Evaluating the effectiveness of the rubella vaccination program in Lesotho using measels and rubella case-based surveillance data

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Dedication

This work is dedicated to everyone involved in the development and deployment of life saving vaccines.

Declaration

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I proclaim that **EVALUATING THE EFFECTIVENESS OF THE RUBELLA VACCINATION PROGRAM IN LESOTHO USING MEASELS AND RUBELLA CASE-BASED SURVEILLANCE DATA**

is my own work and that a comprehensive list of references has been used to credit all sources used.

To ensure its originality, the dissertation was subjected to software testing.

I also verify that this dissertation was never submitted to any other higher education institution including UNISA for the requirements of any other degree.

Signature: **Date: November 2023**

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ABSTRACT

Rubella is one of the leading causes of birth defects globally and is preventable by vaccination. In this study, the purpose was to evaluate the effect of the introduction of a Rubella Containing Vaccine (RCV) on the occurrence of rubella in Lesotho. The study used a cross-sectional quantitative design. The study population was all rubella IgM results of blood samples collected using the integrated measles and rubella case-based surveillance system from January 2018 to December 2022. All samples that were submitted for purposes of surveillance and tested for rubella were considered but only filtered according to inclusion and exclusion criteria. Descriptive statistics were used to analyse the data. This study reports on 1% (95% CI; 0,5% -1.8%) prevalence of rubella in Lesotho. From the study results, it is recommended that Supplementary Immunization Activities (SIAs) are conducted to address rubella immunization gaps and that rubella surveillance is improved so that rubella prevalence can be better estimated and the effect of rubella vaccination on rubella disease burden in Lesotho can be better understood.

KEY CONCEPTS

Case-based surveillance data, measles, rubella, rubella prevalence, vaccinatio

MOHLONO

Kokoana-hloko ea rubella, e ka thibeloang ka ente, e baloa hara mafu a etelletseng pele a bakang bokoa ba tsoalo lefatse ka bophara. Sepheo sa phuputso ena e ne e le ho hlahloba kamo ea ho tlisoa ha ente ea rubella boteng ba rubella Lesotho. Ho ile ha sebelisoa mokhoa phuputso oa boithuto ba bongata bo fapaneng. Palo ea batho ba ithutoang e ne e le liphetho tsohle tsa rubella IgM tsa lisampole tsa mali tse bokelelitsoeng ka mokhoa o kopantsoeng oa ho fuputsa ’maselese le rubella e entsoeng ka Pherekhong 2018 ho ea ho Ts’itoe 2022. Lipalo-palo tse hlalosang li ne li sebelisetsoa ho hlahloba datha. Boithuto bona bo tlaleha ka 1% (95% CI; 0,5% - 1.8%) ea ho ata ha rubella Lesotho. Ho ipapisitsoe le liphetho tsa phuputso, ho khothaletsoa hore lets’olo la liente le etsoe ho koala likheo tsa kentelo ea rubella le hore tlhahlobo ea rubella e ntlafatsoe ho lumella tekanyetso e nepahetseng ea ho ata ha rubella le tlhahlobo ea kamo ea ente ho lefu la rubella Lesotho.

LINTLHA TSA MANTLHA

Case-based surveillance data, ’maselese, rubella, ho ata ha rubella, ente

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LIST OF ACRONYMS

CRS: Congenital Rubella Syndrome

ELIZA: Enzyme Linked Immunosorbent Assay

EPI: Expanded Program on Immunization

IgG: Immunoglobulin G

IgM: Immunoglobilin M

MNP: Microneedle Patches

MR: Measels Rubella

NICD: National Institute for Communicable Diseases

NRL National Reference Laboratory

PPV: Positive Predictive Value

RCV: Rubella Containg Vaccine

SIAs: Supplementary Immunization Activities

SPSS: Statistical Package for Social Sciences

WHO: World Health Organization

CHAPTER 1

ORIENTATION TO THE STUDY

1.1NTRODUCTION

This present chapter summarises the study background including the problem description, purpose, objectives and hypothesis, research questions, conceptual framework, research methodology and design, and the measures taken to ensure ethical and rigorous research.

1.2 BACKGROUND INFORMATION ABOUT THE RESEARCH PROBLEM

Rubella is a viral infection that predominantly presents in childhood and in the early stages of adulthood. Although this infection is said to be mild and self-limiting, its significance is in its potential to cause congenital abnormalities. These abnormalities are called Congenital Rubella Syndrome (CRS) (WHO 2018:3). By the year 2020, the world was supposed to be free of both rubella and CRS (WHO 2012:13). In 2019, 173 World Health Organization (WHO) member states had initiated rubella vaccination. The coverage of rubella vaccination worldwide increased from 39% in 2012 to 71% in 2019 (WHO 2020a:vii). Although gains in rubella control were made, they fell short of the 2020 elimination target with only 82 countries verified rubella free in 2018 (WHO 2020a: vii). The measles and rubella strategic framework for 2021-2030 builds upon achievements made in the past decade and highlights areas of focus to advance global measles and rubella elimination (WHO 2020a:x).

1.2.1 The Rubella Virus and Disease

The rubella virus is an airborne virus. It is a togavirus that belongs to the genus of Rubi virus. The time between exposure to the rubella virus and the appearance of the first symptoms is 14-23 days. Early signs of illness occur in the second week after exposure, and consist of fever, malaise, and mild conjunctivitis. Other presentations include the presence of lymph nodes behind the ear, the occipital region, and the posterior cervical region. An erythematous, pruritic, and maculopapular rash has been described in 50-80% of affected persons. This infection can also be subclinical with no

reported rash in 20-50% of cases. Joint symptoms like arthritis and arthralgia occur predominantly in adult women. Post infectious encephalitis has also been reported (WHO 2020b:309-10).

1.2.2 Congenital Rubella Syndrome

CRS occurs when a mother contracts rubella early in her pregnancy leading to disease and birth defects in the new-born. This can occur in up to 90% of maternal infections. These defects were found to rarely occur after the 16th week of gestation. An exception to this is sensorineural hearing loss, which has been reported in cases where exposure occurred after the 20th week of gestation. CRS is associated with many abnormalities in different organ systems. The ophthalmic abnormalities include congenital glaucoma, congenital cataracts, choriorinitis, microphthalmia and pigmentary retinopathy. Peripheral pulmonary artery stenosis is a congenital heart defect that is common in CRS. Other heart defects include ventricular septal defects and patent ductus arteriosus. Other manifestations like radiolucency in the long bones, meningoencephalitis, hepatitis, thrombocytopenia, hepatosplenomegaly, interstitial pneumonitis, and microcephaly have also been described (WHO 2020b:310-11).
In Lesotho, the most common birth defects associated with CRS were found to be cardiac (patent ductus arteriosus, pulmonary stenosis) and ophthalmic (cataracts, glaucoma, microphthalmia) (Makhupane & Nwako 2020:4-5).
Similar findings were described in studies conducted in the Philippines (Lopez, Raguindin, del Rosario, Najarro, Du, Aldaba, Salonga, Monzon-Pajarillo, Santiago, Ou & Ducusini 2017:21) and South Africa (Hong, Malfeld, Smit, Makhathini, Fortuin, Motsamai, Tselana, Manamela, Motaze, Ntshoe, Kamupira, Khosa-Lesola, Mokoena, Buthelezi, Maseti & Suchard 2022:8). Other manifestations of CRS in Lesotho that have been described include splenomegaly, thrombocytopenia, and mental retardation (Makhupane & Nwako 2020:4-5).

1.2.3 Rubella and congenital rubella syndrome epidemiology

Rubella is known to be one of the major contributors of birth defects globally that is preventable. According to the WHO (2020b:307), CRS accounts for approximately 100000 new deliveries annually worldwide. It is observed that before widespread

rubella vaccination, rubella infection occurred seasonally, and epidemics were reported every 5 to 9 years. It is also observed that countries with immunity gaps among women of fertile age have higher rates of CRS (WHO, 2020b:308).

Between 2007 and 2018, 139 486 cases of rubella were reported to the WHO by its member states worldwide. During the same period, there was also a decline in new cases of rubella reported each year. About 1.7 cases per million were reported in 2018 compared to 13.9 cases per million in 2007 (Patel, Antoni, Danovaro-Holliday, Desai, Gacic-Dobo, Nedelec & Kretsinger 2020:1402). This decline was attributed to the effectiveness of Rubella Containing Vaccines (RCVs) (Patel et al. 2020:1404). Between 2012 and 2016, 9 cases of CRS were identified in Lesotho (Makhupane & Nwako 2020:2). This was considered to be of high public health concern. During the same period, 748 cases of rubella were also recorded (Nwako & Makhupane 2021:25).

1.2.4. Laboratory diagnosis of rubella

Rubella antibodies namely immunoglobulin G (IgG) and immunoglobulin M (IgM) are detectable about two weeks after infection, and this coincides with the appearance of the maculopapular rash (WHO 2020b:311). IgM antibodies were found to wane after about eight weeks of infection while IgG antibodies persist conferring lifelong immunity. The levels of IgG antibodies that are considered to be protective are ≥ 10 IU/ml. Enzyme immunoassays should ideally be used to diagnose rubella infection. The observation of rubella IgM or elevated levels of rubella IgG are an indication of on-going or recent infection. The reverse-transcriptase polymerase chain reaction can also be used to diagnose rubella infection. Its use is however limited to seven days following the start of symptoms because rubella viraemia has been shown to be short lived with viral shedding occurring in low titres (WHO 2020b:311-12).

1.2.5 Long-term outcomes

Diabetes mellitus has been identified in adults with CRS. In this group of patients, it has been found that diabetes occurs early in childhood and is undistinguishable from classical insulin dependent diabetes mellitus. Other late onset endocrine manifestations of congenital rubella include hyperthyroidism and hypothyroidism (Cooper 1985:S7). A review of adults with CRS that were followed up for sixty years

in Australia also showed an increased prevalence of diabetes mellitus and thyroid disorders (Forrest, Turnbull, Sholler, Hawker, Martin, Doran & Burgess 2002: 664-65). Progressive rubella panencephalitis is a rare condition that has also been described in adults with CRS. It is characterized by spasticity, ataxia ,seizures and progressive encephalopathy (Cooper 1985:S7). Prevention of CRS through immunization remains the most important intervention.

1.2.6 Rubella vaccines

The rubella vaccine is an attenuated live vaccine. This vaccine is available in a monovalent formulation. It can also be combined with other antigens like mumps, varicella, and measles. The WHO recommends that RCVs should contain a minimum number of infectious units per dose for safety and efficacy (WHO 2020b:312). These vaccines are stored at 2° to 8°C and a single dose of 0.5ml is administered subcutaneously. After a single dose of RCV an immune response that is like natural infection is elicited with a reported efficacy of ≥95% and immunity is said to persist lifelong. It is therefore not necessary to give extra vaccine doses, however, because this vaccine is often given at the same time with the measles antigen, which requires two doses, a second dose is frequently administered for programmatic reasons. Adverse events commonly reported after vaccination include a low-grade fever, injection site pain or swelling, rash and irritability. Transient thrombocytopenia and febrile convulsions have also been reported (WHO 2020b:312-16).

