

Epidemiology of rubella disease in south-west Nigeria: trends and projection from measles case-based surveillance data

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Although surveillance for rubella does not exist in Nigeria, a measles case-based surveillance system was introduced in 2005 as one of the strategies for measles morbidity control, and included laboratory testing for confirmation of the disease. In this report, we provide the epidemiological distribution of rubella-confirmed cases reported from the south-west zone of the country, and predict the expected number of cases in the ensuing years. A descriptive analysis was carried out of rubella cases reported in the measles case-based surveillance data from the south-west zone of Nigeria for the period 2007-2012. Using an additive time series model, we predicted the expected number of cases until the year 2015. Four hundred and thirty-eight (5.4%) rubella cases were confirmed from 8 046 suspected measles cases. Cases were confirmed from all six states within the zone. The majority (87.3%) were individuals < 15 years of age and 40.9% were female. Seasonal variation existed, with peaks of infection in the first and third triannual periods of the year, while annual trends showed peaks in 2007 and 2010. Based on projections, there was a reduction in the number of expected cases. Rubella testing, in parallel with measles case-based surveillance, provides understanding of the epidemiology of rubella infection in south-west Nigeria.

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Introduction

Rubella, also known as German or three-day measles, is a mild viral illness which shares similar symptoms of rash and fever with measles.^{1,2} However, when a pregnant woman is infected with the disease, particularly during the first trimester, serious consequences, including birth defects, known as congenital rubella syndrome (CRS), can occur in the newborn. These defects can affect all of the body's organs, including the eyes (cataracts and glaucoma), ears (sensorineural deafness), and heart (*patent ductus arteriosus*). Furthermore, infants with CRS who survive the neonatal period are highly vulnerable to developmental abnormalities and delays, including visual and hearing impairment, failure to thrive and autism.³ Rubella is caused by a ribonucleic acid virus, *Rubivirus togaviridae*, which resides in the mucus in the nose and throat of infected persons. Spread is by direct contact with susceptible hosts through droplet sprays during coughing and sneezing. The incubation period ranges from 14-21 days. A person with rubella is contagious from approximately seven days prior to the onset of rash to seven days after the rash appears.^{1,2}

Although a safe and effective vaccine has been available for the prevention of rubella for > 40 years, there has been no global recommendation for inclusion of the vaccine in the routine immunisation programme of most developing countries, including Nigeria. This lack of recommendation is despite reports of outbreaks of CRS in industrialised and underdeveloped countries.⁴ In addition, little is known about the

epidemiology of rubella and the incidence of CRS in Africa. However, an estimate showed that 110 000 CRS cases occur each year during non-epidemic years in developing countries.³ Country-specific data on the burden of the disease at national and subnational level are needed for developing countries to make informed decisions on the inclusion of a rubella vaccine in their national programmes.

Nigeria is the most populous country in Africa with a population of 148 million in 2007 and a growth rate of 3.8% per annum. It is estimated that the population will increase to 210 million in 2025, and 289 million in 2020. The proportion of urban dwellers in 2005 was 46.2%, and exceeded that of sub-Saharan Africa by > 10%. The life expectancy estimate is approximately 48 years, with an infant mortality rate of 99 per 1 000.⁵ Nigeria has six regional zones which reflect varying ecologies, climates and population characteristics, as follows: north-east, north-west, north-central, south-east, southern-south and south-west. South-west Nigeria falls on latitude 6° to the north and 4° to the south, and is marked by longitude 4° to the west and 6° to the east. The geographical location covers approximately 114 271 km², which is approximately 12% of the total land mass of Nigeria. The zone comprises six states (Oyo, Osun, Ondo, Ogun, Ekiti and Lagos), and is bounded in the north by Kogi and Kwara states, in the east by Edo and Delta states, in the south by the Atlantic Ocean, and in the west by the Republic of Benin. With a typical rainforest vegetation, the population of 27 581 992 is agrarian and predominantly constitutes the Yoruba ethnic group.^{5,6}

There is limited information on the incidence of rubella infection and CRS in Nigeria. Seroprevalence studies on hospital personnel and pregnant women in south-west Nigeria using immunoglobulin G (IgG)-specific antibodies, which measure responses to past rather than recent infections, indicated a prevalence range of 68.5-73.0%.⁷⁻⁹ In one study, one in four pregnant women had no IgG-specific antibodies, suggesting that pregnant women are susceptible to rubella infection and their newborns are at risk of CRS.⁷ In addition, the immune response rate was shown to be higher in rural than in urban dwellers. This supports the notion that immune Nigerians are likely to have acquired their immunity through natural infection because a vaccination policy is not in place. However, it is possible that some private practitioners and occupational establishments in major urban centres provide vaccination to infants ≥ 9 months of age in the form of a measles-rubella or measles-mumps-rubella vaccine.³ These vaccination services are not monitored, and the rubella vaccination coverage in the general population is unknown.

