Sero-epidemiology of rubella in Zambia in the pre-vaccination period (2005 – 2016) as baseline for evaluation of introduction of rubella vaccine into the national immunization program

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Abstract

Background

Rubella is highly under-reported in Zambia as in most sub-Saharan countries despite being a disease of major public health concern especially among women of childbearing age. In September 2016, Zambia introduced a combined measles-rubella vaccine in children aged 0-14 years. In this study, we estimated the rubella sero-prevalence and its correlates between 2005 and 2016, a period prior to the introduction of Measles-Rubella vaccine in Zambia to provide baseline reference data for the future evaluation of its impact.

Methods

In a retrospective study, serum samples collected through the national measles surveillance program that tested negative for measles were examined for rubella IgM antibodies using the Siemens, Enzygnost® ELISA kit at the national measles laboratory accredited by WHO. Data on age, sex, province, year and month of onset were extracted from the surveillance data. Logistics regression analysis was conducted to determine independent predictors of rubella infection.

Results

Overall, a sero-prevalence of 29.2% (1313/4497) affecting mostly those between 5 and 24 years was determined. Logistics regression results indicated that only age, province, year and month were independently associated with rubella infection. The regional sero-prevalence varied from 21.8 – 37.3% peaking in the hot dry month of October. Logistics regression indicated that those in the age group 10-14 years (AOR=2.43; 95% CI 2.01 - 2.95) were more likely while those aged <1 year less likely (AOR=0.31; 95% CI 0.21 - 0.48) to have rubella compared to those aged 25 years or older. Persons in 2010 were less likely (AOR=0.12; CI 0.05, 0.28) to have rubella infection compared to those in 2016. While rubella infections were more likely to occur between July and November compared to
December, they were less likely to occur between February and May.

Conclusions

There is evidence that rubella virus was circulating in Zambia between 2005 and 2016 affecting more females than males and persons in the age group 5-24 years with a peak in the hot dry season. It is recommended that immunisation campaigns be targeted in months of lower virus transmission between February and May and in a situation of limited resources to those aged 5-24 years.

Background

Rubella is highly under reported in Zambia as in most sub-Saharan countries, despite being a disease of major public health concern, more so amongst young women in childbearing age causing miscarriage, foetal death or an infant born with malformations [1]. Rubella infection is prevalent in Africa. In a recent review of literature, Goodson [2] reported rubella sero-positivity (IgM) ranging from 68–98% in Africa, partly due to differences in age groups of the study populations. Descriptive studies on measles surveillance programs in Africa indicate higher rubella positivity rates among the 5–9 years [3] and 10-14 years age group [4,5].

Various correlates for rubella sero-prevalence include socio-demographic factors such as age, sex, year, season and region. Comparisons of infection rates between and within countries and different subpopulations may not be valid partly due to differences in criteria for rubella positivity that have varied from 1:8 to 1:40 [6]. Although results on the association of age with rubella infection have not been consistent, generally age has been reported to be significantly associated with rubella. While some studies revealed an association of sero-prevalence with age [7-9], Barreto et al [10] did not find a significant association. Noting limited information on the association with sex, the sero-prevalence of rubella antibodies has been reported to be higher in females than males (Gomwalk et al,
Seasonality has been associated with rubella sero-positivity. A study by Goodson et. al. analyzing the rubella epidemiology in Africa indicates the prevalence peaking in March-April in West sub-Saharan African; in February in the Central sub-Saharan African; in March-April and in September-October in East sub-Saharan African; and in September to October in South sub-Saharan African [2]. Although higher sero-prevalence have been noted in the hot dry seasons, some variations have been recorded with the peak in West, Central and East Africa coinciding with the rain season [2,11]. According to the World Health Organisation (WHO), rubella epidemics tend to occur at 10-year intervals [11] or every 5-9 years [12].

In a literature review, Goodson et al [2] reported that rubella sero-prevalence was higher in rural (63%) than urban (37%) settings. In another study, Mitiku et al, [13] also reported a higher infection rate in urban (19.4%) than rural (11.6%) settings. However, to the contrary, Barreto et al [10] found no significant difference in sero-prevalence of rubella IgG antibodies between rural and urban areas.

Zambia intensified laboratory-backed measles case based surveillance in 2003. During the period under review, Zambia had no programmatic goal towards elimination of rubella and neither did it have a vaccination policy against rubella infection. In October 2016, Zambia introduced a combined measles-rubella vaccine in children aged between 9 months and 14 years through a nationwide campaign. There is scanty evidence in Zambia on the epidemiology of rubella in the pre-vaccination period. The objectives of the study were to estimate the sero-prevalence and correlates of specific rubella Immunoglobulin M (IgM) antibodies as indicators of primary rubella infection in Zambia before the introduction of mass measles-rubella immunization.

