella and CRS, Cameroon should consider including a more inclusive case definition for measles and rubella, establishing sentinel surveillance for CRS and conducting appropriate postvaccine studies once the vaccine is introduced into the national immunisation programme among high-risk susceptible groups of the population. Information from such studies will be useful for rubella elimination strategies in Cameroon.

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