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Epidemiology of rubella infection in Cameroon: A 7 year experience of measles and rubella case base surveillance, 2008 – 2014

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ABSTRACT

Objective: The aim of this study was to determine the burden of rubella disease in Cameroon prior to vaccine introduction into the national immunization program.

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

SETTING: Suspected measles patients from the ten regions of Cameroon were recruited according to the WHO measles case confirmation 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 World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case.

OUTCOME MEASURES: Descriptive analyses, simple logistic regressions were performed. Odd ratios (ORs) were estimated.

RESULTS

A total of 9,907 serum samples from people with fever and rash were received by the laboratory from 2008 to 2014. A total of 7489 (75.59%) samples were tested for rubella; 699(9.3%) were positive for rubella IgM antibodies. Logistic regression analysis revealed that, comparing rubella IgM status by age, children less than one year of age, the risk increased with age from 1 to 4 years (OR: 5.91; 95% CI: 3.61 to 9.65; P<0.0001), through 5 to 9 years (OR: 11.00,; 95% CI: 6.70 to 18.07; P<0.001), to 10 to 14 years of age (OR: 12.34; 95% CI: 7.27 to 20.94; P<0.001). Persons aged ≥15 years were also more likely to have rubella infection than children under one (OR: 3.52; 95% CI: 1.85 to 6.68; P = 0.0001). Men were significantly less susceptible to rubella than women (OR: 0.77; 95% CI: 0.66 to 0.91; P = 0.0014).

CONCLUSIONS

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

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Keywords: Rubella, Cameroon, Surveillance

Strengths and limitations of this study

- This is the first study in Cameroon to investigate rubella infection in across a broad age range, from all the regions and investigating potential risk factors.
- This study confirms that rubella virus circulates in Cameroon and affects mostly children under 15 years and that children under one year are less affected indicating a potential benefit to introduction of rubella vaccine in routine immunization program
- The integration of rubella testing with measles case based surveillance provides an opportunity to gain understanding about the epidemiology of rubella infection.
- The sensitivity of the case definition used for measles surveillance is likely not high enough to identify all rubella cases.
- Existence of missing data for some variables highlighting some issues in the data management and rapid control applications for some key variables.

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INTRODUCTION

Rubella is an acute, contagious viral disease caused by a Togavirus of the genus *Rubivirus* and is characterized 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 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 the South-East Asia (48%) and Africa (38%). Economic analysis evidence for rubella and CRS control suggest that incorporation of rubella-containing vaccine (RCV) into national childhood immunization 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$4,200 in a middle-income country (inflation-adjusted 2012 US$) such as Brazil to over US$200,000 in a high-come country (inflation-adjusted 2012 US$) such as the United States,[8]. At least five of six World Health Organization (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 nine 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

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immunoglobulin M (IgM) antibodies. Cameroon is planning to introduce the rubella-containing vaccine in the EPI program 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.

Objective: This study aims to determine the epidemiology of rubella disease in Cameroon based on the national combined measles/rubella 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 program.

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 a country 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 6 children per woman of child bearing age,[11].

During the study period, blood samples were collected from all persons with rash and fever within 14 days of onset of rash according to the standard World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case (that is, any person with generalized maculo-papular 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). 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

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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 1-5ml of blood was collected by venipuncture into a sterile anti-coagulant free tube. The blood was then allowed to clot then centrifuged at 3000rpm for five minutes to separate the serum. If there was no centrifuge in the health center, the blood was stored in a refrigerator until the clot was completely retracted from the serum. The serum was transferred aseptically into a vial and stored at 2-8°C for at most three days before being transported in a cold chain to Centre Pasteur Cameroon which houses the National Measles 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 seven days. Enzyme linked immunosorbent assay (ELISA) for rubella specific IgM antibodies was carried out according to the manufacturer's instructions (Enzygnost Anti-Rubella Virus/IgM kit; Siemens AG, Erlangen, Germany). Patients with rubella IgM–positive serum samples were classified as having 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 program. Forms collected from the laboratory were reviewed and entered into the WHO electronic database. The case-based surveillance data were reported on a weekly base by the EPI program to the WHO country office.

Statistical analyses were performed using the SPSS statistical package (version 16). Data were cleaned and analysis done using existing variables. Descriptive analysis was completed with bivariate analyses to find key determinant of rubella infection in Cameroon. A 95% confidence interval (CI) was calculated and values of $P < 0.05$ were considered statistically significant.

RESULTS

Prevalence of rubella diseases

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A total of 9,907 samples of suspected cases of measles were received in the laboratory from 2008 to 2014 among which 7489 (75.59%) were tested for rubella; 699 (9.3%) were positive for rubella IgM antibodies. This prevalence of rubella antibodies varied from 4.7% in 2009 to 12.4% in 2012 (Table 1).

Table 1: Prevalence of rubella in Cameroon between 2008 and 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	1107	147 (12.4%)	43 (3.6%)
2013	1342	147 (11.0%)	44 (3.3%)
2014	1866	147 (7.9%)	58 (3.1%)
Total	7489	699 (9.3%)	202 (2.7%)

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 one year of age (representing the targeted age in the routine EPI program) and 96.85% of cases were below 15 years (marking the entrance to child bearing age for young girls).

Rubella distribution by age group

The prevalence by age group shows that the age groups between 5-9 years and 10-14 years were the most affected (Figure 1 and Table 2).

Table 2: Rubella prevalence by age group in Cameroon, 2008-2014

Age group	Number specimen tested	Number tested positive	% Tested positive	Odds ratio	95% confidence interval	P value
< 1 year	1244	17	1.37	1		
1-4 years	3635	326	8.97	7.111	4.35 - 12.41	
5-9 years	1611	247	15.34	13.070	7.93 - 22.93	0.0001
10-14 years	540	87	16.11	13.862	8.06 - 25.12	
>=15 years	452	22	4.87	3.693	1.85 - 7.48	
Total	7481	699	9.34			

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Distribution of rubella cases by sex

More than half (380/699, 54.36%) of positive rubella cases were women. Women were more likely to be positive than men (OR1.33, 95% CI 1.14 to 1.56, P = 0.0001) (Table 3). The sex was not specified for 1 case.

Table 3: Distribution of rubella cases by sex

	Number tested for rubella	Number tested positive (%)	Odds ratio	95% Confidence interval	P value
Female	3584	380 (10.6%)	1.33	1.14 - 1.56	0.0001
Male	3904	319 (8.2%)	1		
Total	7488	699 (9.3)			

Rubella in women of child bearing age (15-49 years)

There were 189 women of childbearing age who were tested, with 11 (4.55%) of them positive for rubella IgM antibodies. The proportion of positive 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

There was no statistically significant difference between urban and rural populations (Table 4). The setting was not specified for 23 cases.

Table 4: Distribution of rubella cases by setting

	Number tested	Number positive (%)	Odds ratio	95% Confidence interval 95%	P value
Urban	2651	264 (9.9%)	1.11	0.94 - 1.31	0.208
Rural	4815	435 (9.0%)			
Total	7466	699 (9.3)			

Seasonal distribution of rubella cases from 2008 to2014

Pooled analysis of the rubella cases during the study period 2008 to 2014, did not show a clear seasonality in Cameroon. Monthly variation showed that the proportions of rubella cases during the months of February to May 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 incidence in the month of June

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through October. In 2012 there was an unusual peak in the month of August and also in the month of November in 2008 (Figure 2).