Although surveillance for rubella or CRS does not exist in Nigeria, a measles case-based surveillance system was introduced in 2005 as a strategy for measles morbidity control, and included laboratory testing for the detection of measles- and rubella-specific IgM antibodies, which indicate responses to recent infections.¹⁰ A national public health laboratory was supported in each of the four zones of the country to receive and process serum samples from the six zones for this purpose. Measles case-based surveillance has helped greatly in documenting the epidemiology of measles and tracking progress towards control efforts. However, little is known of the magnitude and distribution of other known febrile rash illnesses. In Nigeria, like any African country, CRS is under-recognised as a public health problem, and information on the incidence of rubella and CRS is limited. In this report, we summarise the results of rubella antibody testing carried out in the measles case-based surveillance system from 2007-2012, and provide an epidemiological distribution of rubella-confirmed cases reported from the south-west zone of the country. We also modelled the pattern of rubella cases for three periods of four months each in a year, and predict the expected cases for 2012-2015.

Method

The World Health Organization African Regional Office measles case-based surveillance guideline was adapted for use in Nigeria in 2005, but implementation did not commence in the south-west geopolitical zone until the last quarter of 2006.¹⁰ A suspected measles case was defined as an illness in a person who presented with fever, a generalised rash, coughing, coryza or conjunctivitis. Suspected individuals who presented within 30 days of the onset of a rash were investigated using a standardised form. Serum specimens were collected from suspected cases, except for those who were epidemiologically linked to a confirmed measles outbreak. The serum specimens were sent to national measles laboratories, one of which is located in each of the three northern zones, and one in the south-west that serves the remaining three southern zones. Laboratory testing was carried out using a standard commercial indirect enzyme-linked immunosorbent assay kit, Enzygnost® Anti-Measles Virus IgM (Dade Behring, Hesse, Germany). The laboratories were subjected to periodic quality control exercises and accredited annually.

Specimens that tested positive for measles-specific IgM, and which were from patients who had not received a measles vaccination within four weeks prior to specimen collection, were classified as laboratory-confirmed cases. Whereas, serum samples that were measles IgM-negative, or which had two sets of indeterminate results for measles were tested for rubella IgM antibody titers. The positive cases were classified as laboratory-confirmed rubella cases. The completed individual case investigation form and the laboratory results were entered into an electronic Excel® database. Data for this report were extracted and analysed using SPSS®.

The pattern of rubella was plotted to determine if seasonal variation existed in the reported number of cases over the years. The observed pattern of variation suggested an additive time series model, implying that time series (y_t) can be represented by a moving average level that changes over time according to the following equation:

$$y_t = TR_t + SV_t + \epsilon_t$$

where y_t is the observed value of the rubella cases in time period t ; TR_t is the trend in time period t obtained by the moving average method; SV_t is the seasonal factor in time period t and ϵ_t is the irregular factor. We assumed that ϵ_t satisfies the usual regression assumptions of constant variance, independence and normality. To average the irregular variation in the data, we computed a three-period moving average of the y_t . Thus, the estimate of TR_t is as follows:

$$TR_t = \frac{y_{t-1} + y_t + y_{t+1}}{3}$$

using the above assumption, $\epsilon_t = 0$ and $SV_t = y_t - TR_t$.