Methods
Study design
A retrospective analysis of data captured by the national measles laboratory through the national measles case based surveillance from January 2005 to September 2016 was conducted.

Study population and setting
Cases among the laboratory investigated suspected measles cases in Zambia tested for rubella IgM in the virology laboratory at the University Teaching Hospital in Lusaka between January 2005 and September 2016.

Case definition
A suspected measles case was defined as any person who presented with fever, generalized maculopapular rash, and either cough, or coryza, or conjunctivitis regardless of age and sex or any person whom a clinician suspected to have measles [14]. Rubella IgM was determined on samples of patients with fever and rash that tested negative for measles IgM. IgM is the largest antibody, and it is the first antibody to appear in the response to initial exposure to an antigen [15].

Laboratory analysis
Samples collected from suspected measles cases mostly within 14 days of onset of rash according to WHO/AFRO guidelines [16] that tested negative or equivocal to measles IgM were routinely tested for rubella IgM at the Zambia National Measles Laboratory (Virology laboratory, University Teaching Hospital in Lusaka) accredited by WHO. The serum samples were qualitatively analysed for rubella Immunoglobulin M (IgM) by the Enzyme Linked Immunosorbent Assay (ELISA) using the Siemens.Enzygnost® [17]. The kit that was selected had high specificity and sensitivity of 98.5% and 100%, respectively (Siemens.Enzygnost®, 2011)
The difference in the optical densities (Absorbance) as stipulated in the manufacturer’s guidelines, ΔA between the antigen and antigen control wells was calculated and results interpreted as follows:

- **Anti-Rubella-Virus/IgM negative** $\Delta A < 0.100$
- **Anti-Rubella-Virus/IgM positive** $\Delta A > 0.200$
- **Anti-Rubella-Virus/IgM equivocal** $0.100 \leq \Delta A \leq 0.200$

## Data management and analysis

Data capture was done using Epi info version 3.5.4.9 a software developed by Center for Diseases Control and Prevention, Atlanta, USA. The data entry program has drop down options for variables including sex, district and province to eliminate error. Considering date of varying events including date of birth and date of onset of rash was not locked on entry, data cleaning was performed to ensure consistency.

Among the variables extracted from the surveillance data for analysis were age, sex, province, year and month of onset. Logistics regression to determine independent predictors of rubella infection was performed. The magnitude of association was estimated using odds ratio at 95% confidence interval.

## Results

Of the total 5683 suspected measles samples examined between 2005 and September 2016, 4497 measles negative and equivocal samples were tested for rubella IgM. The overall sero-prevalence of rubella was 29.2% (1313/4497). Sero-prevalence among the females was 30.8% and 27.7% among males ($p=0.022$). The age group 10 – 14 years had the highest sero-prevalence (41.8%) followed by the 5 -9 years age group (35.9%), while the lowest (7.5%) was among infants. Throughout the years, the lowest prevalence of rubella IgM antibodies (4.5%) was in 2010 and the highest (49.4%) in 2013. The prevalence
of rubella infection in Zambia started to peak in July through to November with the highest prevalence in October (Table 1). Generally, the peak sero-prevalence of rubella occurred in the hot dry season (Figure 1). North western province recorded the highest sero-prevalence at 37.3% and the lowest was Luapula with 22.8% sero-prevalence (Figure 2). Sex was not independently associated with rubella infection. Age, province, year and month were independently associated with rubella infection. Those in the age group 10-14 years (AOR=2.43; 95% CI [2.01 - 2.95]) were more likely and those aged <1 year (AOR=0.31; 95% CI [0.21 - 0.48]) less likely to have rubella compared to those aged 25 years or older. Persons in 2010 were less likely (AOR=0.12; CI [0.05, 0.28]) to have rubella infection compared to those in 2016. Rubella infections were more likely to occur between July and November (AOR=1.66; CI [1.33, 2.08], AOR=1.86; CI [1.49, 2.32], AOR=1.29; CI [1.03’ 1.60], AOR=2.15; [1.77, 2.62] and AOR=1.60; CI [1.31, 1.95], respectively) compared to December, and less likely to occur between February and May (AOR=0.52; CI [0.37, 0.72], AOR=0.48; CI [0.36, 0.65], AOR=0.62; CI [0.43, 0.88] and AOR=0.44; CI[0.30, 0.65] respectively) as shown in Table 2.