Risk factors

Logistic regression analysis reveals associations of rubella IgM sero-positivity with age. Compared to children less than one year of age, the risk increased with age from 1 to 4 years (OR: 5.91; 95% CI: 3.61 to 9.65; P<0.0001), through 5 to 9 years (OR: 11.00,; 95% CI: 6.70 to 18.07; P<0.001), to 10 to 14 years of age (OR: 12.34; 95% CI: 7.27 to 20.94; P<0.001). In addition, people aged 15 years and above were also more likely to have rubella infection than children under one (OR: 3.52; 95% CI: 1.85 to 6.68; P = 0.0001). There were also significant associations with sex, with men being less susceptible than women (OR: 0.77; 95% CI: 0.66 to 0.91; P = 0.0014).

DISCUSSION

The surveillance of measles and rubella in the national surveillance program of Cameroon enabled the effective detection of rubella. From this study, we observed that during the measles outbreaks between 2008 and 2014, the incidence of rubella ranged from 4.7% in 2009 to 12.4% in 2012. Most rubella cases were reported in children below 15years indicating that rubella was mainly an illness of young and early-school-age children. This was similar to findings in Ethiopia and Zimbabwe were respectively 94% and 98% of cases came from this age group,[13, 14]. Similarly, the lowest proportion of cases was seen in children below 1 year indicating a potential benefit if the rubella vaccine is administered in the national routine EPI before children reach the 5-9 years and 10-14 years age groups where the risk increases by 13 times.

The proportion of women of reproductive age affected by Rubella was very low 4.55%. These findings is not consistent with findings by Ndumbe and collaborators who reported rubella antibodies detection in 83.9% pregnant women during antenatal care in Yaoundé in 1992,[15]. Adewumi and collaborators reported a sero-prevalence rate of 91.54% among pregnant women in Ibadan, Nigeria in 2005,[16]. This difference could be due to the fact that these studies were based on IgG detection which last longer than IgM which are measured in measles and rubella surveillance indicating recent infection.

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There was a seasonal trend of rubella cases where peaks were seen during the period of February to May which represents apparently the end of the dry season and beginning of the raining season in most parts of Cameroon with a sharp decline in incidence in the month of June through October except in 2012 where there was an unusual peak in the month of August and also in the month of November (2008 also). Similar trend was noted by Mitiku *et al,* in Ethiopia where a seasonal distribution of cases occurred each year and peaked from March through June,[13].

Rubella cases in this study do not show any statistical difference between urban and rural populations.

Occurrence of rubella antibodies in children of 5 months in this study indicates possibility of infection at a younger age although congenital rubella syndrome 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 industrialized countries during the pre-vaccination era,[17]. The incidence of CRS per 1000 live births in Cameroon is still unknown. Jivraj *et al* revealed ocular and auditory manifestations of CRS in school-aged children in Mbingo, Cameroon with 28 (10.2%) probable cases. Hearing impaired children were seven times more likely to have positive serology (48.8%) than children with normal hearing (7.4%; $P < 0.0001$),[18].

These results are subject to some limitations. First, the case definition used to detect the rubella cases were designed for the measles case-based surveillance system. Many individuals with rubella cases may not have rash which occurs in 50%–80% of rubella infected persons,[9]. The sensitivity of the case definition used for measles surveillance is likely not high enough to identify all rubella cases. 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 surveillance by adopting a more inclusive case definition for measles and rubella. The following

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definition was used by the Pan American Health Organization for rubella surveillance as the region moved toward an elimination target: a suspected case is one in which a health worker suspects rubella,[19]. The European Centre for Disease Prevention and Control also adopted a modified definition, namely, any person with sudden onset of generalized maculopapular rash and at least one of the following: cervical adenopathy, sub-occipital adenopathy, post-auricular adenopathy, arthralgia or arthritis,[20]. As Cameroon and other African countries work toward introducing rubella containing vaccines 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 low vaccination coverage (under 80%) may decrease virus circulation and shift rubella susceptibility from children to older age groups including women of childbearing age, and therefore increase the prevalence of CRS. Such a shift in susceptibility to older age groups occurred and was documented in Greece and South Africa,[21, 22].

Cameroon should also think of establishing sentinel surveillance for CRS and find additional strategies to fill immunity gaps in older age groups, e.g. women of reproductive age, adolescents >15 years of age and adult after the national campaign. Information from such studies will be useful in monitoring the impact of introduction of rubella vaccine in the EPI program.

CONCLUSION

Rubella virus circulates in Cameroon and affects mostly children under 15 years. Children under one year are less affected indicating a potential benefit to introduction of rubella vaccine in routine immunization program. The highest proportions of rubella cases occurred during the months of February to May which represents the end of the dry season and beginning of the raining season.

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

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Ethical considerations

The Cameroon Measles/Rubella surveillance is a national program approved by the Ministry of Public Health and supported by WHO/AFRO as part of the global goal to control and eliminate measles and rubella. Patient information and specimen collection respected the procedures stipulated in the WHO/AFRO measles/rubella surveillance protocol. Although written consent or ascent form was not required, for the purposes of the national surveillance program, relevant information was provided and verbal permission obtained before samples were collected from a suspected case.

Data sharing statement: The original data can only be accessed by the research investigators working at the Ministry of Public health Cameroon and the WHO country office Cameroon. Nimpa Mengouo can be contacted if the de-identified dataset is required.

Figures and Tables legend

Figure 1: Rubella case distribution by age in Cameroon, 2008-2014

Figure 2: Monthly trends in the percentage of samples testing positive for rubella in Cameroon, 2008-2014.

Table 1: Prevalence of rubella in Cameroon between 2008 and 2014

Table 2: Rubella prevalence by age group in Cameroon, 2008-2014

Table 3: Distribution of rubella cases by sex

Table 4: Distribution of rubella cases by setting

List of Abbreviations

CRS: *congenital rubella syndrome*; WHO: *World Health Organization*; RCV: *rubella containing vaccine*; EPI: *expanded program on immunization*; MCV1: *measles containing vaccine*; IgM: *immunoglobulin M*; EDC-MICS*: Enquête Démographique et de la Santé et à Indicateurs Multiples*; WHO/AFRO: *World Health Organization African Region*; ELISA: *Enzyme linked immunosorbent assay*; CI: *Confidence interval*

Declarations

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

NMM conceiving the study, data collection, data analysis and preparing the draft manuscript. NVN, WCS, KM and BF contributed in data analysis and writing of the manuscript. All authors reviewed the draft and approved the final manuscript.