To model the seasonal pattern, the seasonal variation factor, SV_t , was de-seasonalised using a dummy variable. The seasonal factor was expressed using dummy variables as follows:

$$Snt = \beta_{s1} X_{s1,t} + \beta_{s2} X_{s2,t} + \dots + \beta_{sL} X_{sL,t}$$

where

$$X_{s1,t}, X_{s2,t}, \dots, X_{s(L-1),t}, X_{s1,t}, X_{s2,t}, \dots, X_{s(L-1),t}$$

are dummy variables that are defined as follows:

$$X_{s1,t} = \begin{cases} 1 & \text{if time period } t \text{ is season 1} \\ 2 & \text{otherwise} \end{cases}$$

$$X_{s2,t} = \begin{cases} 1 & \text{if time period } t \text{ is season 2} \\ 2 & \text{otherwise} \end{cases}$$

to

$$X_{s(L-1),t} = \begin{cases} 1 & \text{if time period } t \text{ is season } L \\ 2 & \text{otherwise} \end{cases}$$

The dummy variables ensured that a seasonal parameter ($\beta_{s1}, i = 1, 2, \dots, L$) for each season (L) was added to the trend in each appropriate time period, which was used to predict rubella cases in each of the three seasons in 2012-2015.

Results

Between January 2007 and December 2012, 10 354 suspected measles cases were investigated following blood specimen collection for confirmatory laboratory testing. Of these suspected measles cases, 8 046 (77.7%) were tested for rubella-specific IgM antibodies according

Table I: Number of specimens tested for rubella immunoglobulin M antibodies and the results in south-west Nigeria from 2007-2012

Year	Specimens tested for rubella IgM	No (%) of positive results	No (%) of negative results	No (%) of indeterminate results	No (%) of pending results
2007	667	93 (13.9)	523 (78.4)	51 (7.7)	0 (0.0)
2008	1 249	87 (7.0)	1 106 (88.6)	56 (4.5)	0 (0.0)
2009	1 298	50 (3.9)	1 217 (93.8)	31 (2.4)	0 (0.0)
2010	1 716	137 (8)	1 495 (87.1)	84 (4.9)	0 (0.0)
2011	1 527	68 (4.5)	1 422 (93.1)	37 (2.4)	0 (0.0)
2012	1 589	3 (0.2)	1 547 (97.4)	3 (0.2)	36 (2.3)
Total	8 046	438 (5.4)	7 310 (90.9)	262 (3.3)	36 (0.5)

IgM: immunoglobulin M

Table II: Distribution of laboratory-confirmed rubella cases by states in south-west Nigeria from 2007-2012

States	Rubella IgM-positive cases	Total specimens tested for rubella	Rubella positivity in %
Ekiti	86	1 536	5.6
Lagos	112	2 394	4.7
Ogun	51	1 132	4.5
Ondo	47	700	6.7
Osun	61	1 110	5.5
Oyo	81	1 174	6.9
Total	438	8 046	5.4

IgM: immunoglobulin M

to laboratory procedures. Owing to a shortage of measles and rubella IgM test kits, 36 serum specimens were not tested in 2012. Of the 8 046 cases tested, 438 (5.4%) were laboratory-confirmed as rubella, there were negative results for rubella in 7 310 (90.9%), and there were indeterminate tests for 262 (3.3%) (Table I).

During the period, rubella cases were reported from all six states in the south-west zone of Nigeria (Table II).

The distribution of cases ranged in age from three months to 56 years, with a median age of four years. The majority (87.3%) of cases were individuals < 15 years of age and 40.9% were females. Figure 1 shows the variation of reported rubella cases between different triannual periods in a year.

The pattern of this variation follows the time series additive model. In Table III, the estimate of seasonal variation in each triannual period over the years is depicted. An indication of high positive variation exists in the first triannual period during each year, except in 2009, when only a slight variation of 1.33 reported cases of rubella occurred.

In Table IV, we show the seasonal variation adjusted to ascertain what the exact variation should be for the triannual periods (January-April, May-August and September-December) of any year. The data show higher seasonal variation for triannual periods 1 [Quarter 1 (Q1) = 20.95] and 3 (Q2 = 14.29), than triannual period 2 (Q3 = -6.6513).

$$\text{Increase in trend line per quarter} = \frac{nT_L - nT_{L2}}{n-1} = -0.6942$$

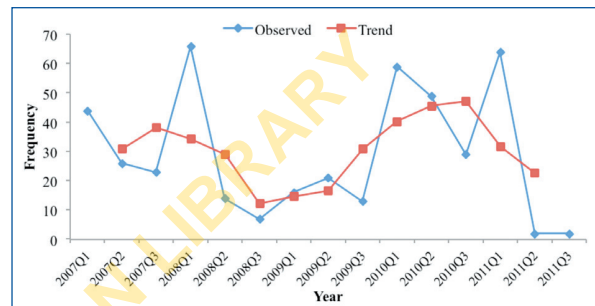


Figure 1: Observed and three-period moving average trend lines in the number of rubella cases reported by quarter from 2007-2012 in south-west Nigeria

