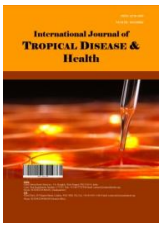

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The Epidemiology of Rubella in Lesotho before the Introduction of a Rubella Containing Vaccine: A Review of Measles Case-based Surveillance, 2012-2016

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Authors' contributions

This work was carried out in collaboration between both authors. Authors ABN and TM designed the study, performed the statistical analysis, wrote the protocol and wrote the draft of the manuscript. Both authors managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of the study was to determine the burden and epidemiology of rubella infection in Lesotho before the introduction of a rubella-containing vaccine. It was also to assess the performance of the measles case-based surveillance system in Lesotho.
Study Design: Retrospective cross-sectional descriptive study.
Place and Duration of Study: The study was done in Lesotho from February to March 2019 based on the 2012 to 2016 data.
Methods: There was a review of the measles case-based surveillance data with a total of 1587 suspected cases reported during the study period. Samples were collected from suspected measles cases and tested for measles. Those samples that tested negative for measles were subsequently tested for rubella IgM at the National Reference Laboratory. The serum samples were analysed for rubella IgM using commercial enzyme-linked immunosorbent assay (ELISA) kits SERION and EUROIMMUN.

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Results: There were 2 measles IgM and 748 rubella IgM positive cases confirmed. The rubella IgM positive cases accounted for 48% of the samples tested for rubella infection. There were also several rubella outbreaks during the study period. The Lesotho surveillance system met the two principal surveillance performance indicators for each year during the period of the study.
Conclusion: This study showed that there was high level of rubella sero-positivity with several outbreaks of rubella infections during the study period. Rubella infection was predominantly seen in those aged between 5 and <13 years of age. This justified the introduction of a rubella containing vaccine in Lesotho in 2017. Although the two principal surveillance performance indicators (non-measles febrile rash illness rates and the percentage of districts that reported at least one case of measles with blood specimen per year) were met during the period under review, there were districts that performed poorly. This study revealed the need for strengthening of rubella-containing vaccine component of routine immunization to lower the impact of rubella infection in Lesotho. A detailed district level review to identify and address the causes of poor performance in some districts is recommended. There is also a need to identify the current challenges and evaluate the impact of the recently introduced rubella-containing vaccine on rubella infection in Lesotho.

Keywords: Rubella; measles; surveillance; outbreak; world health organization; districts; Lesotho.

DEFINITIONS

A case of rubella was defined as rubella IgM positivity in a suspected measles case testing negative to measles IgM.

A rubella outbreak was defined as a cluster of 5 or more IgM confirmed rubella cases occurring within a month period within a district.

In this study, we defined a suspected measles case 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 in whom a clinician suspected measles.

Discarded cases are defined as suspected cases that do not meet the clinical or laboratory definition. Population estimates were provided by the Bureaux of Statistics of Lesotho.

The non- measles febrile rash illness rate was calculated as "discarded_cases following laboratory serological testing of blood specimens x 100 000 per total population in area(country/province)". This indicator measures the level of case finding and investigation taking place within the country.

ABBREVIATIONS

CRS : Congenital Rubella Syndrome.
ELISA : Enzyme-linked immunosorbent assay.
IgM : Immunoglobulin M.
MCV1 : Measles containing vaccine first dose.
MR : Measles Rubella vaccine.
WHO : World Health Organization.

1. INTRODUCTION

1.1 Background

Rubella is an infectious vaccine-preventable disease affecting children and young adults worldwide [1]. It usually causes mild clinical symptoms. It is, however, of high public health importance because of its potential to cause congenital rubella syndrome (CRS) which carries a high morbidity and mortality.

Rubella is caused by rubella virus, which is a member of Matonaviridae (formerly Togaviridae) family and Rubivirus genus [2,3]. Rubella is transmitted through direct or droplet contact from nasopharyngeal secretions. It has an average incubation period of 14 days. Persons with rubella are most infectious when the rash is erupting, but they can shed the virus from 5 days before to 6 days after the rash onset [4]. The clinical presentation of a mild cutaneous maculopapular rash is characteristic. This rash

has been reported to occur in 50%-75% of cases and has been, sometimes, misdiagnosed as measles or scarlet fever. Children infected with rubella usually develop few or no constitutional symptoms. They include low grade fever, sore throat, headache and red eyes. Posterior auricular and anterior cervical lymphadenopathies are also characteristic of this disease and are said to precede the rash by 5-10 days. Arthralgia or arthritis may occur in up to 70% of adult women with rubella. Other complications, although rare, include thrombocytopenic purpura and encephalitis [4].