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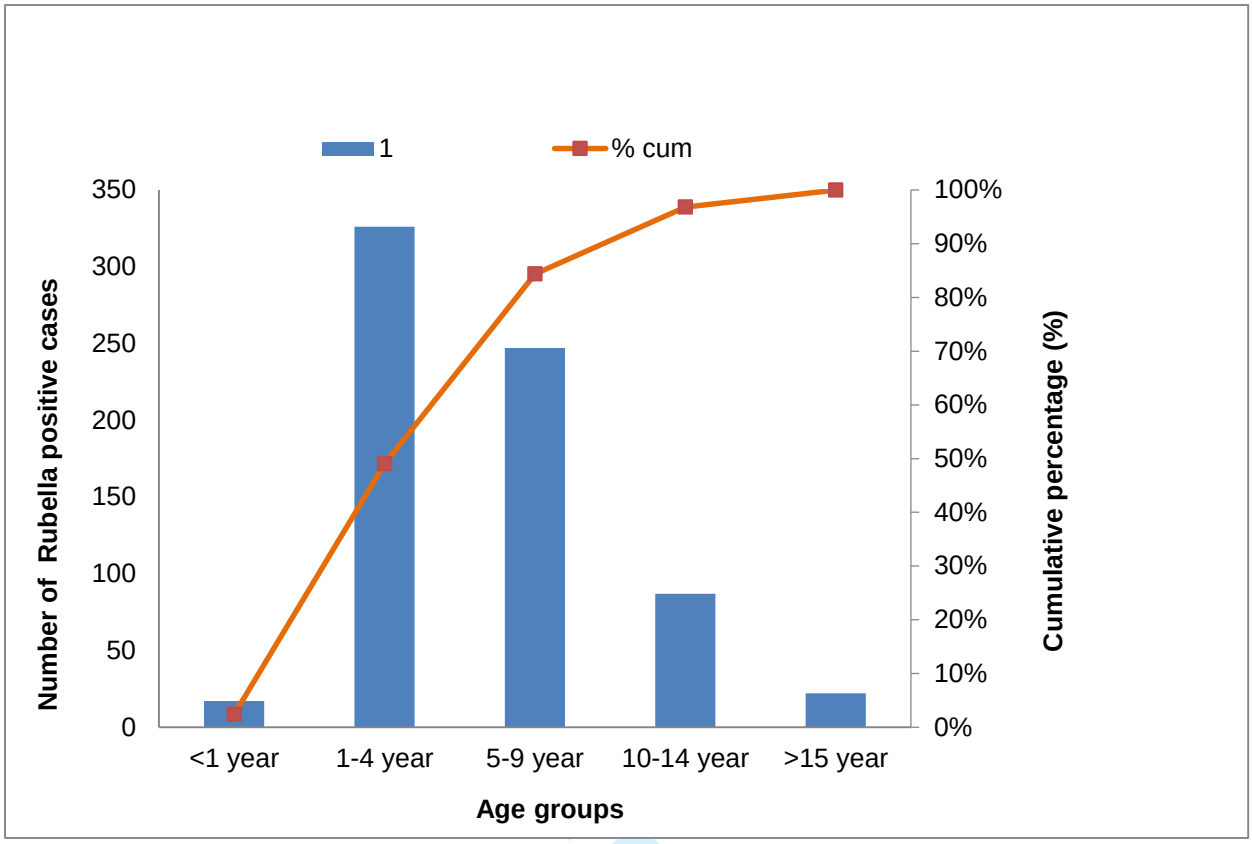

Figure 1 : Rubella case distribution by age group in Cameroon, 2008-2014.
N.B: The bars show the number and proportion of rubella cases for the specified age group and the curve represents the cummulative proportion of cases.

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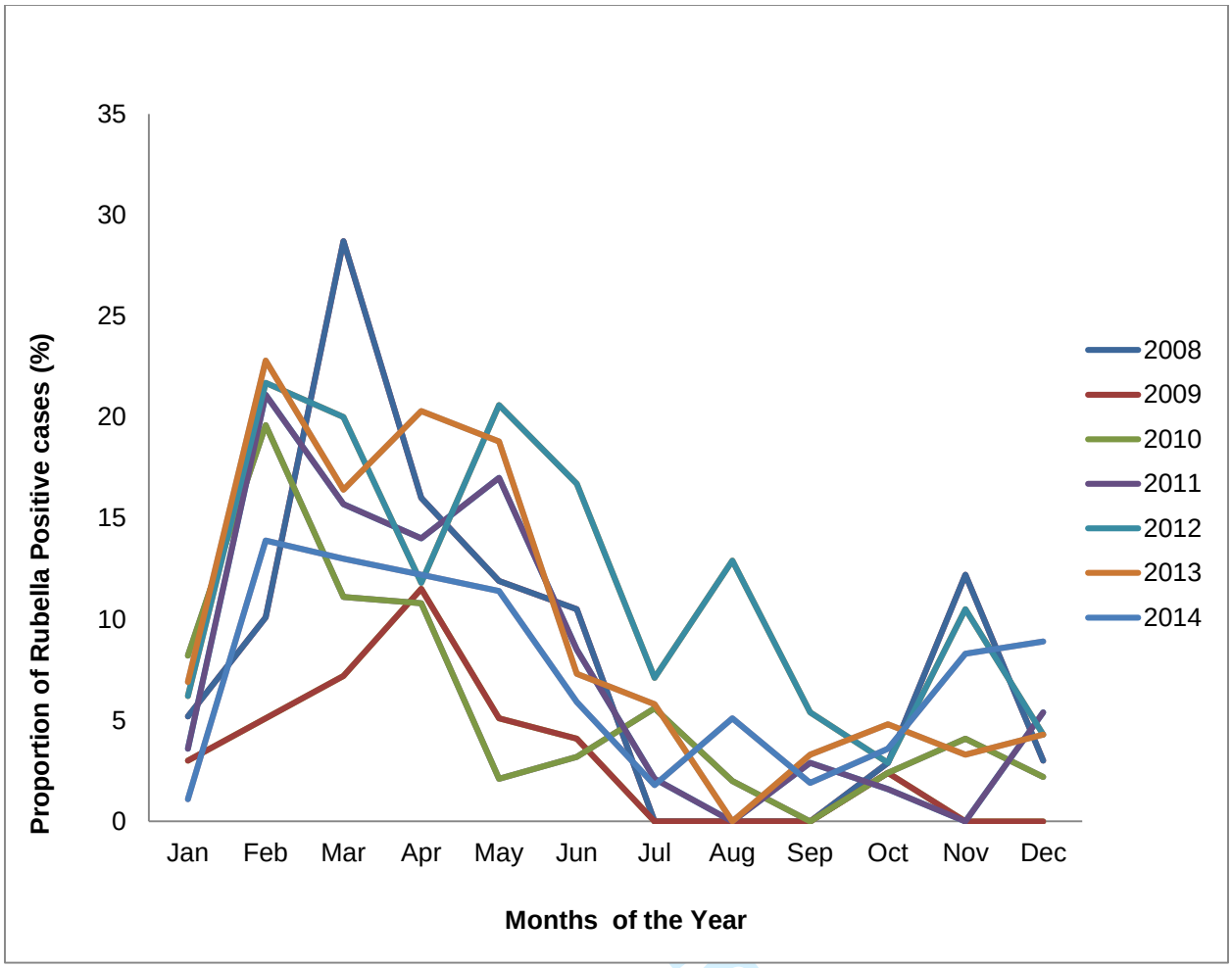

Figure 2: Monthly trends in the percentage of samples testing positive for rubella in Cameroon, 2008-2014.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**4-5**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			**5-6**
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			**6-9**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9

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		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			**9-11**
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			**12**
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Epidemiology of rubella infection in Cameroon: A 7-years experience of measles and rubella case-base surveillance, 2008 – 2014

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Epidemiology of rubella infection in Cameroon: A 7-years experience of measles and rubella case-base surveillance, 2008 – 2014

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ABSTRACT

Objective: This study aim was to determine the burden of rubella disease in a combined measles/rubella case-based surveillance in Cameroon prior to vaccine introduction into the national immunization program.

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

SETTING: Suspected measles patients from the ten 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 World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case.

OUTCOME MEASURES: Descriptive analyses, simple logistic regressions were performed. Odd ratios (ORs) were estimated.

RESULTS

A total of 9,907 serum samples from people with fever and rash were received by 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 revealed that, comparing rubella IgM status by age, the association to a positive rubella IgM increased with age from 1 to 4 years (OR: 5.91; 95% CI: 3.61 to 9.65; P<0.0001), through 5 to 9 years (OR: 11.00; 95% CI: 6.70 to 18.07; P<0.001), to 10 to 14 years of age (OR: 12.34; 95% CI: 7.27 to 20.94; P<0.001). Persons aged ≥15 years were also more likely to have rubella infection than children under one (OR: 3.52; 95% CI: 1.85 to 6.68; P = 0.0001).

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.