Discussion

A rubella sero-prevalence of 29.2% was found among suspected measles cases investigated through the national laboratory backed measles case based surveillance program between 2005 and 2016 in Zambia. Sero-prevalence amongst females was found to be at 30.8% and 27.7% among males, although sex was not independently associated with rubella infection. Logistics regression results indicated that only age, province, year and month were independently associated with rubella infection.

The sero-prevalence in the current study and in similar studies is based on those who had clinical symptoms that met the measles case definition. It is known that rubella infection may be subclinical in up-to 50% of rubella infections, therefore this prevalence may be an
underestimate [18]. Notwithstanding the possible underestimation, the sero-prevalence in the present study is far less than what has been observed in other parts of Africa of 68-98% before 2009 [2]. More recent data indicates Zambia having a lower overall sero-prevalence rate than Zimbabwe (37.6%) [4] and Ethiopia (39.4%) [13] but higher than Cameroon (9.3%) [3] and comparable to Central African Republic (30.2%) [5]. The varying sero-prevalence may indicate the different transmission patterns among countries [19] and variations in climatic conditions [20].

The current study indicates that those between the ages 5 to 24 years were more likely to have rubella compared those aged 25 years or older. Meanwhile persons aged <1 year were less likely to have rubella infection compared to persons aged 25 years or older. Persons under the age of one year are still protected by maternal antibodies and the older they become they lose this protection. Similar findings of a significant association between age and rubella have been reported before [7-9], although in one study no significant association was reported [10].

The prevalence of rubella infection in Zambia peaked in October, the hottest month. Elsewhere in west, central and east Africa, the peak for rubella infection coincides with the rain season. The seasonality of rubella infection in the southern Africa region has not been consistent. The current finding is in agreement with the observation that rubella infection in the southern Africa region generally coincides with the hot dry season [2]. The finding from the current study accords what has been reported in Zimbabwe that rubella infection peaks in October-November just before the start of rain season [4]. Further investigations are warranted to determine climatic factors associated with rubella virus in the southern region of Africa that has varying climatic conditions from the Mediterranean climate climatic in Cape Town, South Africa, desert conditions in Namibia to tropical/sub-tropical climate in Zambia; and in particular a study on association between climate and
rubella infection would be interesting in Zambia since although Zambia has tropical climate generally, the climate is modified by altitude in different regions of the country. The rubella epidemic intervals in the current study were not clearly defined. However, findings elsewhere suggest 10-year intervals [11] and 5-9 years [12]. There is need to gather more data points when epidemics occur in Zambia in order to accrue more evidence for predicting epidemics. The findings that sero-prevalence of rubella infection was lowest in Lusaka and Luapula provinces and highest in Western and North-western provinces is not entirely clear. It may be speculated that the herd immunity to rubella may be higher in Lusaka due to continuous outbreaks over the years. Differences in elevations of the provinces and climatic conditions may explain variations in the rubella infection by province.

Conclusion

There is evidence that rubella virus was circulating in Zambia between 2005 and 2016 affecting persons in the age group 5-24 years, with a peak in the hot dry season. Although vaccination against rubella has been launched, these baseline data are important to provide a reference point when determining the impact of the vaccination program implemented. There is need to understand further why the prevalence is lower in Luapula compared to other areas of similar rural settings. It is recommended that immunisation campaigns be targeted in months of lower virus transmission between February and May and in a situation of limited resources to those aged 5-24 years.

List Of Abbreviations

AFRO Africa Regional Office
AOR Adjusted Odds Ratio
CI Confidence Interval
Declarations

Ethics approval and consent to participate

The data used in this analysis were de-identified in respect to study participants. Ethical approval was granted by ERES Converge IRB ref: 2016-Sept-001.

Consent for publication

Permission to carry out the research was granted by the National Health Research Authority ref: MH/101/23/20/1. The Provincial (Copperbelt and Lusaka), District Medical Officers (Ndola and Lusaka) and Senior Medical Superintendents of Ndola Teaching Hospital, Arthur Davison Children’s Hospital and University Teaching Hospital also granted permission to carry out the study.

Availability of data and material

Data is owned by Ministry of Health and permission to utilise it was sought and approved. Only parameters utilised in this paper can be accessed

Competing interests

There are no competing interests among the authors. All authors have approved the submission and declared that they have no competing interests.