The RCV that is in use in Lesotho is the Measles Rubella (MR) vaccine that is produced by the Serum Institute of India. It is based on the RA27/3 strain (WHO 2020d). It is given to infants at the age of 9 and 18 months (Ministry of health 2017:11). WHO (2020b:319) recommends the introduction of RCVs into routine immunization schedules to limit rubella transmission and to end rubella and CRS globally. This introduction should leverage on the existing measles SIA platforms and should target a wide range of children of both sexes (9-14 years) immediately followed by incorporation of the vaccine into routine immunization schedules. Countries are also required to have coverage of the first measles dose of ≥80% to demonstrate the ability to achieve the same coverage levels with RCV in order to prevent the epidemiological paradoxical effect. The epidemiological paradoxical effect is the rise in CRS cases observed following introduction of RCV and it is caused by a change in the age of

rubella susceptibility from children to women of fertile age. This phenomenon is observed in settings with suboptimal childhood immunization coverage or where the vaccine is only offered to part of the population (WHO 2020b:318).

In 2020, 173 out of the 194 WHO member states had introduced RCVs into their routine immunization schedules. The elimination of rubella has been confirmed in 93 out of the 194 member states including all countries in the Americas (Zimmerman, Knapp, Antoni, Grant & Reef 2022:196).

1.2.7 Measles Rubella vaccine introduction in Lesotho

To interrupt the transmission of rubella infection and to prevent CRS, Lesotho started offering the MR vaccine in 2017. The vaccine was introduced through the integrated measles SIAs that targeted children at the age of 9 months to 14 years as per WHO recommendations (WHO 2020b:320). Other child health interventions that were integrated with these activities were deworming with albendazole, the dispensing of Oral Polio Vaccine (OPV) and vitamin A. The coverage for the MR vaccine was 89% based on administrative data. A post SIA coverage survey was conducted to validate the administrative coverage data. The survey was conducted in line with the WHO methodology reference manual on immunization coverage cluster surveys. The survey coverage for MR was found to be 92% which was within 5% of the administrative coverage but fell short of the recommended target of ≥95% (Ministry of health Lesotho 2017: ix).

1.2.8 Integrated measles and rubella case-based surveillance

Lesotho has been implementing integrated measles and rubella case-based surveillance according to WHO recommendations. The surveillance of these two vaccine preventable diseases has been integrated because they both have similar presentations and similar approaches to investigation and surveillance. To detect suspected cases, however, the measles case definition of a febrile maculopapular rash and one of coryza, cough and conjunctivitis is used. Blood samples are taken from suspected cases and are initially tested for measles specific immunoglobulin (IgM) with only negative samples tested for rubella specific immunoglobulin (IgM) (WHO 2018: 4-5).

By monitoring patterns of diseases that are preventable by vaccination, the disease burden in populations that are at risk are determined, the effectiveness of vaccination programs is assessed and appropriate strategies to address immunity gaps are identified (WHO 2018:4). To achieve this, the surveillance systems must be of high quality. There are two key indicators that evaluate the measles and rubella case-based surveillance systems. The non-measles non-rubella febrile rash illness rate measures the capacity to adequately identify and investigate cases while the proportion of districts investigating suspected measles rubella cases with a blood specimen per year measures the extent to which all districts are playing a role in the detection of cases (Luce, Masresha, Katsande, Fall & Shibeshi 2018:3). Other indicators used to appraise this surveillance system assess the source of transmission (endemic or imported), whether specimens are adequately collected and tested, and whether laboratory results are reported in a timely manner (WHO 2018: 20-22).

A five-year retrospective analysis of surveillance data conducted before the introduction of RCV in Lesotho showed rubella sero-positivity to be around 48% (Nwako & Makhupane 2021:25). This informed the introduction of a RCV in 2017. To evaluate progress towards rubella elimination and identify populations that remain at risk in Lesotho a post introduction review of surveillance data was conducted.

1.3 RESEARCH PROBLEM

Globally, the rubella virus is recognized as a major contributor to birth defects that can be prevented by vaccination. As previously described, this constellation of defects is known as CRS (Zimmerman et al 2022:196). CRS is suspected in infants who present with a triad of hearing loss, congenital heart disease, and a minimum of one of the following eye symptoms: pigmentary retinopathy, congenital glaucoma, or cataract (WHO 2020c: 153). A single dose of a RCV has been shown to provide lifelong protection against rubella (Zimmerman et al 2022:196).

Lesotho reported 748 cases of rubella using measles and rubella surveillance data from 2012 to 2016 (Nwako & Makhupane 2021:25). Nine cases of CRS were also identified during this time (Makhupane & Nwako 2020:2). Rubella vaccination in Lesotho was introduced in order to reduce the burden of rubella and CRS in Lesotho. As far as the researcher is aware, the effectiveness of this intervention has not yet

been studied. This study was therefore the first study conducted in Lesotho that looked at the effectiveness of rubella vaccination in reducing cases of rubella.

Rubella first became a subject of interest for the researcher in 2015 while working as a paediatric registrar at Universitus Academic Hospital in Bloemfontein, South Africa. During this period, the researcher was engaged in the management of infants from Lesotho with CRS who had been referred to this facility for quaternary care. These infants often presented with congenital heart disease among other presentations and required prolonged hospitalization which puts a burden on the families and the health facilities.

1.4 Study purpose

The study purpose describes that which the researcher intends to achieve by conducting research. In public health practice, this is often informed by gaps in knowledge and the need to better understand health and its determinants concerning not only the individual but populations at large. The evaluation of the effectiveness of interventions is also useful in informing policy and in improving health outcomes (Carneiro 2017:xv).

To curb rubella infection transmission and to reduce the number of CRS cases a RCV was introduced in 2017. It is from this perspective that the researcher developed an interest to conduct a study that evaluated the effectiveness of rubella vaccination on the prevalence of rubella in Lesotho.

1.4.1 Research aim/purpose

The purpose of this study was to evaluate the effect of the introduction of a RCV on the occurrence of rubella in Lesotho. This was done by looking at rubella sero-positivity in blood samples taken from suspected cases and recorded in the integrated measles and rubella case-based surveillance system after vaccine introduction. As previously described, rubella vaccination was introduced in Lesotho to decrease the burden of rubella infection and adverse pregnancy outcomes caused by congenital rubella. The study results will be used to identify communities that are not yet fully protected from

rubella and will also be used to inform activities that address inequities in rubella vaccination access.

1.4.2 Research objectives

- To ascertain the burden of rubella in Lesotho after the establishment of rubella vaccination.
- To show the trends of rubella infection between 2018 and 2022 across different regions in Lesotho.
- To evaluate the effectiveness of the measles and rubella case-based surveillance system in Lesotho in detecting rubella cases.

1.4.3 Research questions

- What is the burden of rubella in Lesotho after the establishment of rubella vaccination?
- What are the trends of rubella infection between 2018 and 2022 across the different regions in Lesotho?
- How effective is the measles and rubella case-based surveillance system in detecting cases of rubella in Lesotho?

1.4.4 Research hypothesis

Rubella vaccination in Lesotho, targeting a wide range of children and adolescents of both sexes; coupled with a high vaccination coverage (≥80%) has lowered rubella cases and minimized the spread of rubella infection.

1.5 KEY TERMS DEFINITIONS

Table 1.1. Key terms definitions

Rubella	Rubella is an acute viral infection that is common in children but can also affect young adults (WHO 2018:3). In this study, rubella was considered in persons of any age with a fever, a maculopapular rash and who also had recent serological confirmation of rubella infection.
Suspected measles case	Anyone with a fever, a widespread maculopapular rash, coryza, cough, conjunctivitis, or who a medical practitioner believes may have measles was considered to be a suspected measles case (WHO 2018:5). In this study, this was a person of any age with clinical signs suggestive of measles or where measles was highly suspected.
Suspected rubella case	Any patient, regardless of age, who had a febrile maculopapular rash or who a health professional believed had rubella was defined as a suspected rubella case (WHO 2018:5). In this study, this was any person presenting with a febrile rash or in whom rubella was highly suspected.
A laboratory confirmed measles case	A suspected case of measles that has undergone testing, has recent measles virus infection evidenced by serology,

	and has not had measles immunization within the last 30 days was regarded as laboratory confirmed (WHO 2015:22). In this study, the focus was on the rubella aspect of this surveillance system.
A laboratory confirmed rubella case	A rubella suspected case that was determined to be positive by testing in an experienced laboratory is known as a laboratory-confirmed rubella case (WHO 2018:5). In this study, blood samples were tested for rubella specific immunoglobulins to confirm the diagnosis of rubella.
Epidemiologically linked rubella case	A possible case of rubella that was not tested by a laboratory but was connected geographically, with the rash appearing 12–23 days after a case that was confirmed by a laboratory or another case of rubella that was connected epidemiologically was considered as an epidemiologically linked rubella case (WHO 2018:5) In this study, epidemiologically linked rubella cases were not considered.
Clinically compatible rubella case	A rubella suspected case with a maculopapular rash, fever, and at least one of joint inflammation or joint pain or enlarged lymph nodes was clinically compatible, provided that the case had not been epidemiologically associated

	with a case that had been confirmed in the laboratory or to another communicable disease (WHO 2018:5). In this study, clinically compatible rubella cases were cases with clinical signs suggestive of rubella where investigation with blood samples was either not possible or samples not adequate for testing.
Non-rubella discarded cases	WHO (2018:5) define non-rubella discarded cases as a suspected cases that were investigated in an experienced laboratory and were found to be rubella negative. In this study, a non-rubella discarded cases referred to suspected cases that tested negative for rubella specific immunoglobulins.
Endemic rubella cases	Confirmed cases of rubella that are caused by transmission of a viral strain that is commonly found in that specific area or community are referred to as endemic rubella cases. Continual rubella virus transmission inside a country for at least a year is known as endemic rubella transmission (WHO 2018:7). In this study, these were confirmed rubella cases that were not linked to individuals who had travelled outside the country.

Imported rubella case	An imported rubella case results from exposure to rubella outside of the normal country of residence. This is seen in persons who resided outside the normal country of residence for the entirety of or some of the 12-23 days before the rash started and is substantiated by epidemiological or virological proof of the exposure (WHO 2018:7). In the context of this study, an imported rubella case was a laboratory confirmed rubella infection in persons who had resided outside of Lesotho two weeks prior to rash onset.
Rubella outbreak	WHO (2015:47) defines a rubella outbreak as a group of at least 5 cases of rubella that have been confirmed by testing for rubella specific immunoglobulins and were detected in a specific district within a period of a month. In this study, 5 or more laboratory confirmed cases of rubella that occurred in a period of a month in a specific district were considered as a rubella outbreak.
Cluster	A cluster is an accumulation of relatively rare occurrences or diseases in time or place that were thought to be more numerous than would be predicted by chance (WHO 2015:58). In this study context, a cluster referred to an unusual

	accumulation of suspected cases in a specific area or population.
Epidemiology	Epidemiology refers to the review of the recurrence, spread, and causes of health occurrences and how this knowledge is applied to improve health outcomes (Friis & Sellers 2021:2). In this study, the emphasis was on the rate of occurrence of rubella cases and its distribution in different districts in Lesotho.
Vaccines	Vaccines are biological substances that are administered to elicit immunity against a specific disease (WHO 2016:vii). The vaccine of interest in this study was the measles-rubella vaccine.
Surveillance system	Surveillance is the exercise of collecting, analysing and disseminating data that are used to inform strategies to protect and improve the health of populations (WHO 2016:vi). In this study, the surveillance system of interest was the integrated measles and rubella surveillance system.

1.6 THEORETICAL FOUNDATIONS OF THE STUDY

Theoretical foundations are concepts that shape practice and guide research within specific scientific fields and can also be used to explain research (Grove & Gray 2022: 187).