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Keywords: Rubella, Cameroon, Surveillance

Strengths and limitations of this study

- This is the first study in Cameroon to investigate rubella infection in across a broad age range, from all the regions and investigating relationship.
- This study confirms that rubella virus circulates in Cameroon with important number of cases in children under 15 years and that children under one year are less affected indicating a potential benefit to introduction of rubella vaccine in routine immunization program
- The integration of rubella testing with measles case-based surveillance provides an opportunity to gain understanding about the epidemiology of rubella infection.
- The sensitivity of the case definition used for measles surveillance is likely not high enough to identify all rubella cases.
- The existence of missing data for some variables highlights some issues in data management process.

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INTRODUCTION

Rubella is an acute, contagious viral disease caused by a Togavirus of the genus *Rubivirus* and is characterized 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 rubella infected adult women 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 immunization 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$4,200 (inflation-adjusted 2012 US$), in a middle-income country such as Brazil to over US$200,000 (inflation-adjusted 2012 US$), in a high-come country such as the United States,[8]. At least five of six World Health Organization (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 nine 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/rubella case-based surveillance system, established in 2004, includes laboratory testing for the detection of measles specific and rubella-

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specific immunoglobulin M (IgM) antibodies. Cameroon is planning to introduce the rubella-containing vaccine in the EPI program 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 combined measles/rubella 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 program.

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 6 children per woman of child bearing 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 World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case (that is, any person with generalized maculo-papular 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). 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

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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 1-5ml of blood was collected by venipuncture into a sterile anti-coagulant free tube. The blood was then allowed to clot then centrifuged at 3000rpm for five minutes to separate the serum. If there was no centrifuge in the health center, the blood was stored in a refrigerator until the clot was completely retracted from the serum. The serum was transferred aseptically into a vial and stored at 2-8°C for at most three 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 seven days. Enzyme linked immunosorbent assay (ELISA) for rubella specific IgM antibodies was carried out according to the manufacturer's instructions (Enzygnost Anti-Rubella Virus/IgM kit; Siemens AG, Erlangen, Germany). Patients with rubella IgM–positive serum samples were classified as having 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 program. Forms collected from the laboratory were reviewed and entered into the WHO electronic database. The case-based surveillance data were reported on a weekly base by the EPI program to the WHO country office.

Statistical analyses were performed using the SPSS statistical package (version 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 to find key determinant of rubella infection in Cameroon. A 95% confidence interval (CI) was calculated and values of $P < 0.05$ were considered statistically significant.

RESULTS

Proportion of rubella diseases

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A total of 9,907 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).

Table 1: Proportion of rubella cases in Cameroon between 2008 and 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	147 (7.9%)	58 (3.1%)
Total	7489	699 (9.3%)	202 (2.7%)

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 one year of age (representing the targeted age in the routine EPI program) and 96.85% of cases were below 15 years (marking the entrance to child bearing 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).

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

	Number tested for rubella	Number tested positive (%)	Odds ratio	95% Confidence interval	P value
Age group					
< 1 year	1244	17(1.37)	1		0.0001
1-4 years	3635	326 (8.97)	7.111	4.35 - 12.41	
5-9 years	1610	247 (15.34)	13.070	7.93 - 22.93	
10-14 years	540	87 (16.11)	13.862	8.06 - 25.12	
>=15 years	452	22 (4.87)	3.693	1.85 - 7.48	
Total	7481	699 (9.3)			
Sex					

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Female	3584	380 (10.6)	1.33	1.14 - 1.56	0.0001
Male	3904	319 (8.2)	1		
Total	7488	699 (9.3)			
Setting					
Urban	2651	264 (9.9)	1.11	0.94 - 1.31	0.208
Rural	4815	435 (9.0)			
Total	7466	699 (9.3)			

Distribution of rubella cases by sex

More than half (380/699, 54.36%) of positive rubella cases were females. Females were 1.3 times more associated to a positive rubella IgM than males (OR1.33, 95% CI 1.14 to 1.56, P = 0.0001) (Table 2). The sex was not specified for 1 case.

Rubella in women of child bearing age (15-49 years)

There were 189 females of childbearing age who were tested, with 11 (4.55%) of them 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

There was no statistically significant difference in proportion of rubella cases between urban and rural populations (Table 2). The setting was not specified for 23 cases. The proportion of rubella positive cases by regions in Cameroon between 2008 to 2014 shows that, the East, North west and the South west had higher proportions of rubella cases (Figure 2).

Seasonal distribution of rubella cases from 2008 to2014

Pooled analysis of the number of rubella cases during the study period 2008 to 2014, did show 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 month of July through September, (Figure 3).

Logistic regression analysis

Logistic regression analysis reveals associations of rubella IgM sero-positivity with age. Compared to children less than one year of age, the association increased with age from 1 to 4 years (OR: 5.91; 95% CI: 3.61 to 9.65; P<0.0001), through 5 to 9 years (OR: 11.00; 95% CI: 6.70 to 18.07; P<0.001),

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to 10 to 14 years of age (OR: 12.34; 95% CI: 7.27 to 20.94; P<0.001). In addition, people aged 15 years and above were also more likely to have rubella infection than children under one (OR: 3.52; 95% CI: 1.85 to 6.68; P = 0.0001). There were also significant associations with sex, with males being less associated to a positive rubella IgM than females (OR: 0.77; 95% CI: 0.66 to 0.91; P = 0.0014).

DISCUSSION

The surveillance of measles and rubella in the national case-based surveillance program of Cameroon enabled the effective detection of rubella. 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. The increase in the proportion of rubella cases during this period could actually be indicating a rubella outbreak also and this type of observation necessitates a clear case definition of rubella infection. 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 were respectively 94% and 98% of cases came from this age group,[13, 14]. Similarly, the lowest proportion of cases was seen in children below 1 year indicating a potential benefit if the rubella vaccine is administered in the national routine EPI before children reach their reproductive age.

The proportion of females of reproductive age affected by rubella was very low 4.55% which is higher than that obtained in Tanzania (0.3%) and Burkina Faso (1%) among pregnant women,[15, 16] but lower than that observed in some parts of Nigeria,[17, 18]. 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, 17-21]. Ndumbe and collaborators reported rubella IgG antibodies detection in 83.9% pregnant women during antenatal care in Yaoundé, Cameroon in 1992,[22]. Adewumi and collaborators reported a sero-prevalence rate of 91.54% among pregnant women in Ibadan, Nigeria in 2005,[23]. This difference could be due to the fact that these studies were based on IgG detection which last longer than IgM which are

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measured in measles and rubella surveillance indicating recent infection. 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 period of February to April which represents apparently the end of the dry season and beginning of the raining season in most parts of Cameroon with a sharp decline in number in the month of July through September then gradually begins to increase from October through December. Similar trend was noted by Mitiku *et al,* in Ethiopia where a seasonal distribution of cases occurred each year and peaked from March through June,[13].

Rubella cases in this study do not show any statistical difference between urban and rural populations.

Occurrence of rubella antibodies in children of 5 months in this study indicates possibility of infection at a younger age although congenital rubella syndrome 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 industrialized countries during the pre-vaccination era,[24]. The incidence of CRS per 1000 live births in Cameroon is still unknown. Jivraj *et al* revealed ocular and auditory manifestations of CRS in school-aged children in Mbingo, Cameroon with 28 (10.2%) probable cases. Hearing impaired children were seven times more likely to have positive serology (48.8%) than children with normal hearing (7.4%; $P < 0.0001$),[25].

These results are subject to some limitations. First, the case definition used to detect the rubella cases were designed for the measles case-based surveillance system. Many individuals with rubella cases may not have rash which occurs in 50%–80% of rubella infected persons,[9]. The sensitivity of the case definition used for measles surveillance is likely not high enough to identify all rubella 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.