Rubella infection causes epidemics usually every 6 to 9 years during the pre-vaccine era [2]. Studies have shown that rubella infections may vary with seasons across the year being high in February/March and in November [5]. It was also shown that rubella infection is less common both in the first year of life and in the older age groups.

Congenital rubella syndrome (CRS) results from maternal infection with rubella virus during early pregnancy. Congenital anomalies rarely occur after infection in the 20th week of gestation [1] but, when present, are difficult to treat, have a high morbidity and mortality and hence the need for prevention.

Measles elimination by the year 2020 was a goal set to the Africa Region by the World Health Organization (WHO) in 2011. Lesotho has been implementing measles case-based surveillance in accordance with the WHO recommendations. This would allow for the identification of populations at risk and inform immunization strategies. The two key indicators that are used to evaluate the performance of this system are: ≥80% of districts with ≥ 1 suspected measles case with blood specimen reported per year and a non-measles febrile rash illness rate of ≥ 2 per 100 000 populations [6].

The rubella disease surveillance in Lesotho depends on measles case-based surveillance with only negative measles cases tested for rubella. This is because measles and rubella have similar presentations. Thus any suspected cases are first tested for measles. Those who tested negative for measles are then further tested for rubella. The remaining samples are discarded and not investigated further.

The national measles immunization coverages in Lesotho were reported to be 60% in 2012, 61% in 2013, 58% in 2014, 66% in 2015 and 60% in 2016 [7]. These coverage rates have been consistently below the target level which is ≥95% coverage with the first dose of measles-containing vaccine (MCV1) at national level and in each district [1].

Lesotho introduced the measles-rubella (MR) vaccine into the routine immunization schedule in February 2017. This was in line with the global vision for measles and rubella elimination which aims to achieve and maintain a world without measles, rubella and congenital rubella syndrome by the year 2020 [8].

A recent study has attempted to estimate the burden of CRS in Lesotho with a finding of about nine cases between 2012 and 2016 [9]. This was considered to be of public health importance. Thus identifying the burden and trend of rubella infection in Lesotho would be useful in later evaluating the impact of the vaccine and progress towards elimination of rubella in Lesotho.

1.2 Study Population and Setting

Lesotho is a land locked country situated in Southern Africa. It has an estimated population of 2 million people. It is divided into 10 administrative districts. The national reference laboratory where all samples are processed is situated in the capital city, Maseru.

1.3 Objective

The objective of this study was to determine the burden of acute rubella infection in Lesotho before the introduction of the rubella-containing vaccine in 2017. It was also to show the trend of rubella infections between 2012 and 2016 and across geographical areas in Lesotho. Furthermore, it was to show the performance of the measles and rubella case-based surveillance system in Lesotho.

2. METHODS

2.1 Study Design

This was a retrospective analysis of data captured through the national measles case-based surveillance system, from January 2012 to December 2016. Samples were collected from suspected measles cases and tested for measles immunoglobulin M (IgM) or for viral isolation. The samples were collected from all over the country after due notification. Those samples that tested

negative for measles were subsequently tested for rubella Immunoglobulin M at the National Reference Laboratory. The serum samples were analysed for rubella IgM using commercial enzyme-linked immunosorbent assay (ELISA) kits SERION and EUROIMMUN. The result of the samples sent for measles and rubella immunoglobulin analysis were recorded in the measles case-based surveillance dataset. The data were double-checked for error and cleaned. The data was stored and analysed using Microsoft excel. Results were presented using frequency tables and charts.

The variables were age measured in years, districts according to the place where the sample was taken and the period of the data examined which were made in months from January to December and in years from 2012 to 2016. The age was re-categorized into those less than one year, 1 to less than 5 years, 5 years to less than 13 years and those 13 years and above.

3. RESULTS

3.1 Measles Characteristics

A total of 1587 suspected measles cases were reported of which 1574 samples were tested for measles between the period of January 2012 and December 2016, as indicated in Table 1 below. Mafeteng district had the highest suspected cases reported, followed by Maseru district. The least number of suspected cases were reported from Butha-Buthe and Mokhotlong districts. There were only 2 confirmed measles IgM positive cases during the study period.

Table 2 shows the distribution by age and sex of the reported cases. Most cases were between one and twelve years old with a mean age of 7.7 years and median age of 7.5 years. In more than half of the cases, the male gender was affected (51% of the notifications).

The total number of suspected measles cases per year have been displayed in Fig. 1, with most cases reported in 2013 and 2014.