1.6.1 Research paradigm

Research paradigms are defined as ideas and precepts that influence a researcher's worldview (Kivunja & Kuyini 2017:26). They guide the way scientific research is conducted and make assumptions about how the world operates. These paradigms have five components. Ontology describes the nature of reality, epistemology describes knowledge and how that knowledge is developed, axiology refers to the guiding principles of the process of research, methodology outlines how scientific research is done and finally rigor evaluates the quality of the research (Park, Konge & Artino 2020:690).

In this study, the positivism paradigm was applied. This paradigm relies on the hypothetico-deductive model. In this model a testable hypothesis is formulated and this is followed by the development of a study that will either confirm or reject that hypothesis. These hypotheses are often stated quantitatively with the aim being to describe cause and effect relationships between two variables (independent and dependant variables). In order to make these causal inferences external influences need to be isolated with only the variables of interest being studied. The positivism paradigm also requires dualism and objectivity in order to operate. The researcher and respondents must be separated in order to eliminate bias. This paradigm also favours larger sample sizes that make the results more reliable and more generalizable (Park et al. 2020: 690-91).

1.6.2 Theoretical /conceptual framework/formal theory

The herd immunity theory was used to evaluate the hypothesis that rubella vaccination in Lesotho lowered rubella cases and minimized the spread of rubella infection. Topley and Wilson were among the first to use the term “herd immunity” in 1923. In the experiments they conducted, they showed reduced mortality rates in immunized mice. They also showed an interruption in the spread of infection, when immunized mice

were placed in the same cages as unimmunized mice (Topley & Wilson 1923:247). Furthermore, they wanted to find out what percentage of the population would need to be immunized to reduce disease transmission (Topley & Wilson 1923:248-9). This is also known as the herd immunity threshold (Fine, Eames & Heymann 2011:912).

A theorem to calculate this threshold was developed in the 1970s and is expressed as *Vc = 1/Ro*. *Vc* is the percentage of the populace that needs to receive immunizations to meet the herd immunity threshold, assuming that immunizations are administered randomly. *Ro* is the number of subsequent cases resulting from a person who is infected when all other individuals in the population are vulnerable (Fine at al. 2011:913). The higher the *Ro* of a particular disease, the higher the rate of infectiousness and the higher the herd immunity threshold.

This theorem has limitations. It assumes 100% vaccine effectiveness, random vaccination and a homogenous population that mixes at random (Fine et al. 2011:913-14). In this study, the RCV that is being reviewed has a proven efficacy of about 95% (WHO 2020b:315). Vaccination coverage in the population being studied has also been shown to differ depending on geographic distribution, level of education of mothers and wealth index quintiles (Bureau of statistics 2019: 102).

These limitations in accurate calculations of herd immunity thresholds however do not take away from the effectiveness of vaccines in reducing disease, which is not in dispute as indicated above but rather highlight the complexities of applying theory to public health practice (Fine et al. 2011:914).

The interactions between the variables of interest have been displayed below.

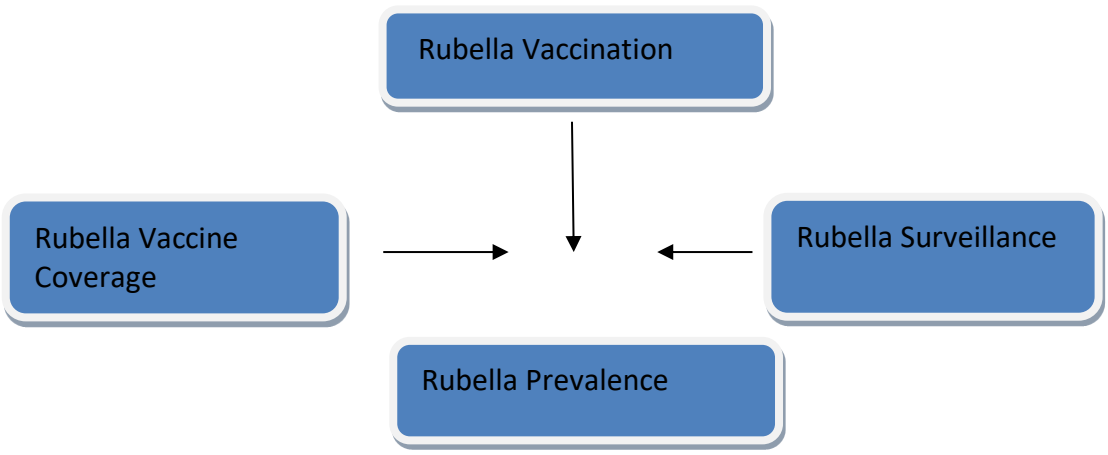

Figure 1.1. Conceptual framework

Rubella vaccination was the independent variable and rubella prevalence in Lesotho the dependent variable, the aim being to look at the relationship between these two variables. Rubella vaccination coverage was therefore the moderating variable; regardless of how effective the vaccine is, if it is not administered to a large enough population there will not be an interruption in virus transmission and reduction in rubella prevalence. A well-functioning rubella surveillance system was also a moderating variable. The goal of rubella surveillance is to detect and monitor rubella cases within countries. As previously discussed for this surveillance system to be considered well-functioning, it must demonstrate the ability to adequately detect rubella cases and all districts in the country must be represented in the case investigation efforts. If a surveillance system is not functioning well enough, the data it generates becomes unreliable making it difficult to confidently determine if a possible reduction of rubella cases is due to the impact of vaccination or the result of poor surveillance.

1.7 RESEARCH METHODOLOGY AND RESEARCH DESIGN

Research designs are methods that are applied by the researcher to meet the study objectives (Thomas 2021:65). The research designs predominantly used in epidemiology are ecological, cross-sectional, cohort and case-control research designs (Carneiro 2017:15-16).

1.7.1 Study Approach

This study used a non-experimental quantitative approach. In quantitative approaches, numerical data are collected using standardized methods and data analysis is predominantly statistical (Thomas 2021:60). As previously described, deductive reasoning was applied. This application begins with an established hypothesis and data are collected to test whether the hypothesis is supported. As a result, how the dependant variable and the independent variable relate can be quantified (Thomas 2021:60).

Quantitative studies can be either experimental or non-experimental. In experimental quantitative studies, variables of interest can be introduced, observed, or manipulated by the researcher while in non-experimental approaches, causes and outcomes are

retrospectively linked. Non-experimental studies are used when variables cannot be manipulated or the events that are being studied have already occurred (Thomas 2021:61).

1.7.2 Research Design

This study utilized a cross-sectional quantitative design. These designs are employed to present a picture of what is happening in a population at a certain time. They are relatively inexpensive to conduct and pose little or no ethical difficulties as study respondents are typically not directly exposed or treated (Thomas 2021:68-69). This study design was the most suitable for this research because it enabled the association between the exposure variable (rubella vaccination) and outcome variable (rubella prevalence) to be studied.

In this study, the rubella positivity rate was evaluated using measles and rubella surveillance data. Information on geographic distribution, age and sex of rubella positive cases was also analysed. Numerical data was collected in a standardized way.

1.7.3 The study setting, sampling, and sample size

The environment where research is being conducted is the study setting, while the study population is the population from which observations are made and data is collected in order to make conclusions about. The process of selecting a group that represents a specific population is called sampling. This is done when it is not possible to observe or collect data on all members of the said population (Thomas 2021:135-136). When the characteristics of interest are present in the sample, it is considered to be representative of the population under study. Inferences made from observations of the sample population can therefore be extrapolated to the entire population that it represents. Conclusions drawn from larger sample sizes are also more likely to reflect the parameters of the population (Thomas 2021:155). Carneiro (2017:82) describes the main concepts that are applied when calculating sample sizes. The possibility of finding an effect when it truly exists is known as statistical power, whereas the chance of finding an effect if it does not exist is known as statistical precision.

Statistical power and precision of 80-90% and 5% respectively are required to detect a reliable effect estimation (Carneiro 2017:82).

Lesotho, a Southern African country , was the study setting. There are reportedly about 2 million people living there. It is categorized as a low middle-income country (Lesotho 2021:7). There are 10 districts in the country: Maseru, Berea, Leribe, Butha-Buthe, Mokhotlong, Thaba-Tseka, Mafeteng, Mohale's Hoek, Quthing and Qacha's Nek. The National Reference Laboratory, located in the capital city of Maseru, processes all samples taken from suspected cases.

Inclusion criteria:

- The study population was all suspected measles cases of any age that presented to a health facility or outreach sites that were investigated with a blood sample and were captured in the integrated measles and rubella surveillance system from January 2018 to December 2022.

Exclusion criteria:

- Cases that were defined only by clinical symptoms and were not investigated with a blood sample.
- Cases where blood samples were found to be insufficient for laboratory investigation.
- Cases with incomplete immunization history and cases with a history of rubella vaccination within 30 days preceding blood sample collection were also excluded from the study. As previously described, both rubella infection and vaccination stimulate the production of IgM antibodies (WHO 2020b: 311). The vaccination history is therefore important in determining whether positive cases are due to natural infection or the result of vaccination.

1.7.4 Data collection and analysis

Data are defined as measured facts that are collected with the aim of making inferences (Thomas 2021:142). Carneiro (2017:85) describes two methods of collecting data. Indirect data collection methods involve collection of data that are routinely collected, are already available and can be found in health surveys, registries, medical records, and other sources. In this study, the data that was collected already existed but needed to be extracted. Data quality in indirect data collection methods can however be poor due to incomplete or inaccurate data

(Carneiro 2017:85). In direct data collection methods, data are collected directly from study respondents. This can include the use of questionnaires, structured interviews and clinical examination methods.

This was a retrospective study. Rubella epidemiology (rubella prevalence and distribution) in the five-year period after rubella vaccination became available in Lesotho was evaluated using surveillance data or records. This surveillance data was obtained from the integrated measles and rubella case- based surveillance system. This system is an already established surveillance system in Lesotho. This study, however, only focused on the rubella aspect of this surveillance system.

The study period was from January 2018 to December 2022. The year 2017 was considered as the vaccine introduction period.

During this period, blood samples were taken by health care workers from individuals presenting at health facilities and outreach sites who met the WHO case definition of a suspected measles case. Case investigation forms that capture variables like age, sex, date of rash onset, travel history in the two weeks preceding rash onset, date of sample collection, immunization history and district of residence were also completed. The travel history in relation to the date of rash onset is used to determine whether infection occurred in the country or if infection was due to importation while the vaccination history is used to determine whether the presence of rubella specific immunoglobulins in samples taken is due to natural infection or the result of vaccination. Information on national identification numbers is not routinely collected. The blood samples and accompanying case investigations forms were dispatched to the National Reference Laboratory (NRL) from all districts in the country. The blood samples were then tested for measles specific IgM antibodies by laboratory technicians. The samples that tested negative for measles specific IgM antibodies were then tested for rubella specific IgM antibodies using enzyme-linked immunosorbent assays (ELIZA).

The laboratory results and copies of the case investigation forms were then taken to the Expanded Program on Immunization (EPI) office at the Ministry of Health headquarters, where they were captured into an electronic database by the EPI data clerk. Limited access to this electronic database was granted to the researcher by the EPI data clerk. To ensure the confidentiality of study respondents all information that could identify study respondents was removed by the EPI data clerk before access to this electronic data base was granted to the researcher. RCV coverage data was also

made available by the EPI data clerk. Population projections were obtained from the Bureau of Statistics of Lesotho. These projections together with all the data that is required to fulfil the study objectives were captured into the data-collecting tools by the researcher.