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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 toward an elimination target: a suspected case is one in which a health worker suspects rubella,[26]. The European Centre for Disease Prevention and Control also adopted a modified definition, namely, any person with sudden onset of generalized maculopapular rash and at least one of the following: cervical adenopathy, sub-occipital adenopathy, post-auricular adenopathy, arthralgia or arthritis,[27]. As Cameroon and other African countries work toward introducing rubella containing vaccines 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 low vaccination coverage (under 80%) may decrease virus circulation and shift rubella susceptibility from children to older age groups including women of childbearing age, and therefore increase the prevalence of CRS. Such a shift in susceptibility to older age groups occurred and was documented in Greece and South Africa,[28, 29].

Cameroon should also think of establishing sentinel surveillance for CRS and find additional strategies to fill immunity gaps in older age groups, e.g. women of reproductive age, adolescents >15 years of age and adult after the national campaign. Information from such studies will be useful in monitoring the impact of introduction of rubella vaccine in the EPI program.

CONCLUSION

Rubella virus circulates in Cameroon with important number of cases in children under 15 years. Children under one year presented with low proportions indicating a potential benefit to introduction of rubella vaccine in routine immunization program. The highest number of rubella positive cases

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occurred during the months of February to April which represents the end of the dry season and beginning of the raining season.

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

Ethical considerations

The Cameroon Measles/Rubella surveillance is a national program approved by the Ministry of Public Health and supported by WHO/AFRO as part of the global goal to control and eliminate measles and rubella. Patient information and specimen collection respected the procedures stipulated in the WHO/AFRO measles/rubella surveillance protocol. Although written consent or ascent form was not required, for the purposes of the national surveillance program, relevant information was provided and verbal permission obtained before samples were collected from a suspected case.

Data sharing statement: The original data can only be accessed by the research investigators working at the Ministry of Public health Cameroon and the WHO country office Cameroon. Nimpa Mengouo can be contacted if the de-identified dataset is required.

Figures and Tables legend

Figure 1: Rubella case distribution by age in Cameroon, 2008-2014

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.

Table 1: Proportion of rubella cases in Cameroon between 2008 and 2014

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

List of Abbreviations

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CRS: *congenital rubella syndrome*; WHO: *World Health Organization*; RCV: *rubella containing vaccine*; EPI: *expanded program on immunization*; MCV1: *measles containing vaccine*; IgM: *immunoglobulin M*; EDC-MICS*: Enquête Démographique et de la Santé et à Indicateurs Multiples*; WHO/AFRO: *World Health Organization African Region*; ELISA: *Enzyme linked immunosorbent assay*; CI: *Confidence interval*

Declarations

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

NMM conceiving the study, data collection, data analysis and preparing the draft manuscript. NVN, WCS, KM and BF contributed in data analysis and writing of the manuscript. All authors reviewed the draft and approved the final manuscript.

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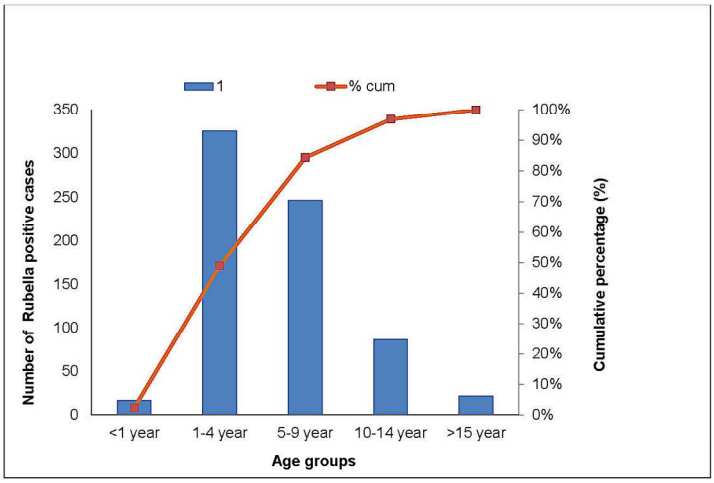

Figure 1 : Rubella case distribution by age group in Cameroon, 2008-2014.
N.B: The bars show the number and proportion of rubella cases for the specified age group and the curve represents the cummulative proportion of cases.

Figure 1: Rubella case distribution by age in Cameroon, 2008-2014

143x186mm (300 x 300 DPI)

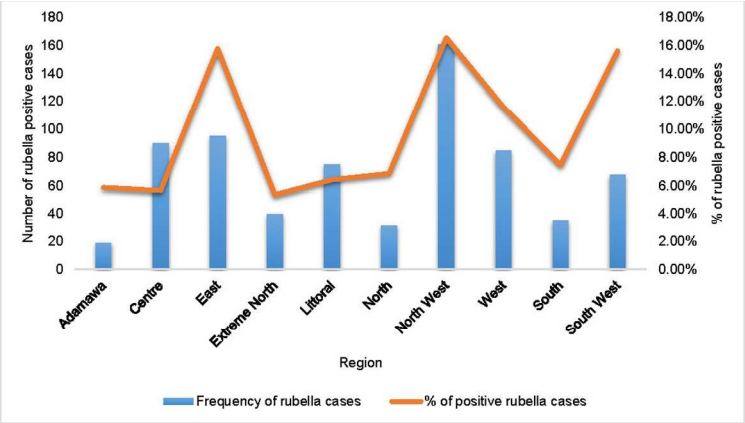

Figure 2: Distribution of rubella positive cases by region in Cameroon, 2008-2014

Figure 2: Distribution of rubella positive cases by region in Cameroon, 2008-2014

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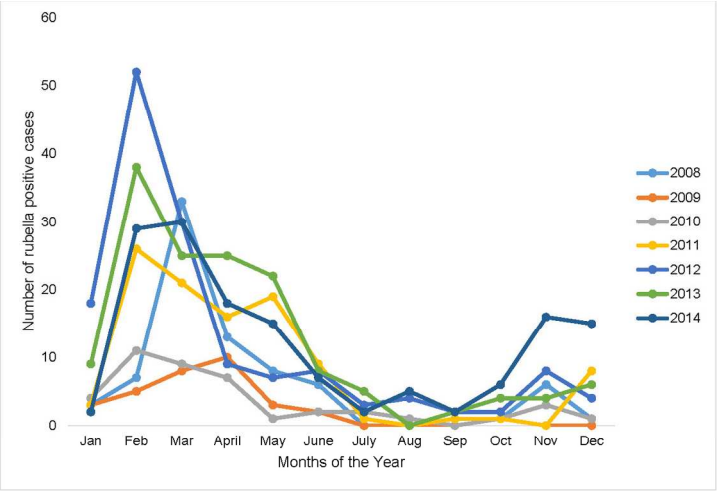

Figure 3: Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008-2014.

Figure 3: Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008-2014.

215x279mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**4-5**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			**5-6**
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			**6-9**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9

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		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			**9-11**
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			**12**
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Epidemiology of rubella infection in Cameroon: A 7-years 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 immunization program.

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

SETTING: Suspected measles patients from the ten regions of Cameroon were recruited according to the World Health Organization (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 World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case.

OUTCOME MEASURES: Descriptive analyses, simple logistic regressions were performed. Odd ratios (ORs) were estimated.

RESULTS

A total of 9,907 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 rubella IgM 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).

CONCLUSIONS

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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(EPI).