3.2 Rubella Characteristics

Table 1 shows samples tested for rubella as well as rubella IgM positive results per district. There were 1570 cases tested for rubella of which 748 tested IgM positive. Mafeteng, Maseru and Leribe had the highest number of rubella IgM positive cases. Mokhotlong district had the highest proportion of rubella IgM positive cases from those tested for rubella IgM antibody (71%). About 48% of all cases tested for rubella IgM were positive, which was very high.

Fig. 1 shows the number of cases that were rubella IgM positive per year. There were more cases in 2013 and 2014, with a decrease before the introduction of the rubella-containing vaccine in 2017.

The monthly trends of rubella IgM positive cases per district and per year have been displayed in Fig. 2. Rubella outbreaks (defined as 5 or more cases per month per district) occurred predominantly in Mafeteng, Maseru and Qachas' Nek districts. This was mostly seen between 2012 and 2015. This showed that many outbreaks occurred over this period. There was no rubella outbreak in 2016.

3.3 Surveillance Performance

Table 3 and 4 shows the performance of the case-based measles surveillance during the period under review. Table 3 shows that Lesotho surveillance on average performed well and met the reporting and investigation targets. There were more than 80% of districts that reported at least one case of suspected measles with blood specimen per year with all the districts having 100% in 2013 and 2014 and 90% in 2012, 2015 and 2016. The district of Qachas' Nek did not report in 2012 while Butha- Buthe did not report in 2015 and 2016. Mafeteng and Maseru districts had the highest number of reporting with blood specimen while Butha- Buthe reported the least over this period.

Table 4 shows the non-measles febrile rash illness rates during the study period. Lesotho scored higher than the set target of 2.0 per 100,000 populations. The national average was highest in 2014 and 2015 with rates of 27.0 and 27.5 per 100,000 populations respectively. The minimum was recorded in 2016 with a rate of 3.3 per 100,000 populations. All the districts performed well in 2015 when the national rate was highest. The districts of Maseru, Leribe, Mafeteng and Thaba-Tseka performed more than the minimum target throughout the period of the study. However, the rest of the districts had at least a year with poor performance of which Butha-Buthe and Mokhotlong districts were the least performers during the study period.

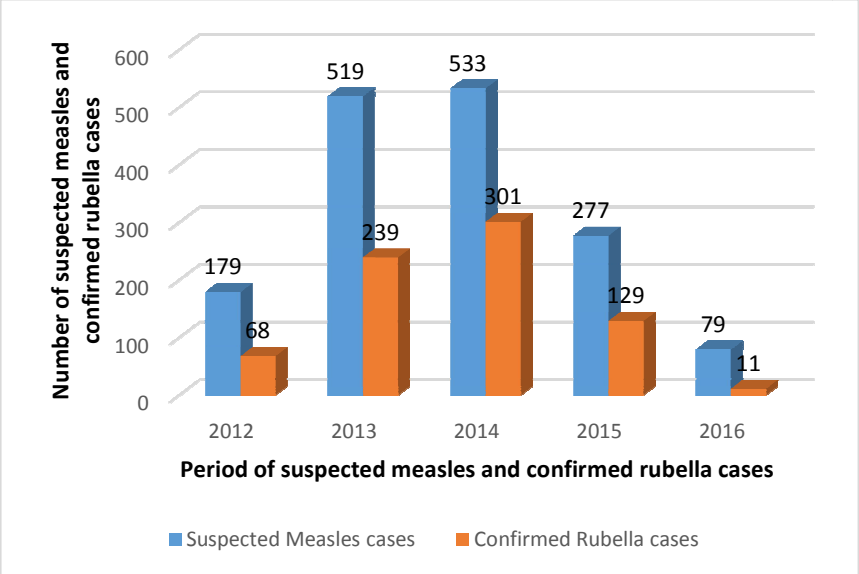

Fig. 1. Suspected cases of measles and confirmed rubella cases reported per year

Table 1. Proportion of reported cases that were rubella IgM positive by district from 2012 to 2016

Districts	Number of suspected measles cases reported	Number of samples tested for Rubella	Number of cases with Rubella IgM positive results	Proportion of cases with Rubella IgM positive results
Mafeteng	409	408	195	48%
Maseru	398	394	176	45%
Leribe	189	189	81	43%
Qacha's Nek	139	138	83	60%
Thaba - Tseka	139	138	61	44%
Quthing	95	95	50	53%
Berea	83	83	36	43%
Mohale's Hoek	81	71	35	49%
Mokhotlong	35	35	25	71%
Butha-Buthe	19	19	6	32%
Total	**1587**	**1570**	**748**	**48%**