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Authors’ contributions
MLM – participated in conception, design, data collection, laboratory and data analysis, interpretation of data and drafting of the manuscript. SS - participated in conception, design, analysis, interpretation of data and drafting of the manuscript. MM - was involved in the conception, design, data collection, analysis, interpretation of data and drafting of the manuscript. DC - was involved in the conception, design, data collection, analysis, interpretation of data and drafting of the manuscript.

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References

1. Grant GB, Reef SE, Patel M, Knapp JK, Dabbagh A. progress in rubella and congenital rubella syndrome control and elimination - Worldwide, 2000-2016. MMWR Morb Mortal Wkly Rep. 2017;66(45):1256-60.
2. Goodson JL, Masresha B, Dosseh A, Byabamazima C, Nshimirimana D, Cochi S, Reef S. Rubella epidemiology in Africa in the prevaccine era, 2002-2009. J Infect Dis. 2011;203 Suppl 1:215-25.
3. Nimpa Mengouo M1, Ndze VN2,3, Baonga F4, Kobela M4, Wiysonge CS5. Epidemiology of rubella infection in Cameroon: a 7-year experience of measles and rubella case-based surveillance, 2008-2014. BMJ Open. 2017;7(4):e012959.
4. Chimhuya S, Manangazira P, Mukaratirwa A, Nziramasanga P, Berejena C, Shonhai A, et
al. Trends of rubella incidence during a 5-year period of case based surveillance in Zimbabwe. BMC Public Health 2015;15:294.

5. Farra A, Pagonendji M, Manikariza A, Rawago D, Ouambita-Mabo R, Guifara G, Gouandjika-Vasilache I. Epidemiology of primary rubella infection in the Central African Republic: data from measles surveillance, 2007-2014. BMC Infect Dis. 2016;16(1):505.

6. Gomwalk NE, Ahmad AA. Prevalence of rubella antibodies on the African continent. Rev Infect Dis. 1989;11(1):116-21.

7. Odelola HA, Fabiyi A, Familusi JB. Distribution of rubella antibodies in Nigeria. Trans R Soc Trop Med Hyg. 1977;71:425-6.

8. Addy PAK, Abedmadzor F. Rubella in Ghana: seroepidemiological studies of healthy urban female Ghanians. Ghanian Med J. 1976;15:168-72.

9. WHO. Seroepidemiology of rubella. Wkly Epidemiol Rec. 1976;51:394-6.

10. Barreto J, Sacramento I, Robertson SE, Langa J, de Gourville E, Wolfson L, et al. Antenatal rubella serosurvey in Maputo, Mozambique. Trop Med Int Health. 2006;11(4):559-64.

11. Clarke M, Schild GC, Boustred J, McGregor IA, Williams K. Epidemiological studies of rubella virus in a tropical African community. Bull World Health Organ. 1980;58(6):931-35.

12. WHO. Rubella vaccines: WHO position paper. Wkly Epidemiol Rec. 2011;86(29):301-16.

13. Mitiku K, Bedada T, Masresha B, Kegne W, Nafo-Traore F. The epidemiology of rubella disease in Ethiopia: data from the measles case-based surveillance system. J Infect Dis. 2011;203 Suppl 1:239-42.

14. MoH [Zambia]. Technical guidelines for Integrated Disease Surveillance and response in Zambia. Version 1.3, August 2011.

15. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. B Cells and Antibodies.
16. WHO [Regional Office for Africa]. Guidelines for measles surveillance Revised December 2004. http://www.measlesrubellainitiative.org/wp-content/uploads/2013/06/Guidelines-surveillance.pdf. Accessed 10 Oct 2018.

17. Siemens. Enzygnost®. Anti-Rubella Virus/IgM handbook, July 2011.

18. CDC. Manual for the surveillance of vaccine-preventable diseases. Centers for Disease Control and Prevention. Atlanta, GA 2012; Chapter 14. http://www.cdc.gov/vaccines/pubs/surv-manual/index.html. Accessed 10 Oct 2018.

19. Mirambo MM, Majigo M, Aboud S, Groß U, Mshana SE. Serological makers of rubella infection in Africa in the pre vaccination era: a systematic review. BMC Res Notes 2015;8:716.

20. Kamruzzaman AKM, Jahan MS, Rahman MR, Khatun M. Impact of climate change on the outbreak of infectious diseases among children in Bangladesh. Am J Health Res. 2015;3(1):1-7.