Keywords: Rubella, Cameroon, Surveillance

Strengths and limitations of this study

- This is the first study in Cameroon to investigate rubella infection across a broad age range, from all the regions and investigating association with some sociodemographic factors.
- The integration of rubella testing with measles case-based surveillance provides an opportunity to gain understanding about the epidemiology of rubella infection.
- The sensitivity of the case definition used for measles surveillance is likely not high enough to identify all rubella cases.
- The existence of missing data for some variables highlights some issues in data management process.

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INTRODUCTION

Rubella is an acute, contagious viral disease caused by a Togavirus of the genus *Rubivirus* and is characterized 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 rubella infected adult women 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 immunization 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$4,200 (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 United States,[8]. At least five of six World Health Organization (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 nine 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

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immunoglobulin M (IgM) antibodies. Cameroon planned to introduce the rubella-containing vaccine into the EPI program 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 program.

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 6 children per woman of child bearing 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 World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case (that is, any person with generalized maculo-papular 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 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,

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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 1-5ml of blood was collected by venipuncture into a sterile anti-coagulant free tube. The blood was then allowed to clot then centrifuged at 3000rpm for five minutes to separate the serum. If there was no centrifuge in the health center, the blood was stored in a refrigerator until the clot was completely retracted from the serum. The serum was transferred aseptically into a vial and stored at 2-8°C for at most three 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 seven days. Enzyme linked immunosorbent assay (ELISA) for rubella specific IgM antibodies was carried out according to the manufacturer's instructions (Enzygnost Anti-Rubella Virus/IgM kit; Siemens AG, Erlangen, Germany). Patients with rubella IgM–positive serum samples were classified as having 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 program. Forms collected from the laboratory were reviewed and entered into the WHO electronic database. The case-based surveillance data were reported on a weekly base by the EPI program to the WHO country office.

Statistical analyses were performed using the SPSS statistical package (version 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 Chi square or Fisher exact tests for categorical variables to find key determinant of rubella infection in Cameroon. Logistic regression analysis was done using IgM antibodies detection as the outcome variable. Age, sex and setting were explanatory variables. A 95% confidence interval (CI) was calculated for the Odd ratios and values of $P < 0.05$ were considered statistically significant.

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RESULTS

Proportion of rubella diseases

A total of 9,907 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.

Table 1: Proportion of rubella cases in Cameroon between 2008 and 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%)

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 one year of age (representing the targeted age in the routine EPI program) and 96.85% of cases were below 15 years (marking the entrance to child bearing 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).

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

	Number tested for rubella	Number tested positive (%)	Odds ratio	95% Confidence interval	P value
Age group					

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< 1 year	1244	17(1.37)	1		0.0001
1-4 years	3635	326 (8.97)	7.11	4.35 - 12.41	
5-9 years	1610	247 (15.34)	13.07	7.93 - 22.93	
10-14 years	540	87 (16.11)	13.86	8.06 - 25.12	
>=15 years	452	22 (4.87)	3.69	1.85 - 7.48	
Total	7481	699 (9.3)			
Sex					
Male	3904	319 (8.2)	1		0.0001
Female	3584	380 (10.6)	1.33	1.14 - 1.56	
Total	7488	699 (9.3)			
Setting					
Rural	4815	435 (9.0)			0.208
Urban	2651	264 (9.9)	1.11	0.94 - 1.31	
Total	7466	699 (9.3)			

Distribution of rubella cases by sex

The sex was available for 698 cases (99.85%) out of 699. More than half (380/699, 54.36%) of positive rubella cases were females. Females were 1.3 times more associated to a positive rubella IgM than males (OR1.33, 95% CI 1.14 to 1.56, P = 0.0001) (Table 2).

Rubella in women of child bearing age (15-49 years)

There were 189 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 676 cases (96,7%) out of 699. There was no statistically significant difference in proportion of rubella cases between urban and rural populations (Table 2). The proportion of rubella positive cases by regions in Cameroon between 2008 to 2014 shows that, the East, North west and the South west regions had higher proportions of rubella cases (Figure 2).

Seasonal distribution of rubella cases from 2008 to2014

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

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Logistic regression analysis reveals associations of rubella IgM sero-positivity with age. Compared to children less than one 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 cases per year. The increase in the proportion of rubella cases during this period could 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 detection 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 (AFP) 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 immunization programme which targets children of this age group. Vaccinating children in the routine immunization programme at this age will provide protection against rubella in these children before they reach the reproductive age. This

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will further reduce the risk of acquiring rubella infection during pregnancy and also reduce the burden of congenital rubella syndrome.

The proportion of females of reproductive age affected by rubella 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, 16-20]. 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,* in Ethiopia where a seasonal distribution of cases occurred each year and peaked from March through June,[13]. Rubella cases in this study do not show any statistical significant difference between urban and rural populations. Mitiku *et al,* noted a significantly higher number of positive cases in the urban areas compared to rural areas,[13].

Occurrence of rubella antibodies in children of 5 months in this study indicates possibility of infection at a younger age although congenital rubella syndrome 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 industrialized countries during the pre-vaccination era,[21]. The incidence of CRS per 1000 live births in Cameroon is still unknown. Jivraj *et al* revealed ocular and auditory manifestations of CRS in school-aged children 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].

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These results are subject to some limitations. First, the case definition used to detect the rubella cases were designed for the measles case-based surveillance system. Many individuals with rubella cases may not have rash which occurs in 50%–80% of rubella infected persons,[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 toward 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 generalized maculopapular rash and at least one of the following: cervical adenopathy, sub-occipital adenopathy, post-auricular adenopathy, arthralgia or arthritis,[24]. As Cameroon and other African countries work toward introducing rubella containing vaccines 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 child bearing age, thereby secondarily increasing the risk of CRS. Such a shift in susceptibility to older age groups occurred and was documented in Greece and South Africa,[25, 26].

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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 program.

CONCLUSION

Rubella virus circulates in Cameroon with an important number of children under 15 years being affected. Children under one year presented with low proportions indicating a potential benefit of introducing a rubella vaccine into the national routine immunization program, 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 post vaccine studies once the vaccine is introduced into the national immunization program among high risk susceptible groups of the population. Information from such studies will be useful for rubella elimination strategies in Cameroon.

Ethical considerations

The Cameroon Measles surveillance is a national program approved by the Ministry of Public Health and supported by WHO/AFRO as part of the global goal to control and eliminate measles and rubella. Patient information and specimen collection respected the procedures stipulated in the WHO/AFRO measles/rubella surveillance protocol. Although written consent or ascent form was not required, for the purposes of the national surveillance program, relevant information was provided and verbal permission obtained before samples were collected from a suspected case.

Data sharing statement: The original data can only be accessed by the research investigators working at the Ministry of Public health Cameroon and the WHO country office Cameroon. Nimpa Mengouo can be contacted if the de-identified dataset is required.

Figures and Tables legend

Figure 1: Rubella case distribution by age in Cameroon, 2008-2014

Figure 2: Distribution of rubella positive cases by region in Cameroon, 2008-2014

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Figure 3: Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008-2014.

Table 1: Proportion of rubella cases in Cameroon between 2008 and 2014

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

List of Abbreviations

CRS: *congenital rubella syndrome*; WHO: *World Health Organization*; RCV: *rubella containing vaccine*; EPI: *expanded program on immunization*; MCV1: *measles containing vaccine*; IgM: *immunoglobulin M*; EDC-MICS*: Enquête Démographique et de la Santé et à Indicateurs Multiples*; WHO/AFRO: *World Health Organization African Region*; ELISA: *Enzyme linked immunosorbent assay*; CI: *Confidence interval*

Declarations

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

NMM conceiving the study, data collection, data analysis and preparing the draft manuscript. NVN, WCS, KM and BF contributed in data analysis and writing of the manuscript. All authors reviewed the draft and approved the final manuscript.