Table 2. Suspected measles cases reported by age and gender

Age in years	Male	Female	Total cases
<1	1	2	3
1 – <5	160	134	294
5 – <13	584	558	1142
13+	71	76	147
Unspecified	1	0	1
Total	817	770	1587
Mean age (years)	7.7		
Median age (years)	7.5		

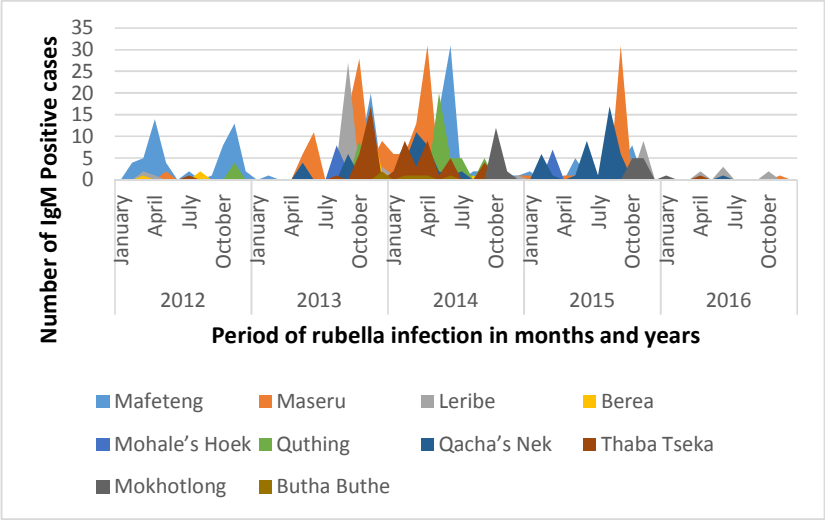

Fig. 2. Trends in rubella IgM positive cases by districts from 2012 to 2016

Table 3. Reporting of suspected measles cases with a blood specimen by year and district (Target: Proportion of districts that have reported at least 1 case of measles with a blood specimen per year)

District	2012	2013	2014	2015	2016	All year
BEREA	7	49	19	6	2	83
MASERU	16	143	127	95	14	395
MAFETENG	120	109	135	37	8	409
MOHALES'HOEK	3	32	21	12	3	71
QUTHING	8	18	62	5	2	95
QACHA'S NECK	0	26	52	59	2	139
THABA-TSEKA	7	68	51	6	7	139
MOKHOTLONG	1	1	15	17	1	35
LERIBE	15	65	39	41	29	189
BUTHA-BUTHE	2	5	12	0	0	19
All districts	179	516	533	278	68	1574

4. DISCUSSION

There were 1587 suspected measles cases recorded during the study period. This high number could be due to the increased effort in surveillance as a response to Lesotho's commitment to the WHO resolution on increased measles and rubella surveillance and elimination [8]. The high number of cases in Mafeteng, Maseru and Leribe districts could be due to increased surveillance and may also be affected by their higher population. These were likely a reflection of increased rubella prevalence in these districts. The lower numbers in Butha Buthe could be due to underreporting.

Most of the cases were between the ages of one year to 12 years with few cases in the first year of life and after 13 years. Similar age distribution was observed in a study in Zambia and Ethiopia [10,11]. There is also male preponderance over females. This was also an observation seen in the Zambian study [10].

There were only 2 Measles IgM positive cases recorded within this period. This few cases could not be explained by the low national immunization coverages of measles vaccine (MCV1) during this period. Lesotho measles coverage over this period were below 70%. There is usually inverse relationship observed between measles cases in an area and measles immunization coverage [2]. The higher the measles immunization coverage, then the higher the herd immunity against measles infection. This would lead to more protection of the population and thus less measles cases [12].

Table 4. National and district annualized non-measles febrile rash illness rates between 2012 and 2016

	2012			2013			2014			2015			2016		
District	**Population**	**Discarded cases**	**Rate**	**Population**	**Discarded cases**	**Rate**	**Population**	**Discarded cases**	**Rate**	**Population**	**Discarded cases**	**Rate**	**Population**	**Discarded cases**	**Rate**
Maseru	468151	16	3,4	473367	143	30,2	474,791	127	26,7	484,287	95	19,6	485817	14	2,9
Butha-Buthe	109515	2	1,8	109536	5	4,6	104,690	12	11,5	106,784	0	0	104132	0	0
Leribe	293083	15	5,1	293508	65	22,1	296,007	39	13,2	301,927	41	13,6	297366	29	9,6
Berea	254065	7	2,8	255065	49	19,2	257,905	19	7,4	263063	6	2,3	260308	2	0.8
Mafeteng	183342	120	65,5	182680	108	59,1	183,268	135	73,7	186933	37	19,8	182395	8	4,4
Mohale's Hoek	171036	3	1,8	170491	32	18,8	171,069	21	12,3	174490	12	6,9	170426	3	1,8
Quthing	119231	8	6,7	118674	18	15,2	118,948	62	52,1	121327	5	4,1	118107	2	1,7
Qacha's Nek	68790	0	0	68789	26	37,8	69,225	52	75,1	70610	59	83,6	69396	2	2,9
Mokhotlong	101808	1	1	102740	1	1	104,577	15	14,3	106669	17	15,9	106810	1	0,9
Thaba-Tseka	133581	7	5,2	134391	68	50,6	136,094	51	37,5	138816	6	4,3	138056	7	5,1
Total	**1,902,602**	**179**	**9,4**	**1,909,241**	**515**	**27**	**1,916,574**	**533**	**27,5**	**1,954,906**	**278**	**14**	**1,932,813**	**68**	**3 ,3**