Table III: Estimated seasonal variation in the number of rubella cases in children in south-west Nigeria from 2007-2011

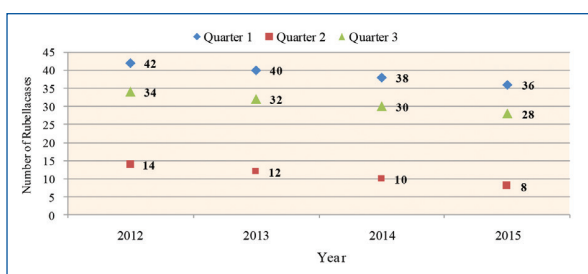
Quarter	Year	Number of rubella cases (y _t)	Moving total	Trend (T _t)	Seasonal variation (SV = y _t - T _t)
1	2007	44	-	-	-
2		26	93	31.00	-5.00
3		23	115	38.33	-15.33
1	2008	66	103	34.33	31.67
2		14	87	29.00	-15.00
3		7	37	12.33	-5.33
1	2009	16	44	14.67	1.33
2		21	50	16.67	4.33
3		13	93	31.00	-18.00
1	2010	59	121	40.33	18.67
2		49	137	45.67	3.33
3		29	142	47.33	-18.33
1	2011	64	95	31.67	32.33
2		2	68	22.67	-20.67
3		2	-	-	-

SV: seasonal variation, T_t: the trend line for each season, y_t observed value of the rubella cases in time period t

Figure 2 is the dot plot of the predicted number of cases of rubella for 2012-2015. The data showed a likely reduction in the reported cases of rubella over the years.

Table IV: Estimated seasonal variation adjustment per quarter for number of rubella cases in children in south-west Nigeria from 2007-2011

Year	January-April (Quarter 1)	May-August (Quarter 2)	September-December (Quarter 3)
2007	–	–5.00	–15.33
2008	31.67	–15.00	–5.33
2009	1.33	4.33	–18.00
2010	18.67	3.33	–18.33
2011	32.33	–20.67	–
Total	84.00	–33.01	–56.99
Average	21.00	–6.60	–14.25
Shared	–0.05	–0.05	–0.05
Adjusted value	20.95	–6.65	14.30

**Figure 2:** Dot plot of predicted number of cases of rubella for 2012-2015 in south-west Nigeria

Discussion

Analysis of the measles case-based surveillance in south-west Nigeria for 2007-2012 revealed that rubella infections occurred widely within the zone and primarily affected young children. This finding is consistent with the results of surveillance data and other seroprevalence studies on rubella in Nigeria, which suggest that the disease occurs widely in the country. By 15 years of age, most children have developed immunity from natural infection.^{4,7-9,11-13} In a review of measles case-based surveillance data for the whole country, 94% of cases were < 15 years of age and 49% were females.⁴ Our findings are also consistent with those in studies from other parts of Africa that have reported on the measles case-based surveillance system.^{3,4,14} In Ethiopia, 95% of cases were < 15 years of age and 54% were females.³ In Zambia, the incidence of rubella was highest in those aged 5-14 years.¹⁴ In comparison with other regions, our findings were only similar to those observed during the pre-vaccine era. Rubella is primarily a childhood disease that occurs mainly in children aged 5-9 years in Europe and the America. In the USA, prior to the use of the rubella vaccine, 80% of cases occurred by 14 years of age and 92% by 20 years. However, seroprevalence studies estimated the susceptibility to rubella in persons aged 17-22 years to be 15-20%.⁴

A declining trend in the incidence of rubella cases was observed over 2007-2012, and our projection showed that this trend will persist until 2015, the year we projected to. However, this is interesting, bearing in mind that no specific preventive measures, including vaccines, are in use to control the disease. We assumed that increasing herd immunity from acquired natural infections could be responsible for the observed

trend. Periodic seroprevalence surveys, especially among children and young adults, would be required to prove or disprove such speculation. In addition, we observed the annual seasonality of rubella cases, with an increase in the number of cases in the first and third triannual periods of the year. Similar patterns were reported in the Africa subregion and in the USA during the pre-vaccine era.^{3,4,14} In Ethiopia, increases in the number of cases were observed from February, with a major peak between April and May, before cases declined to the lowest level in August. A minor peak in the number of cases was also observed between October and November.³ In Zambia, the seasonal pattern indicates that most cases occur from August to December.¹⁴