The data collecting tools were also stored in a locked cabinet so that the privacy of study respondents was maintained.

1.7.5 Data analysis

Descriptive and inferential statistics are the main data analysis methods used in quantitative research. Descriptive statistics are used to summarize data sets reducing them into simple values that are used to describe the characteristics of the data sets quantitatively (Thomas 2021:151). Descriptive statistics are further categorized into measures of central tendency and include the mean, the media, the mode, measures of spread or dispersion like the standard deviation and range and measures of association such as correlation and regression. Other descriptive statistics include percentages, proportions, ratios and rates (Thomas 2021:152). When study intends to extrapolate or generalize the results beyond the population under investigation, inferential statistics are used. These inferences are only credible if the sample population is reflective of the whole population (Thomas 2021:153). Inferential statistics are also used to determine whether differences or associations observed are due to chance or are real. Both parametric and non-parametric tests are used to make these determinations. Parametric tests require the normal distribution of data and include the T-test, Z-test, and analysis of variance. The Chi square test is an example of a non- parametric test and it does not require data to be normally distributed (Thomas 2021:152-4).

Descriptive statistics were employed. The data gathered was captured into Microsoft Excel. Version 28 of the Statistical Package for Social Sciences (SPSS) was used to analyse the data. An IgM negative measles case that tests rubella IgM positive was regarded as a confirmed rubella case. These cases were analysed by age, sex, district of residence and year of notification. For categorical variables, absolute numbers and percentages were used, and medians and ranges were used for continuous variables. The data was presented in summary tables, and graphs. The chi-square test was used

to determine if the association between the relevant variables was important. For statistical significance, p-value less than 0.05 is usually required. The effectiveness of the surveillance system was measured using two key indicators: the non-measles non-rubella febrile rash illness rate and the proportion of districts investigating suspected measles rubella cases with a blood specimen per year.

1.8 ENSURING RIGOUR

In quantitative research, rigour is defined as the pursuit of high quality in research. This usually calls for discipline, attention to detail, precision, and accuracy (Grove & Gray 2022:39). Reliability or precision is the capacity of a measurement device to generate similar results when measured on separate occasions on the same individual or population. Validity or accuracy refers to the capacity of a measuring device to provide a correct reading or to record what it is intended to record (Friis & Sellers 2021:417-18).

In this study, rubella prevalence was estimated using surveillance data. To guarantee the validity of the results obtained, the blood samples were all processed at the NRL using standardized testing methods. The NRL is accredited and is part of the WHO vaccine preventable disease laboratory network. To ensure reliability, 10% of the blood samples obtained routinely undergo repeat assessment at the South African National Institute for Communicable Diseases (NICD).

Notably, the case definition used to recruit cases likely has a limited capacity to identify all rubella cases because not all rubella cases are symptomatic, and this may lead to under reporting.

1.9 ETHICAL CONSIDERATIONS

Ethics refer to a field of study that looks at what is right or wrong in different situations (Tseng & Wang 2021:1). There are two prominent theories in ethics that guide decision making in the health care context. The utilitarian theory holds that the decision that results in the best for the most people is the most morally just choice. Deontological theories emphasize the duty of care to the individual regardless of the outcome produced. In essence utilitarianism is society centred while deontology focuses on the individual (Chukwuneke & Ezenwugo 2022:19). The utilitarian approach is commonly

used in public health practice. A recent application of this approach was the use of quarantine and vaccination mandates during the Covid-19 pandemic, where isolation of infected individuals and mass vaccination was deemed to be in the best interest of society at large.

In medical research, ethical dilemmas and conflicts are common. New therapies and technologies are continuously being evaluated and it may not always be clear if the proposed protocols to evaluate such studies are ethically sound. The ill treatment of human subjects in the Tuskegee syphilis study prompted the development of the Belmont report. This report outlines the principles that guide the selection of study respondents and the process of obtaining informed consent (Grove & Gray 2022:104). These principles include autonomy, beneficence, non-maleficence and justice (Boswell & Cannon 2020:93). Autonomy is the freedom to make decisions that are free from outside interference. It also requires the protection of individuals with diminished autonomy who are vulnerable to coercion. These individuals include children, those on medications and the mentally ill. The expectation that the information gathered would be kept private and the right to privacy is also enshrined in this principle (Grove & Gray 2022:106-109).

Beneficence and non-maleficence refer to the obligation to ensure the well-being of respondents and to do no harm while justice refers to treatment that is fair and includes the equitable distribution of both the advantages and risks of a study (Boswell & Cannon 2020:94)

The application of these principles in this study has been described below.

1.9.1 Respondents

This study involved a retrospective record review with no direct contact with study respondents. The researcher, however, recognized that this study involved the collection of data that was not originally intended for research and that respondents did not consent to their data being used for research. The researcher also recognized that the study may also involve respondents below the age of 18. This assumption was made based on patterns in the age ranges of respondents observed in similar studies that were conducted in other settings (Luce et al. 2018:11) and (Hong et al. 2022:5). The processing of information of children is prohibited by the protection of personal information act of 2013 (Republic of South Africa 2013:44). This prohibition,

however, does not apply if the processing of said information is for the purposes of research, is of public interest and the obtaining of consent is deemed impossible or excessive. Nevertheless, the law, however, also requires that safeguards are put in place to ensure the privacy of these respondents. As a result, to guarantee the autonomy of study respondents and in compliance with this law the medical records of study respondents were de-identified before access was given to the researcher. No information that could identify the individuals being studied was collected by the researcher. To safeguard against the unlawful access to the personal information of study respondents, data collecting forms were stored in a locked cabinet. The computer utilized for data capturing and analysis was password protected and was only used by the researcher. The principles of beneficence and non-maleficence were applied by ensuring that respondents were not adversely affected by the way that their personal data was handled and by also ensuring that the study results are used to guide policies that promote equitable access to vaccines for all communities. The principle of justice was applied by making sure that respondents were included or excluded from the study based only on scientific criteria.

1.9.2 Institutions

The authorization to carry out this study was given by the Head of the Family Health Division of the Ministry of Health of Lesotho who is the gatekeeper of the records that were reviewed. Ethical approval was also given by the ethics and review committee of the Ministry of Health of Lesotho.

The UNISA ethics policy was also consulted and its guidelines on integrity, accountability and rigour in research adhered to. Ethical approval was therefore also secured from the UNISA ethics review committee before undertaking the study.

1.9.3 Researcher

The researcher endeavoured to produce good quality research and adhered to the steps outlined in the study protocol. The researcher will also share the results of the research with the EPI program and its stakeholders with the hope that the findings will be used to inform immunization strategies that will improve immunization services for all communities in Lesotho.

1.9.4 Domain specific ethical concerns

As previously indicated, the study respondents were not directly exposed or treated. Additionally, the researcher will ensure that the study respondents and their communities will not suffer from the publication of the study findings.

1.10 STRUCTURE OF THE DISERTATION

There are five chapters in this dissertation. In chapter 1, an introduction to the study is provided. The chapter also included a description of the study problem, the study purpose, the research questions and the theoretical foundations of the study. The research methodology and ethical considerations were also described.

Chapter 2 presents the literature review while chapter 3 outlines the research design and method. In chapter 4, the data analysis is decribed and the study findings are presented and discussed. Lastly, chapter 5 discussed the study limitations, conclusions and recommendations.

1.11 SUMMARY

The present chapter summarised the study background including the problem description, purpose, objectives and hypothesis, research questions, conceptual framework, research methodology and design, and the measures that were taken to ensure ethical and rigorous research.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, literature was reviewed on rubella, the case for rubella elimination, the evolution of rubella vaccination strategies and how they have impacted the epidemiology and burden of disease from rubella and new innovations to improve measles and rubella vaccination coverage.

2.2 AN OVERVIEW OF RUBELLA

Rubella was previously thought to be a different form of scarlet fever or measles. This perception later changed in the 1940s when congenital cataracts were observed in babies born to mothers who were diagnosed with rubella early in their pregnancy. This phenomenon was later described as CRS (Perera 1946:viii) The rubella virus was later isolated in the early 1960s. This together with the availability of diagnostic tests resulted in other CRS presentations like hepatitis and splenomegaly being recognized and these were added to the triad of deafness, cataract and congenital heart disease that were already described (Plotkin 2021:S361).

In CRS, the rubella virus spreads to the foetus through the placenta, disrupting organ development and causing inflammation (Lambert, Strebel, Orenstein, Icenogle & Poland 2015:2). Vaccination remains the most effective strategy to disrupt rubella transmission and prevent CRS (WHO 2020b: 318). Advances in rubella control have been made in recent years as evidenced by the increase in the global rubella vaccination coverage from 21% in 2000 to 66% in 2021. However, rubella remains endemic in many parts of the world with 10,363 and 10,029 cases of rubella reported in 2020 and 2021 respectively globally by member states in the WHO/UNICEF joint reporting form on immunization (WHO immunization data portal).

2.3 THE CASE FOR RUBELLA ELIMINATION

Rubella is said to be eliminated if there is no endemic rubella transmission within a country persistently for more than 12 months and when there are no CRS cases that

result from local rubella transmission when the rubella surveillance system in that country is of good quality (WHO 2020a: vii). Rubella, CRS and measles were supposed to be eliminated by 2020 but this goal was not realized (WHO 2012:13). The failure to meet that goal was attributed to a shift in disease epidemiology with cases occurring in infants and older age groups, immunity gaps in displaced populations that have poor access to vaccination services and the interruption of routine immunization services during the pandemic caused by Covid-19 (WHO 2020a: viii). Other contributors to low coverage that have impeded progress toward elimination have been described. They include weak health systems that lead to low vaccination coverages with the persistence of unimmunized children, increasing vaccine hesitancy and inadequate monitoring and surveillance systems that do not have the capacity to identify chains of transmission to prevent and interrupt outbreaks (WHO 2020a: viii).

Plotkin (2021: S364-5) argues that rubella elimination may be more feasible than measles. The lower rubella reproductive number (R_0) relative to measles; 7 compared to 12, and the longer rubella incubation period of 12-23 days compared to 10-21 days in measles that allow for an anamnestic response in persons who have been vaccinated support this argument. In anamnestic immune responses, a function of immunological memory, more rapid and effective immune responses are elicited upon exposure to a previously encountered pathogen (Kirman, Quinn & Seder 2019: 615). In other settings, the rubella R_0 has been estimated to be between 3-8 in Europe and around 12 in developing countries. The heard immunity threshold required to interrupt rubella transmission has therefore been estimated to be between 67%-87% in European countries and between 85-91% in African settings; the implication being that if population immunity is sustained above these levels, rubella can be eliminated (Lambert et al 2015: 4). The reduced infectiousness of rubella relative to measles and the feasibility of rubella elimination is further supported by the absence of widespread rubella outbreaks even during periods of reduced vaccination coverage while measles outbreaks have been reported (Lambert et al 2015: 4). The effectiveness of the rubella vaccine has also been established. This is supported by rubella and CRS being eliminated from all countries in North and South America, 41 countries in Europe, 5 countries in the Western Pacific Region and 4 countries in the Eastern Mediterranean Region (WHO immunization data portal). Rubella antibodies have also been demonstrated in 95-100% of persons 9 months old and above after one dose of RCV.