The national rubella IgM antibody positivity was 48%, which was higher than what was reported in studies conducted in Zimbabwe, Ethiopia and Uganda [11,13,14]. There were also several rubella outbreaks that were detected in the analysis of monthly trend of rubella infection. These outbreaks were seen mainly during March and November of each year which was also observed in some studies [5,11]. This was predominant in Mafeteng, Maseru and Qacha's Nek. These occurrences were due to the absence of rubella vaccine in Lesotho in the national immunization programme during these period. It has been shown that rubella IgM positive cases were high in areas with no rubella-containing vaccines in the national immunization programmes [2]. This informed the introduction of a rubella-containing vaccine in 2017 and efforts at strengthening the surveillance system in Lesotho.

There were more rubella cases reported in 2013 and 2014. This could be due to the response towards improved surveillance after commitment by Lesotho with the African region of WHO. It could also be due to an uncontrolled outbreak which might have occurred during this period.

More than 80% of the districts reported at least one case of suspected measles with blood specimen per year with all the districts having 100% in 2013 and 2014. This showed a good level of surveillance performance and was probably due to increased surveillance reporting. However, Qacha's Nek did not report any case in 2012 and Butha-Buthe also did not report in 2015 and 2016. Different levels of reporting were observed in some countries in a study [5].

The study showed that Lesotho had non-measles febrile rash illness rates higher than the minimum target of 2.0 per 100,000 populations during the study period. The national average was highest in 2014 and 2015 with rates of 27 and 27.5 per 100,000 populations respectively with a minimum of 3.3 per 100,000 populations in 2016. This could also be due to the high level of surveillance during the period and hence increased detection of rubella cases. Different levels of performance using the non-measles febrile rash illness rates was also shown in the study on performance of national measles case-based surveillance system in Africa and also within different regions of South Africa [5,15,16].

5. CONCLUSION

There were 2 cases of measles infections and 748 cases of rubella infections recorded during the study period. There were also several outbreaks of rubella peaking during the months of February/March and November of each year observed in the monthly trend during the study period. Rubella infections occurred mostly in children in the age group from 5 up to 13 years and with slight male preponderance. The Lesotho measles case-based surveillance on average performed above the target level with greater than 80% of the districts reporting at least one case of suspected measles with blood specimen per year. The non-measles febrile rash illness rates were also greater than the target of 2 per 100,000 populations. However, two districts were shown to have not reported at least one case in a year. Furthermore, some districts failed to report at all or reported less than two cases of non-measles febrile rash illness per 100,000 populations. The inclusion of rubella testing in measles case-based surveillance has allowed for a better understanding of the epidemiology of Rubella in Lesotho and this study has also given the baseline for monitoring the trends of rubella infections in Lesotho. There is a need for a thorough review to identify and address the causes of poor performance in some districts. There is also a need for a more inclusive case definition in order to have a more accurate estimate of the true rubella prevalence in Lesotho. Furthermore, this study revealed the need for strengthening of the rubella-containing vaccine component of routine immunization to lower the impact of rubella infection in Lesotho Future studies to evaluate the impact of the introduction of a rubella-containing vaccine on the trend of rubella infection in Lesotho are also recommended.

6. LIMITATIONS

This study did not look at other causes of febrile eruptions. The case definition used was designed to detect measles cases not rubella. Rubella infection can also present with little or no symptoms making detection difficult. This study was also not able to assess the difference between urban and rural populations.

CONSENT

All authors declare that written informed consent from the patients was not required for retrieving of measles case-based surveillance data.

ETHICAL APPROVAL

All authors declare that this study was approved by the ethics committee of the ministry of Health of Lesotho with approval number ID146-2018.

No information that could identify the patients was made available.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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