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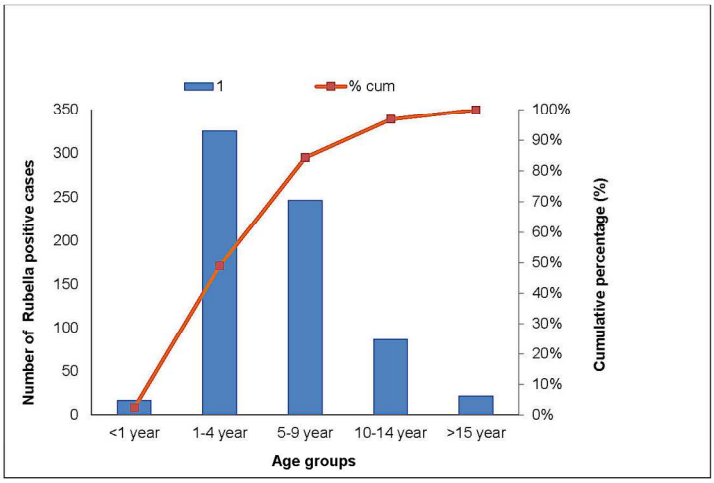

Figure 1 : Rubella case distribution by age group in Cameroon, 2008-2014.
N.B: The bars show the number and proportion of rubella cases for the specified age group and the curve represents the cummulative proportion of cases.

Figure 1: Rubella case distribution by age in Cameroon, 2008-2014

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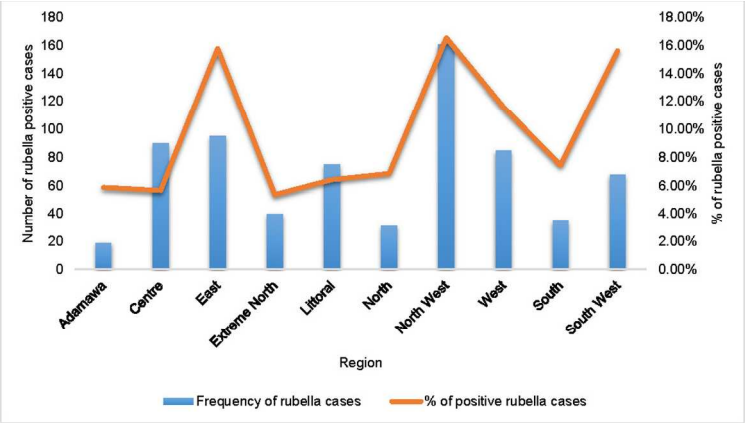

Figure 2: Distribution of rubella positive cases by region in Cameroon, 2008-2014

Figure 2: Distribution of rubella positive cases by region in Cameroon, 2008-2014

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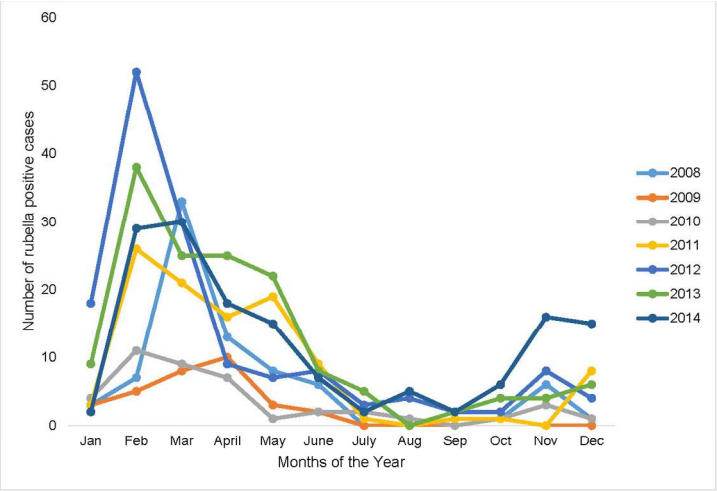

Figure 3: Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008-2014.

Figure 3: Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008-2014.

215x279mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**4-5**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			**5-6**
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			**6-9**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9

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		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			**9-11**
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			**12**
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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Secondary Subject Heading:	Epidemiology
Keywords:	Rubella, Cameroon, Surveillance

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Epidemiology of rubella infection in Cameroon: A 7-years 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 immunization program.

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

SETTING: Suspected measles patients from the ten regions of Cameroon were recruited according to the World Health Organization (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 World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case.

OUTCOME MEASURES: Descriptive analyses, simple logistic regressions were performed. Odd ratios (ORs) were estimated.

RESULTS

A total of 9,907 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

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significant difference in proportion of rubella cases were 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(EPI).

Keywords: Rubella, Cameroon, Surveillance

Strengths and limitations of this study

- This is the first study in Cameroon to investigate rubella infection across a broad age range, from all the regions and investigating association with some sociodemographic factors.
- The integration of rubella testing with measles case-based surveillance provides an opportunity to gain understanding about the epidemiology of rubella infection.
- The sensitivity of the case definition used for measles surveillance is likely not high enough to identify all rubella cases.
- The existence of missing data for some variables highlights some issues in data management process.

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INTRODUCTION

Rubella is an acute, contagious viral disease caused by a Togavirus of the genus *Rubivirus* and is characterized 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 rubella infected adult women 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 immunization 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$4,200 (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 United States,[8]. At least five of six World Health Organization (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 nine 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

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immunoglobulin M (IgM) antibodies. Cameroon planned to introduce the rubella-containing vaccine into the EPI program 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 program.

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 6 children per woman of child bearing 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 World Health Organization – African Regional Office (WHO/AFRO) case definition for a suspected measles case (that is, any person with generalized maculo-papular 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 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,

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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 1-5ml of blood was collected by venipuncture into a sterile anti-coagulant free tube. The blood was then allowed to clot then centrifuged at 3000rpm for five minutes to separate the serum. If there was no centrifuge in the health center, the blood was stored in a refrigerator until the clot was completely retracted from the serum. The serum was transferred aseptically into a vial and stored at 2-8°C for at most three 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 seven days. Enzyme linked immunosorbent assay (ELISA) for rubella specific IgM antibodies was carried out according to the manufacturer's instructions (Enzygnost Anti-Rubella Virus/IgM kit; Siemens AG, 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 program. Forms collected from the laboratory were reviewed and entered into the WHO electronic database. The case-based surveillance data were reported on a weekly base by the EPI program to the WHO country office.

Statistical analyses were performed using the SPSS statistical package (version 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 Chi square or Fisher exact tests for categorical variables to find key determinant of rubella infection in Cameroon. A 95% confidence interval (CI) was calculated for the Odds ratios and values of $P < 0.05$ were considered statistically significant. Logistic regression analysis was used to estimate Odds ratios of IgM seropositivity as outcome variable with age, sex and setting as explanatory variable

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RESULTS

Proportion of rubella diseases

A total of 9,907 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.

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%)

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 one year of age (representing the targeted age in the routine EPI program) and 96.85% of cases were below 15 years (marking the entrance to child bearing 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).

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

	Number tested for rubella	Number tested positive (%)	Odds ratio	95% Confidence interval	P value
Age group					

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< 1 year	1244	17(1.37)	1		0.0001
1-4 years	3635	326 (8.97)	7.11	4.35 - 12.41	
5-9 years	1610	247 (15.34)	13.07	7.93 - 22.93	
10-14 years	540	87 (16.11)	13.86	8.06 - 25.12	
>=15 years	452	22 (4.87)	3.69	1.85 - 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 - 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 - 1.31	
Total	7466	699 (9.3)			

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 child bearing 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 to 2014 shows that, the East, North west and the South west regions had higher proportions of rubella cases (Figure 2).