Increases in cases occurred in early winter, peaked in March, and decreased to a low point in late summer and autumn in the USA during the pre-vaccine era.⁴ However, the three-period moving average trend line, after removing the seasonal pattern from the graph, suggests an epidemic peak in Q3 2007 and Q1 2008, and a second peak in Q3 2010 and Q1 2011. Going by this trend line, and giving that the current state of no intervention with vaccine subsists, an epidemic in Q3 2014 and Q1 2015 could be predicted. If vaccination is introduced and the coverage is adequate, the inter-epidemic periods should lengthen, and the epidemics would hopefully be milder. With sustenance of proper coverage, the epidemics are expected to stop altogether, and transmission would be interrupted. If, on the other hand, vaccine coverage is poor, vaccine immunity will not be sufficient, and the susceptible age group in adults will increase. Outbreaks of CRS could then occur with greater intensity. Most of the infections currently occur in people under the age of 15 years, which is preferable than occurrence in those of older childbearing age.

The results obtained in this study are subject to limitations. The case definition used to detect the rubella cases was designed for a measles case-based surveillance system and is specific to measles. Many individuals with rubella cases may not have any significant fever, and up to 50% of individuals with rubella cases may present without a rash or have subclinical illness. It is likely that the sensitivity of the case definition was not high enough to identify all of the rubella cases. Therefore, the descriptive analysis given herein may represent a minute fraction of all of the rubella cases that occurred during the period under review.^{3,4} Moreover, studies that have estimated the completeness or sensitivity and representativeness of the measles surveillance system within the country have indicated that only a very small fraction of suspected measles cases was reported, while the quality of the system was low.^{15,16} This negatively affects the low number of cases of rubella that the system is able to identify in relation to the real number in the community. Secondly, the number of cases detected per month was very small, hence there was a need to group cases that occurred within four months in order to make a meaningful projection.

We have very few time points in our data in terms of obtaining a truly correct view of trends. Our trend line was skewed by having two very low data points in Q2 2011 and Q3 2011. Time series data are often used to make sense of a great number of data entries over long periods in order to correctly monitor, and therefore forecast trends. However, because rubella cases are not included in the Nigeria disease notification system, and are rarely monitored,¹⁰ we decided to use the opportunity

presented by the measles case-based surveillance data, and make use of the available data on the disease to describe the trend in the number of cases over the years. We excluded 2012 in the prediction model owing to its incompleteness, to avoid an element of bias that the shortfall of that year's data might have caused with respect to the outcome. Additionally, we used a three-period moving average trend line to clarify the epidemic after removing the seasonal pattern and predicting when future outbreaks would be likely to occur.

There were negative results for both measles and rubella antibodies for a high proportion of suspected measles cases reported using the surveillance system, suggesting that the case definition includes a low positive predictive value for the diseases. Two factors may be responsible in this regard. The first could be the timing of the collection of the specimen. It is known that IgM antibody levels may not be high enough to be detected in specimens collected within the first three days of the onset of a measles rash, or after 28 days, using standard methodology.^{1,3,4,10} However, according to surveillance protocols, the collection of a specimen is encouraged any time within the first month after the onset of the rash, so that opportunities for laboratory testing are not missed.^{1,3} The second responsible factor could be that the rash was neither due to measles nor rubella, but to some other disease that usually presents with febrile rash illnesses, such as chickenpox, *erythema infectiosum*, *roseola infantum*, meningococcal infections, scarlet fever, enteroviral infections or a drug rash.^{1,3,10} Confirmatory tests for these illnesses are not part of the surveillance system.

In conclusion, the investigation of rubella testing, in parallel with measles case-based surveillance, provided an understanding of the epidemiology of rubella infection in south-west Nigeria. It is likely that the adoption of a case definition that is more sensitive to rubella would lead to an increase in case detection and a better understanding of the epidemiology. In addition, sentinel surveillance for CRS and seroprevalence studies, to assist with defining a rubella susceptibility profile of school and female reproductive age groups, would be useful in determining the burden of rubella in the country. These elements are necessary to identify, plan, implement and evaluate appropriate control strategies for the disease.

Conflict of interest

The authors have no commercial or other associations that might have

posed a conflict of interest with respect to the study.

Declaration

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