Immunity after administration of a RCV is assumed to be lifelong and breakthrough infections in vaccinated persons have been rarely reported (WHO 2020b:313-15). Breakthrough infections or vaccine failure is classified into primary and secondary vaccine failure. In primary vaccine failure, persons being vaccinated fail to seroconvert after vaccination and there is no measurable immune response while in secondary vaccine failure there is a sub-optimal immune response or declining immunity over a period of time (Fappani, Gori, Canuti, Terraneo, Colzani, Tanzi, Amendola & Bianchi 2022: 5).

Although rubella vaccine failure is rarely reported, there is evidence of diminishing immunity over time. In a longitudinal study looking at the persistence of rubella specific antibodies at two time points in adolescents and young adults, rubella specific antibody titres were shown to decline with increasing time since vaccination (47.18 IU/mL vs. 36.83 IU/mL, $p < 0.001$), but these titres remained above the 10IU/ml threshold that is considered protective in most study participants (Crooke, Riggenbach, Ovsyannikova, Warner, Chen, Hao, Icenogle, Poland & Kennedy 2020:3). Crooke et al also demonstrated a decline in neutralizing antibody titres (53.11 vs. 47.49, $p = 0.018$) and the responses of memory B cells (5.25 SFUs/2×10^5 cells vs. 4.75 SFUs/2×10^5 cells, $p = 0.004$) but found no proof that this decline increased the risk of rubella or CRS.

Davidkin, Jokinen, Broman, Leinikki and Peltola (2008:953) also demonstrated a decline in rubella specific antibodies levels over time. In a 20-year cohort study that followed persons who received the measles mumps and rubella (MMR) vaccine in two doses, rubella seropositivity was 100% 15 years after the vaccine was given for a second time. Rubella antibody levels however declined from 67 to 28 to 22 IU/mL at 1-, 8- and 15-years post vaccination respectively. This decline was more pronounced in the initial eight years after the vaccine was given for a second time.

2.4 THE EVOLUTION OF RUBELLA VACCINATION STRATEGIES AND IMPACT ON RUBELLA EPIDEMIOLOGY AND DISEASE BURDEN

The rubella vaccines first became available on the commercial market between the later part of 1960 and early 1970. Rubella vaccination strategies have evolved over time. This evolution has been mostly informed by changes in disease epidemiology (Plotkin 2021: 361-3). There are two rubella vaccination approaches. The universal

approach intends to eliminate rubella as well as CRS and requires the introduction of RCVs into routine immunization schedules that include the vaccination of adults who are at risk of rubella. The selective vaccination approach aims to lower the incidence of CRS by vaccinating both teenage girls and women of fertile age or either of the two (WHO 2011: 310-11). The selective approach was used in the United Kingdom in 1970. This approach was selected because at that time, the duration of protection after rubella vaccination was not yet known and the measles vaccination coverage was not optimal. This was important because the rubella and measles vaccine was intended to be given simultaneously (Dixon, Reef, Zimmerman & Grant 2022:226). This approach led to a decline in new CRS cases and abortions due to rubella. However, rubella virus circulation still continued and unvaccinated women continued to be at risk of rubella as evidenced by babies still being born with CRS but at a reduced rate. Due to the deficiencies of the selective approach and advances in the immunization program, the UK later pivoted to the universal approach (Dixon et al. 2022:227). In contrast, the United States adopted a universal approach in 1969 with children aged 1 year to puberty being targeted for vaccination. With this approach, women of fertile age remained at risk of infection. In 1978, vaccination was expanded to adults resulting in the United States no longer having cases of rubella and CRS from local transmission since 2004 (Dixon et al. 2022:227).

Continued rubella disease transmission due to selective vaccination strategies was also observed in Japan. Minakami, Kubo and Unno (2014:99) report on an outbreak of rubella that took place in Japan in 2012 and 2013 that resulted in 13 cases of CRS. Of note is that of the 11,489 cases of rubella that were reported in the first 6 months of this outbreak, 70% were in males 20 years of age and older. At that stage rubella vaccination in Japan was recommended for children aged 12 to 90 months but was not mandatory. Also, supplementary immunization activities to address immunity gaps targeted only adult females.

In Romania 1840 cases of probable and confirmed rubella were reported in 2011 predominantly among adolescents that were not vaccinated (Janta, Stanescu, Lupulescu, Molnar & Pistol 2012:1-2). Prior to 2004, a rubella containing vaccine was only offered to adolescent girls aged 13 to 18 years of age in Romania. The program was later expanded in 2004 to include children aged 12-15 months of age. In this

outbreak, 58% of cases occurred in adolescent males indicating a rubella immunity gap in that population.

In Poland, a rubella outbreak that predominantly affected adult males was also described, reflecting the selective vaccination of adolescent females which was the policy in Poland since 1989. This policy later changed to a universal two dose approach in 2004 (Paradowska-Stankiewicz, Czarkowski, Derrough & Stefanof 2013:1). In this outbreak, the ratio of males to females of the reported cases of rubella was 10:1. The males that were mostly affected were 15–19, 20–24 and 25–29 years old and they accounted for 57%, 19% and 5% of cases respectively.

The WHO recommendations on rubella vaccines have also evolved over time. In 2011, both the universal approach and the selective approach were recommended. Countries would then choose an approach depending on whether their goal was CRS reduction or elimination of both rubella and CRS. Factors that countries were encouraged to take into consideration in their decision-making process were the epidemiology of rubella, susceptibility profile of their population to rubella, the CRS burden and the availability of resources to sustain rubella vaccination and surveillance activities (WHO 2011:314-15). WHO (2011: 312) also recommended that the desired time frame to reduce CRS or eliminate rubella be taken into consideration. A universal approach which is more comprehensive and includes the vaccination of children, adolescents and adults would eliminate rubella and CRS in 10 years if a high coverage of 85-90% is achieved. In contrast, a childhood only vaccination program targeting children aged 1 to 4 years would eliminate rubella in 20 to 30 years. In 2020, WHO (2020b:319-20) updated the rubella vaccination recommendations to focus primarily on infants after an introductory campaign targeting children aged 9-14 years of age of both sexes and follow up campaigns targeting populations based on country specific rubella susceptibility profiles.

2.5 INNOVATIONS TO IMPROVE MEASLES RUBELLA VACCINATION COVERAGE

There is ongoing research that is looking at how safe and immunogenic the measles and rubella vaccine is when given through Microneedle Patches (MNPs). MNPs are devices that contain microneedles that deliver vaccines when applied to the skin. These devices are intended to address the challenges that are encountered when

delivering vaccines in resource limited settings and improve vaccination coverage. Because of the much simpler administration, MNPs are expected to reduce the requirement for a lot of trained health care workers that are currently needed to deliver the vaccine through the subcutaneous route. Other potential benefits would be improved thermostability, reduced transmission of diseases caused by needle injuries and reduced wastage of vaccines due to the use of multi-dose vials that are currently in use (Adigweme, Akpalu, Yisa, Donkor, Jarju, Danso, Mendy, Jeffries, Njie, Bruce, Royals, Goodson, Prausnitz, McAllister, Rota, Henry & Carke 2022:6).

2.6 CONCLUSION

Literature review on rubella, the case for rubella elimination, the evolution of rubella vaccination strategies and how they affect rubella epidemiology and disease burden and new innovations to improve measles and rubella vaccination coverage was presented in this 3.

CHAPTER 3

RESEARCH DESIGN AND METHOD

3.1 INTRODUCTION

This present chapter covers the design of the study and research methodologies, which encompass population description, sampling, data collection and data analysis. How validity and reliability were ensured, and the study's application of ethical principles are also covered.

3.2 RESEARCH DESIGN

Research designs are described as the methods and techniques that are used when conducting research. According to Saliya (2023:74-76), the research design is chosen based on the study goals and expected outcomes of the study. The research design also outlines the specific steps that need to be followed in the research process.

A cross-sectional quantitative design was used. In cross-sectional studies, information about a specific population is collected at a certain time point of the study. The associations between different variables are analysed. These studies however cannot be used to analyse causal relationships between variables but are useful in collecting data that can inform future research (Saliya 2023: 91).

The cross-sectional study design was used to evaluate the effectiveness of rubella vaccination in Lesotho in the five-year period following the introduction of the RCV. For this study, the design was suitable because there were not a lot of resources required to execute the study.

3.3 RESEARCH METHODS

Quantitative research methods were utilized. In quantitative research, different phenomena are investigated, and the data collected are presented in a quantifiable manner which in this study was rubella (Zeni 2019: 228).

3.3.1 Study setting

The study setting is where a study is carried out (Grove & Gray 2022:41). In this study, the setting was Lesotho, which is a mountainous country encircled by South Africa. The country has an estimated population of about 2 million people (Lesotho 2021:7). All blood samples that were collected for rubella investigation from all districts in the country were processed at the NRL which is in the capital city of Maseru.

3.3.2 Population

The population of the study was all rubella immunoglobulin M laboratory results of blood samples that were drawn from patients of any age that met the WHO case definition of a suspected measles case and were submitted to the NRL between January 2018 to December 2022. During this period 1050 suspected measels cases were reported through the intergrated measels and rubella case-based surveillance system. Of the 1050 suspected measels cases reported, 1041 cases were tested for rubella and these rubella results were later filtered according to the inclusion and exclusion criteria.

3.3.3 Sampling

Sampling refers to the exercise of choosing respondents that have characteristics that reflect the population that is being studied (Grove and Gray 2022: 41). In this study, samples of blood were drawn from patients of any age who presented with symptoms of measles and were processed by the NRL for measles and rubella investigation between 2018 and 2022. These samples were initially tested for measles and then subsequently tested for rubella specific immunoglobulins. The researcher considered all rubella IgM blood results that were recorded in the integrated measles and rubella case-based surveillance system from January 2018 to December 2022.

3.3.4. Data collection tools

The data collecting tools were adapted from the Lesotho measles compulsory notification case laboratory investigation form. The variables that were included in these tools were the case number, the date of birth, the sex, the district where respondents resided, the rubella immunization status and the date of the last rubella vaccination, the date that the skin rash initially appeared and the travel history in the

two weeks before the illness started. The date of last rubella vaccination was used to determine whether rubella seropositivity was due to vaccination or acute rubella infection, while the travel history was used to determine whether rubella cases were endemic or exported. Other variables included the blood sample adequacy, rubella IgM results, the Lesotho rubella vaccination coverage, and the population projections per district. The rubella IgM results were used to estimate rubella prevalence, which was the dependent variable. Rubella vaccination coverage was the moderating variable. Population projections were used to calculate the non-measles non-rubella febrile rash illness rate.

3.3.5 Data collection

The data were drawn out of the integrated measles and rubella case-based surveillance system data base by the EPI data clerk. These data included rubella IgM blood results of study respondents and accompanying demographic information and other information required to fulfil the goals of the study. This data was given to the researcher who filtered them according to the inclusion and exclusion criteria. The data were then recorded into the data collecting tools by the researcher and were stored in a computer that can only be accessed by using a password. No information that could identify study respondents was provided to the researcher. The anonymity of respondents was ensured by using numbers to label the rubella IgM results.

3.3.6 Data analysis

The data was summarized using descriptive statistics. A positive rubella IgM test in an individual who had not been vaccinated in the past 30 days prior to blood sample collection was used as an indicator of acute rubella disease. The data were grouped in terms of sex, rubella serostatus, age categories (0 - < 1 year), (1year to < 5 years), (5 - <13 years) and (13 years and above), district of residence and year of notification. The percentages of the rubella positive blood results were calculated according to the age categories of respondents and the overall percentages of rubella positive results were the estimated rubella prevalence. The formula below was used to compute rubella prevalence which was reported as a percentage.

$$\text{Rubella prevalence} = \frac{\text{rubella IgM positive results}}{\text{total rubella IgM results}}$$

The Positive Predictive Value (PPV) was used to determine the sensitivity of the measles case definition in detecting rubella cases. It was calculated by dividing all positive rubella IgM cases by all suspect cases that underwent rubella testing.