Seasonal distribution of rubella cases from 2008 to2014

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).

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Logistic regression analysis

Logistic regression analysis reveals associations of rubella IgM sero-positivity with age. Compared to children less than one 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 cases per year. The increase in the proportion of rubella cases during this period could 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 detection 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 (AFP) 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 immunization programme which targets children of this age group. Vaccinating children in the routine immunization programme at this age

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will provide protection against rubella in these childrenthrough 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 congenital rubella syndrome.

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, 16-20]. 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,* in Ethiopia where a seasonal distribution of cases occurred each year and peaked from March through June,[13]. Rubella cases in this study do not show any statistical significant difference between urban and rural populations. Mitiku *et al,* noted a significantly higher number of positive cases in the urban areas compared to rural areas,[13].

Occurrence of rubella antibodies in children of 5 months in this study indicates possibility of infection at a younger age although congenital rubella syndrome 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 industrialized countries during the pre-vaccination era,[21]. The incidence of CRS per 1000 live births in Cameroon is still unknown. Jivraj *et al* 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

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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 were designed for the measles case-based surveillance system. Many individuals with rubella disease may not have rash which occurs in 50%–80% of rubella infected persons,[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 toward 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 generalized maculopapular rash and at least one of the following: cervical adenopathy, sub-occipital adenopathy, post-auricular adenopathy, arthralgia or arthritis,[24]. As Cameroon and other African countries work toward introducing rubella containing vaccines 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 child bearing age, thereby

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secondarily increasing 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 program.

CONCLUSION

Rubella virus circulates in Cameroon with an important number of children under 15 years being affected. Children under one year presented with low proportions indicating a potential benefit of introducing a rubella vaccine into the national routine immunization program, 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 post vaccine studies once the vaccine is introduced into the national immunization program among high risk susceptible groups of the population. Information from such studies will be useful for rubella elimination strategies in Cameroon.

Ethical considerations

The Cameroon Measles surveillance is a national program approved by the Ministry of Public Health and supported by WHO/AFRO as part of the global goal to control and eliminate measles and rubella. Patient information and specimen collection respected the procedures stipulated in the WHO/AFRO measles/rubella surveillance protocol. Although written consent or ascent form was not required, for the purposes of the national surveillance program, relevant information was provided and verbal permission obtained before samples were collected from a suspected case.

Data sharing statement: The original data can only be accessed by the research investigators working at the Ministry of Public health Cameroon and the WHO country office Cameroon. Nimpa Mengouo can be contacted if the de-identified dataset is required.

Figures and Tables legend

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Figure 1: Rubella case distribution by age in Cameroon, 2008-2014

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.

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

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

List of Abbreviations

CRS: *congenital rubella syndrome*; WHO: *World Health Organization*; RCV: *rubella containing vaccine*; EPI: *expanded program on immunization*; MCV1: *measles containing vaccine*; IgM: *immunoglobulin M*; EDC-MICS*: Enquête Démographique et de la Santé et à Indicateurs Multiples*; WHO/AFRO: *World Health Organization African Region*; ELISA: *Enzyme linked immunosorbent assay*; CI: *Confidence interval*

Declarations

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

NMM conceiving the study, data collection, data analysis and preparing the draft manuscript. NVN, WCS, KM and BF contributed in data analysis and writing of the manuscript. All authors reviewed the draft and approved the final manuscript.

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involved in laboratory testing, and all health care workers involved in case identification and sample collection at all health institutions of Cameroon.

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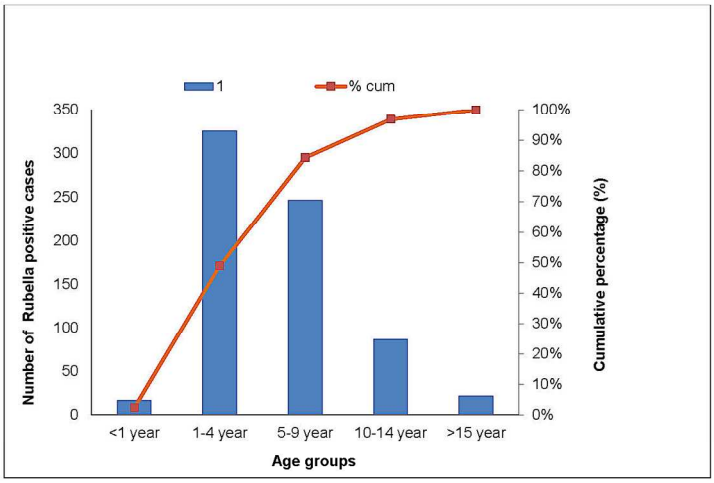

Figure 1 : Rubella case distribution by age group in Cameroon, 2008-2014.
N.B: The bars show the number and proportion of rubella cases for the specified age group and the curve represents the cummulative proportion of cases.

Figure 1: Rubella case distribution by age in Cameroon, 2008-2014

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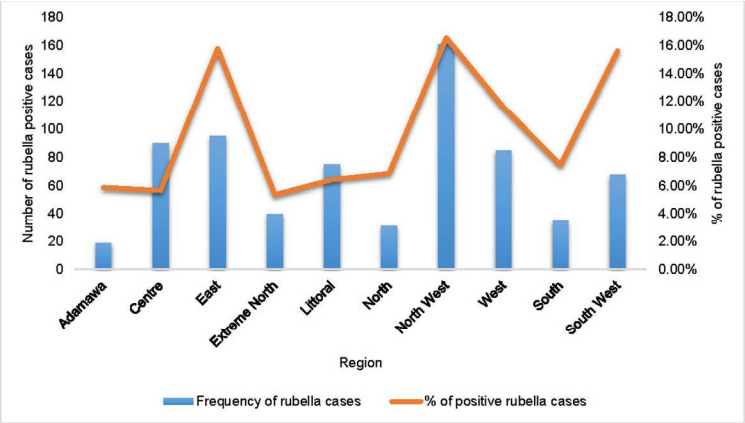

Figure 2: Distribution of rubella positive cases by region in Cameroon, 2008-2014

Figure 2: Distribution of rubella positive cases by region in Cameroon, 2008-2014

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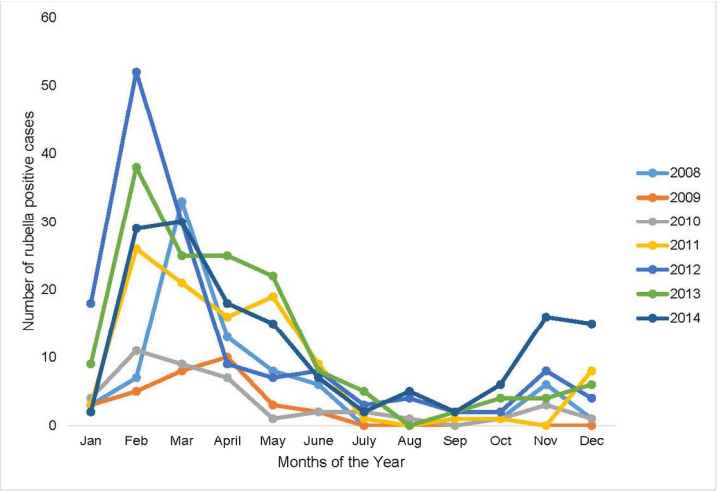

Figure 3: Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008-2014.

Figure 3: Monthly trends in the number of samples testing positive for rubella in Cameroon, 2008-2014.

215x279mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			**4-5**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			**5-6**
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			**6-9**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-8
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9

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		(*b*) Report category boundaries when continuous variables were categorized	7-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			**9-11**
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			**12**
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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