Tables

Table 1: Distribution of rubella IgM antibody levels by sex, age, month and year in measles-negative serum samples between 2005 and September 2016

| Factor       | Total tested | Rubella IgM |                 |       |
|--------------|--------------|-------------|----------------|-------|
|              |              | Positive n (%) | Negative n (%) | Equivocal n (%) |
| Total sample | 4497 (100)   | 1313 (29.2)  | 2928 (65.1)    | 256 (5.7)       |
| Sex          |              |              |                 |       |
| Male         | 2333 (100)   | 647 (27.7)   | 1545 (66.2)    | 141 (6.0)        |
| Female       | 2160 (100)   | 666 (30.8)   | 1379 (63.8)    | 115 (5.3)        |
| Age (years)  |              |              |                 |       |
| <1           | 254 (100)    | 19 (7.5)     | 230 (90.6)     | 5 (2.0)           |
| 1 - 4        | 1336 (100)   | 278 (20.8)   | 1001 (74.9)    | 57 (4.3)          |
| 5 - 9        | 1322 (100)   | 475 (35.9)   | 744 (56.3)     | 103 (7.8)         |
| 10 - 14      | 739 (100)    | 309 (41.8)   | 380 (51.4)     | 50 (6.8)          |
Table 2: Bi-variable analysis of rubella sero-positivity

| Factor       | Odds Ratio (95% CI) |
|--------------|---------------------|
| Age (years)  |                     |
| <1           | 0.31 (0.21 - 0.48)  |
| 1 - 4        | 0.98 (0.82 - 1.17)  |
| 5 - 9        | 1.97 (1.66 - 2.34)  |
| 10 - 14      | 2.43 (2.01 - 2.95)  |
| 15-24        | 1.34 (1.06 - 1.69)  |
| 25+          | 1                   |
| Province     |                     |
| Region      | Value (95% CI) |
|------------|----------------|
| Central    | 1.00 (0.79 - 1.27) |
| Copperbelt | 0.91 (0.76 - 1.08) |
| Eastern    | 1.10 (0.82 - 1.49) |
| Luapula    | 0.63 (0.48 - 0.83) |
| Lusaka     | 0.84 (0.71 - 0.99) |
| North-Western | 1.40 (1.05 - 1.85) |
| Northern   | 1.16 (0.92 - 1.45) |
| Southern   | 0.93 (0.76 - 1.13) |
| Western    | 1.40 (1.05 - 1.85) |

| Month      | Value (95% CI) |
|------------|----------------|
| January    | 1.04 (0.75 - 1.43) |
| February   | 0.52 (0.37 - 0.72) |
| March      | 0.48 (0.36 - 0.65) |
| April      | 0.62 (0.43 - 0.88) |
| May        | 0.44 (0.30 - 0.65) |
| June       | 0.88 (0.66 - 1.18) |
| July       | 1.66 (1.33 - 2.07) |
| August     | 1.86 (1.49 - 2.32) |
| September  | 1.29 (1.03 - 1.60) |
| October    | 2.15 (1.77 - 2.62) |
| November   | 1.60 (1.31 - 1.95) |
| December   | 1.00 (0.74 - 1.36) |

| Year       | Value (95% CI) |
|------------|----------------|
| 2005       | 1.43 (1.16 - 1.75) |
| 2006       | 1.06 (0.78 - 1.43) |
| 2007       | 0.93 (0.73 - 1.19) |
| 2008       | 1.68 (1.39 - 2.04) |
| 2009       | 1.00 (0.74 - 1.36) |
| 2010       | 0.12 (0.05 - 0.28) |
| 2011       | 1.32 (0.91 - 1.91) |
| 2012       | 1.95 (1.49 - 2.56) |
| 2013       | 2.53 (1.99 - 3.23) |
| 2014       | 1.50 (1.14 - 1.98) |
| 2015       | 0.87 (0.68 - 1.12) |
| 2016       | 1.00 (0.74 - 1.36) |

*Figures*
Figure 1

*Seasonal trends by year of rubella prevalence in Zambia, 2005 – September 2016*

Figure 2

*Map Prevalence of rubella by province 2005-2016*

| Province      | Percent |
|---------------|---------|
| Central       | 29.5    |
| Copperbelt    | 30.5    |
| Eastern       | 27.8    |
| Luapula       | 21.8    |
| Lusaka        | 23.5    |
| North-Western | 37.3    |
| Northern      | 33.8    |
| Southern      | 30.0    |
| Western       | 36.3    |
Figure 3

Rubella sero-prevalence by year (Zambia 2005 - 2016)