The non-measles non-rubella febrile rash illness rate was computed using the formula: discarded cases after laboratory testing of blood samples divided by the total population of a district multiplied by 100. The proportion of districts reporting at least one case of measles with a blood sample per year was computed using the formula: number of districts reporting at least one measles case with a blood sample per year divided by total number of districts in the country that conduct measles and rubella surveillance. Data analysis was done using SPSS version 28 with technical support from the UNISA School of Interdisciplinary Science. The data was shown in graphs and tables.

3.4 RIGOUR OF THE STUDY: VALIDITY AND RELIABILITY

Grove and Gray (2022:39) define rigour as the precision and accuracy that is required to ensure high quality in research.

3.4.1 Validity

According to Zeni (2019:203) validity refers to whether measuring instruments used in research assess what the study intended. The researcher only used the blood results that were confirmed by the laboratory and were submitted to the EPI program.

3.4.2 Reliability

An instrument or measurement is said to be reliable when the data it generates is consistent and dependable (Zeni 2019:204). In this study, reliability was ensured by using only rubella blood results that were produced by the NRL. This laboratory is accredited and is part of the WHO vaccine preventable disease laboratory network. Also, during the study period, 10% of samples were taken to the NICD in South Africa for repeat testing.

3.5 ETHICAL CONSIDERATIONS

Ethical considerations are moral principles that guide society in determining what is right or wrong in different situations (Chukwuneke & Ezenwugo 2022:19).

3.5.1 Consent

Ethical approval for the study was granted by the UNISA College Research Ethics Committee (CREC) and the National Health Research and Ethics Committee of the Ministry of Health of Lesotho. Further authorization was also obtained from the Head of the Family Health Division of the Ministry of Health of Lesotho who is the gatekeeper of all EPI related data. The researcher also adhered to the guidelines stipulated in the Lesotho Data Protection Act of 2011(Lesotho Government Gazette 2011: 263) and the protection of personal information act of 2013 of the Republic of South Africa (Republic of South Africa 2013: 44). Among these guidelines are the de-identification of personal information and the use of appropriate safeguards to prevent the loss of damage of or unlawful access to personal information (Lesotho Government Gazette 2011, 265).

3.5.2 Confidentiality

The rubella IgM results of study respondents were kept confidential. The data collecting tools were stored in a computer that is protected by a password. To ensure that respondents remain anonymous, the rubella IgM results were labelled with numbers. No information that could identify study respondents was made available to the researcher.

3.5.3 Justice

According to Aschengrau and Searge (2020:894), the principle of justice is used to ensure the equal distribution of both the benefits and adverse effects of research. This principle also requires that the selection of study respondents is made only based on the problem being studied. This principle was adhered to in this study. The study results will also be shared with all stakeholders and will be used to inform activities that address inequities in rubella vaccination access.

3.5.4 Beneficence

The principle of beneficence requires that study respondents benefit from the study and that these benefits are weighed against potential risks to study respondents. It also requires the use of safety reports or results from other studies to inform the risk assessment processes and encourages the continuous assessment of risks throughout the study (Aschengrau & Searge 2020:893). The respondents will benefit from improvements in vaccination service delivery that were informed by the study results. The risks to study respondents were also minimized by using secondary data, namely rubella IgM results rather than human respondents. These blood results were only used to fulfil the research goals and not for any other purpose except for rubella prevalence estimation.

3.6 CONCLUSION

This present chapter covered the design of the study and research methodologies, which encompassed population description, sampling, data collection and data analysis. How validity and reliability were ensured, and the study's application of ethical principles were also covered.

CHAPTER 4

ANALYSIS, PRESENTATION AND DESCRIPTION OF THE RESEARCH RESULTS

4.1 INTRODUCTION

In this chapter, the analysis of data that was extracted from 1050 suspected measles cases reported to the integrated measles and rubella case-based surveillance system in Lesotho from January 2018 to December 2022 are presented. Included in this presentation are the specifics of how the data was managed and analysed, an outline and a discussion of the results of the study.

4.2 DATA MANAGEMENT AND ANALYSIS

The generated data were stored in a computer that can only be accessed by using a password by the researcher. Any information such as names and addresses that could identify study respondents was taken out to preserve anonymity. The data were only used to fulfil the goals of the study.

4.3 RESEARCH RESULTS

Out of the 1050 suspected measles cases reported from all districts in Lesotho between January 2018 and December 2022 (Figure 4.1), a total of 1042 (99.2%) blood samples were received. A total of 1042 (99.2%) samples underwent measles testing, and 1041 (99.1%) samples underwent rubella testing. In the remaining 9 (0.9%) of cases, samples were either not taken or insufficient for testing. Among the 1042 cases tested for measles, 10 (1%) tested positive. Notably, three of the 10 measles positive cases were also positive for rubella. These 10 cases were excluded from further analyses as the focus of this study was rubella, and 1031 rubella IgM results underwent further analysis.

4.3.1 Suspected cases reported

The total number of cases reported to the integrated measles and rubella case-based surveillance system are illustrated in Figure 4.1 below. There were more cases reported in 2022.

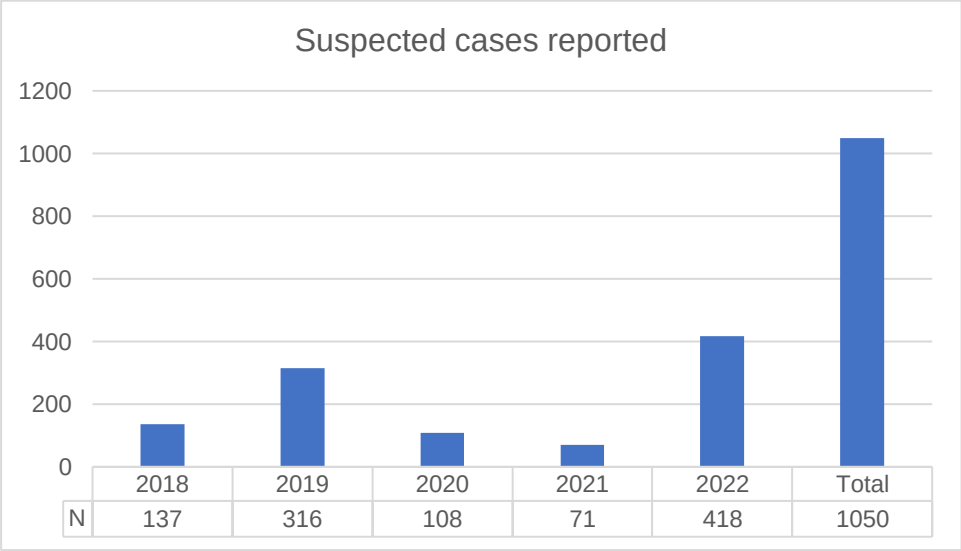

Figure 4.1. Suspected measles cases reported in Lesotho from January 2018 to December 2022

4.3.2 Gender distribution

Out of the 1031 rubella IgM results that were analysed, information on gender was available for 1030 of the 1031 cases and has been displayed in figure 4.2 below. There were more males than females reported at 532 (51,6%) and 498 (48,3%) respectively.

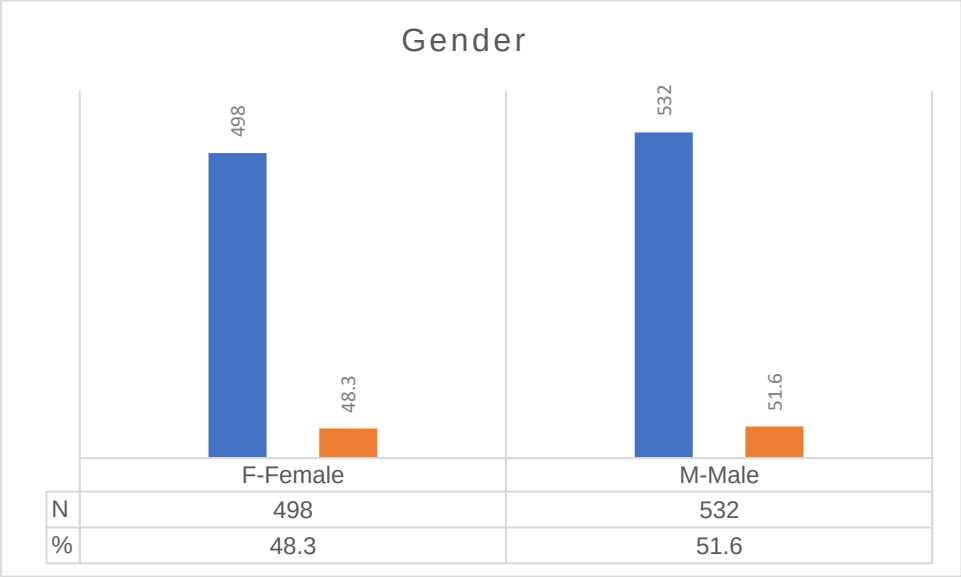

Figure 4.2. Gender distribution of rubella IgM results. (Unknown gender N=1)

4.3.3 Age distribution

The distribution of ages of rubella IgM results is displayed in figure 4.3 below. Of the 1029 results that were analysed, 27 (2,6 %) were < 1 year, 292 (28,3%) were 1- < 5years, 642 (62,3%) were 5 - < 13 years and 68 (6.6%) were 13 years old and above. Unknown age N=2. There were more cases reported in the 5 - <13-year age category followed by the 1 - <5-year age category. The median age of the respondents was 6.0 (IQR 4.0 – 8.0.) years.

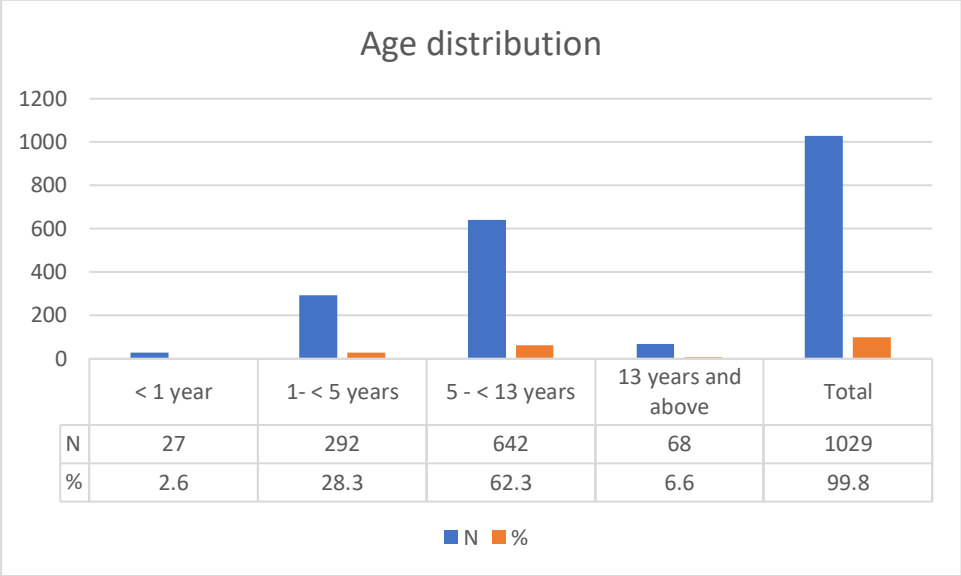

Figure 4. 3. Age distribution of rubella IgM results. (Unknown age N =2)

The age and gender distribution of rubella results is shown in figure 4.4 below. There were more cases reported in the 5 - < 13-year category followed by the 1 - < 5-year category. There were also more males than females in both these age categories.

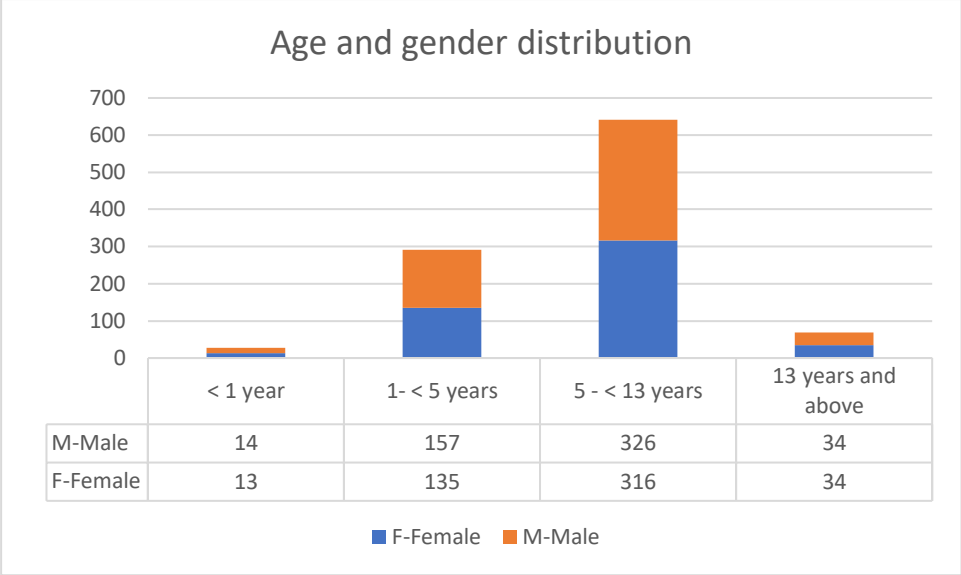

Figure 4. 4. Age and gender distribution of rubella IgM results.

4.3.4 Rubella prevalence

Table 4.1 below shows the prevalence of rubella in different age categories, by gender and by district of notification. Out of the 1031 blood samples tested for rubella, 1017 tested negative, 11 tested positive and 3 yielded indeterminate results. Among 11 rubella positive cases, details regarding the date of last rubella vaccination were only available for 10 out of the 11 cases. The details of the date of last vaccine dose are used to determine whether a positive rubella IgM test is due to acute infection or a result of vaccination. The case without information on date of last rubella vaccination was therefore excluded and this case belonged to the < 1 year age category. Among the 10 remaining positive cases, 7 fell into the age category of 5 - <13 years and 3 were in the 1 - < 5-year age category. Additionally, it is worth mentioning that 7 of the positive cases had received rubella vaccination while 3 had not. The gender distribution of rubella positive cases was similar, 5 males and 5 females. These rubella positive cases were identified in 6 out of the 10 districts in the country, 3 cases detected in 2019 and 7 cases in 2022. The travel history information of the 10 positive cases could not be obtained therefore the researcher was unable to distinguish between endemic and exported cases. The estimated rubella prevalence was 1% (95% CI; 0,5% -1.8%). The overall PPV was 1.2% (12/1041). Due to the paucity of rubella positive cases, inferential statistics could not be applied. These would have

been used to determine whether there was an association between rubella prevalence which was the outcome of interest and various demographic data.

Table 4.1. Rubella prevalence

Variable	Confirmed rubella negative	Confirmed rubella positive	Indeterminate
Age			
< 1 year	26	∗1	0
1 - < 5 years	288	3	1
5 - < 13 years	633	7	2
13 years and above	68	0	0
Unknown	2	0	0
Total	1017	11	3
Gender			
Male	526	∗(1)5	0
Female	490	5	3
Total	1017	11	3
District			
Berea	115	0	1
Butha -Buthe	32	1	0
Leribe	223	∗1	1
Mafeteng	158	0	1
Maseru	158	2	0
Mohale's Hoek	51	3	0
Mokhotlong	68	1	0
Qacha's Nek	115	2	0
Quthing	65	1	0
Thaba-Tseka	55	0	0
Total	1017	11	3

∗Excluded from final analysis

4.3.5 Coverage of the first dose of MR vaccine

The coverage for the first dose of the MR vaccine has been displayed in figure 4.5 below. In 2018, only one district met the recommended coverage target of ≥ 80%. This improved in 2019, with all ten districts meeting the expected target. In 2020, there was a notable decline in coverage in all ten districts with Quthing district also having persistently low coverage in subsequent years.

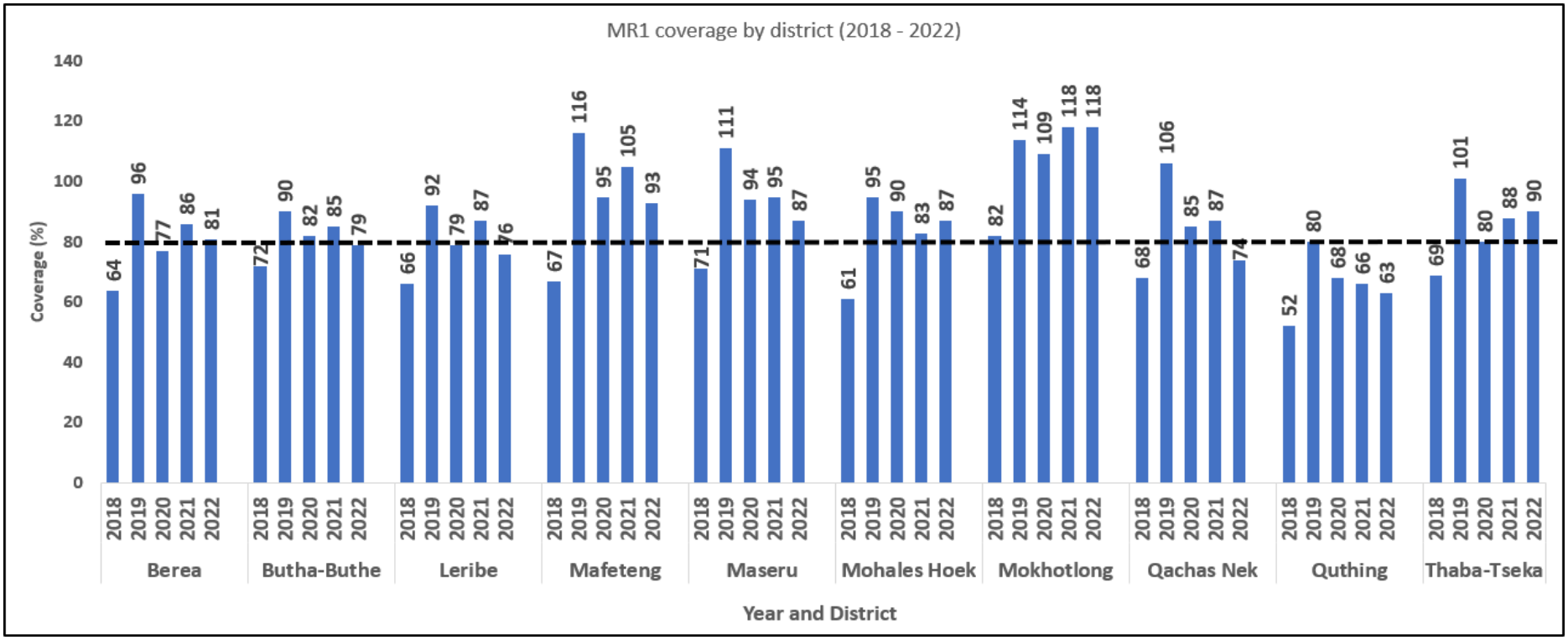

Figure 4. 5. Coverage of the first dose of the MR vaccine per district from 2018 to 2022

The MR vaccination coverage data was based on administrative data and was obtained from the Lesotho EPI program.

4.3.6 WHO surveillance indicators

Table 4.2 Proportion of districts reporting at least one case of measles with a blood sample 2018 to 2022.

	2018	2019	2020	2021	2022
% of districts reporting	100%	100%	100%	90%	100%

The proportion of districts reporting at least one case of measles with a blood sample per year has been shown in table 4.2 above. The recommended target of ≥ 80% was met in all five years of the study.

Table 4.3 shows the performance of measles and rubella surveillance from 2018 to 2022. The surveillance target of the non-measles non-rubella illness rate of 2 per 100 000 population was not met in Butha-Buthe district in 2018 and 2019 and in Quthing district in 2020. In 2021, only 2 out of 10 districts met this target while in 2022 all districts met the target.

Table 4.3. Measles rubella surveillance performance by district 2018 to 2022

	2018			2019			2020			2021			2022		
District Name	**District Population**	**Non-measles non-rubella cases**	**Non-measles non-rubella cases Illness rate per 100 000 population**	**District Population**	**Non-measles non-rubella cases.**	**Non-measles non-rubella cases Illness rate per 100 000 population**	**District Population**	**Non-measles non-rubella cases**	**Non-measles non-rubella cases. illness rate per 100 000 population**	**District Population**	**Non-measles non-rubella cases.**	**Non-measles non-rubella cases Illness rate per 100 000 population**	**District Population**	**Non-measles non-rubella cases.**	**Non-measles non-rubella cases Illness rate per 100 000 population**
BEREA	265478	12	4.5	**266722**	50	18.7	267965	18	6.7	269174	3	1.1	270354	33	12.2
BUTHA-BUTHE	120018	2	1.7	**120827**	2	1.7	121639	10	8.2	122438	2	1.6	123228	16	13.0
LERIBE	347314	18	5.2	**352031**	32	9.1	356786	16	4.5	361538	7	1.9	366291	151	41.2
MAFETENG	175309	20	11.4	**173677**	45	26.0	172012	13	7.6	170293	14	8.2	168524	67	39.8
MASERU	538223	27	5.0	**547505**	46	8.4	556874	12	2.2	566260	9	1.6	575675	41	7.1
MOHALES HOEK	163266	4	2.4	**161944**	20	12.3	160595	10	6.2	159197	2	1.3	157756	15	9.5
MOKHOTLONG	101077	6	5.9	**101318**	15	14.8	101556	17	16.7	101778	0	0	101986	30	29.4
QACHAS NEK	75660	24	31.7	**76156**	67	89.0	76654	4	5.2	77144	1	1.3	77628	19	24.5
QUTHING	113724	3	2.6	**112739**	11	9.6	111734	2	1.8	110695	32	29.0	109624	17	15.5
THABA-TSEKA	136577	14	10.3	**137093**	17	12.4	137607	6	4.4	138102	1	0.7	138580	17	12.3
National	**2036646**	**130**	**6.3**	**2050014**	**305**	**14.9**	**2063422**	**108**	**5.2**	**2076618**	**71**	**3.4**	**2089647**	**406**	**19.4**

Population projections were obtained from the Bureau of Statistics of Lesotho. For the non-measles non-rubella rash illness rate per 100 000 population, the green colour shows that the surveillance targets were met while the red colour shows that these targets were not met.

4.4 DISCUSSION OF THE RESEARCH RESULTS

The effect of the introduction of a RCV on the occurrence of rubella in Lesotho was evaluated. A retrospective review of case-based surveillance data collected over a five-year period was conducted. Out of the 1031 rubella results that were analysed, rubella prevalence was found to be 1% (95% CI; 0,5% -1.8%). In India, there was a 48% decrease in rubella cases in the years following rubella vaccine implementation (Murugan, VanderEnde, Dhawan, Haldar, Chatterjee, Sharma, Dzeyie, Pattabhiramaiah, Khanal, Sangal, Bahl, Tanwar, Morales & Kassem 2022: 1574). Rubella cases were identified in 6 out of the 10 districts in Lesotho. Throughout the study period 2018 to 2022, rubella cases were only identified in 2019 and 2022. Rubella was evenly distributed among males and females and was predominantly seen in the 5 - <13-year age category. In South Africa, rubella cases were predominantly detected in the 4 – 9-year age category (Hong et al 2022:7).

The lowest coverage of the first dose of the MR vaccine was reported in 2018, with only 1 out of 10 districts meeting the expected coverage target of ≥ 80%. However, improvements in MR vaccination coverage were observed in all districts in Lesotho between 2019 and 2022 except in Quthing and Qacha's Nek districts. The Bureau of Statistics (2019: 102) also reported variations in MR vaccination coverage in different geographic regions of Lesotho.

This study also assessed the sensitivity of the surveillance system. Throughout the study period, all districts in Lesotho reported no less than 1 case of measles with a blood sample except in 2019 where 9 out of 10 districts reported cases with a blood sample. To ensure high surveillance sensitivity, a target of at least 80% is recommended (WHO 2015:41).

The poorest performance of the non-measles non-rubella rash illness rate was observed in 2021, where only 2 out of 10 districts met the expected surveillance target. Murugan et al. (2022: 1574) noticed a decrease in the detection of measles and rubella cases that was attributed to the pandemic caused by Covid-19, and this was later alleviated by providing training for health care workers on the safe continued provision of immunization and surveillance services during that period.

4.5 CONCLUSION

In this chapter, the analysis of data that was extracted from 1050 suspected measles cases reported to the integrated measles and rubella case-based surveillance system in Lesotho from January 2018 to December 2022 was presented. Included in this presentation were the specifics of how the data was managed and analysed, an outline and a discussion of the research results.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

The interpretation of the research results concerning the prevalence of rubella in Lesotho are covered in this chapter. Limitations, conclusions, and recommendations of the study are also included in this chapter.

5.2 INTERPRETATION OF THE RESEARCH RESULTS

Rubella prevalence in Lesotho after vaccine introduction was estimated using surveillance data. Among the 1050 suspected measles cases reported, 1042 (99,2%) blood samples were received for testing, surpassing the target set by WHO of more than 80% (WHO 2015:75). The PPV of the surveillance system to predict rubella cases was 1.2%. This implies that most cases reported were not true rubella cases and underscores the need for laboratory investigation of suspected cases to confirm the diagnoses. The low PPV could be due to the use of the measles case definition to identify rubella, a disease that can present with little or no symptoms and this can result in inaccurate estimation of rubella prevalence (WHO 2020b: 322). However, low PPVs have also been reported in settings with low disease incidence (Nsubuga, Ampaire, Kasasa, Luzze & Kisakye 2017: 4-5).

Out of the 1031 rubella IgM blood results that were analysed, the prevalence of rubella was found to be 1%. This was a sharp decline compared to the 48% prevalence that was reported by Nwako and Makhupane (2021:25) before vaccine implementation. This decline is attributed to rubella vaccination. A decline in the occurrence of rubella after introduction of a RCV was also demonstrated by Luce et al. (2018:3-4). In their review, they demonstrated lower numbers of confirmed rubella cases ranging from 48% to 96% in 5 African countries after RCV introduction. These countries had also introduced rubella vaccination by SIAs that were targeted to boys and girls that were 9 months to 14 years old. In Ghana, reduced circulation of rubella after vaccine introduction was also demonstrated, 596 cases in 2011 compared to 19 cases in 2017 (Dongdem, Alhassan, Opare, Boateng, Bonsu, Amponsa-Achiano, Sarkodie, Dzotsi, Adjabeng, Afagbedzi, Alhassan, Agyabeng & Asiedu-Bekoe 2021:9), while in

Tanzania, rubella cases declined by >90% after vaccine implementation (Michael, Mirambo, Lyimo, Kyesi, Msanga, Joachim, Nyaki, Magodi, Mujuni, Tinuga, Bulula, Nestory, Mongi, Makuwani, Katembo, Mwengee, Mphuru, Mohamed, Kayabu, Nyawale, Konje & Msana 2022:1).

In this study, rubella was equally distributed among males and females. This differed from observations made by Dongdem et al. (2021:3), where higher proportions of rubella positive cases were confirmed among females. Rubella was predominant in the 5 - <13-year age category. Similar findings were reported by Dongdem et al. (2021:8) and Luce et al. (2018:4).

Rubella cases were only identified in 2019 and 2022, and most of these cases were identified in 2022. Additionally, this was the year when the most suspected cases were reported and the year where all districts in Lesotho met the WHO surveillance target for the non-measles non- rubella febrile rash illness rate. In contrast, this surveillance target was only met by 2 out of 10 districts in 2021 indicating a reduced sensitivity to identify rubella cases in 2021.

The WHO surveillance target for the proportion of districts reporting not less than one case of measles with a blood sample per year was met throughout the study period demonstrating the capacity of most districts in Lesotho to notify and investigate cases.

The coverage of the first dose of RCV declined in all districts in 2020. This decline could be explained by the Covid-19 pandemic's effects on health service provision. A decline in the uptake of routine immunizations during the Covid-19 pandemic was also observed by Murugan et al. (2022: 1574). The low prevalence of rubella could not be explained by the low rubella vaccination coverage during this period as high vaccine coverage is required to interrupt disease transmission (WHO 2020b:318). Conversely, the low rubella prevalence in 2020 could be explained by the non-pharmacologic interventions during the Covid-19 pandemic like mask wearing, hand washing and social distancing that led to a decline in transmitted diseases. An unwillingness to seek health care services during that period may also have contributed to the absence of rubella cases.

Persistently low vaccine coverage levels were reported in Quthing district in the years following the Covid-19 pandemic with Butha-Buthe and Leribe districts also failing to obtain the recommended coverage levels of ≥ 80% in 2022. The accumulation of children that are susceptible to rubella in these districts could lead to rubella outbreaks. Vaccination coverage levels of more than 100% were reported in 5 out of 10 districts in this review. This could be due to inaccurate estimates of the number of surviving infants which are used as denominators when calculating vaccination coverage or poor data quality.

In this study, three cases were identified that were IgM positive for measles as well as rubella and were excluded from further analysis. This could be due to recent infection from viruses like adenovirus that induce cross-reactive IgM antibodies. Rheumatoid factor is also known to interfere with IgM essays leading to false positive results. This is seen in settings with low rubella disease prevalence where the PPV of a rubella positive IgM result is also low and the possibility of the febrile rash being caused by other pathogens increases (Hübschen, Bork, Brown, Mankertz, Santibanez, Mamou, Mulders & Muller 2017:513). In South Africa, cases that were IgM positive for measles as well as rubella were thought to be more likely due to rubella infection because of the higher PPV of a rubella positive IgM result. Rubella is common in South Africa and the rubella vaccine is yet to be included in the vaccination schedule. Molecular testing to conform measles or rubella diagnosis has been recommended in these cases (Yousif, Hong, Malfeld, Smit, Makhathini, Motsamai, Tselana, Manamela, Kamupira, Maseti, Ranchod, Otwombe, McCarthy & Suchard 2022:7-8).

Out of the 10 cases that tested positive for rubella, 7 had received rubella vaccination while 3 had not. Although the study was intended to look at the effects of population immunity rather than individual immunity, the causes of vaccination failure in this review warrant further investigation. In other settings, rubella vaccination failure was not implicated in disease transmission, and it is thought to be caused by the presence of pre-existing rubella antibodies that neutralize the live viral strain of the rubella vaccine (Lambert et al. 2015:4,10).

5.3 CONCLUSIONS

The strength of this study was that rubella serology was conducted on almost all blood samples submitted allowing for the confirmation of rubella diagnosis. The results of the study suggest that rubella vaccination has led to a reduction in rubella prevalence in Lesotho. These results may however be confounded by the case definition that is used to recruit suspected cases which may not be sensitive enough to detect rubella cases. The non measels non rubella surveillance target was not met at certain time points during the study period indicating poor performance and a reduced sensitivity of the surveillance system to detect rubella cases. Failure to meet this surveillance indicator may also have led to an underestimation of rubella cases.

5.4 CONTRIBUTION OF THE STUDY

This was the first study to document rubella cases after vaccine introduction in Lesotho and it highlights the effectiveness of rubella vaccination and the need to achieve and sustain high population immunity. It can be used to advocate for resources that are needed to address inequities in rubella vaccination access.

5.5 RECOMMENDATIONS

Considering the results of the study, it is recommended that:

- The quality of the measles rubella surveillance system is improved, including adapting a case definition that is more sensitive to detect rubella. This will allow for a more accurate estimation of rubella disease prevalence and assessment of the impact of vaccination on disease burden.
- Measles and rubella catch-up campaigns are conducted to close immunization gaps which will lower the number of children that are susceptible to rubella and limit outbreaks.
- A high rubella vaccination coverage is maintained, and that surveillance data is used to inform immunization policy and to update these policies as the evidence evolves.
- Research is conducted to identify causes of rubella breakthrough infections in Lesotho and appropriate mitigating strategies.

5.6 LIMITATIONS OF THE STUDY

The study was limited by missing information particularly on age, gender, vaccination status and travel history of respondents. The surveillance data were reviewed for only a period of 5 years after vaccine introduction and may not be reflective of future trends of rubella transmission.

5.7 CONCLUDING REMARKS

The interpretation of the research results concerning the rubella prevalence in Lesotho was covered in this chapter. Limitations, conclusions, and recommendations of the study were also included in this chapter.

In general, the study results revealed that rubella vaccination was effective in reducing the number of rubella infections in Lesotho. It is important to create awareness among health care workers on the value of surveillance in monitoring disease patterns and how surveillance data can be used to identify populations at risk of rubella and guide the development of appropriate immunization strategies. The adoption of a more sensitive case definition to detect rubella cases should also be considered.

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ANNEXURES

Annexure A: Ethical Clearance Certificate from Unisa

UNISA university of south africa

COLLEGE OF HUMAN SCIENCES RESEARCH ETHICS REVIEW COMMITTEE

13 April 2023

NHREC Registration # :
Rec-240816-052
CREC Reference # :
16740688_CREC_CHS_2023

Dear Dr Thabelo Makhupane

Decision:
Ethics Approval from 13 April 2023 to 13 April 2024

Researcher(s): Name: Dr T. Makhupane
Contact details: 16740688@mylife.unisa.ac.za
Supervisor(s): Name: Prof. D. S. K. Habedi
Contact details: habeddsk@unisa.ac.za

Title: RUBELLA PREVALENCE IN LESOTHO USING MEASLES AND RUBELLA CASE BASED SURVEILLANCE DATA.

Degree Purpose: Masters

Thank you for the application for research ethics clearance by the Unisa College of Human Science Ethics Committee. Ethics approval is granted for one year.

The ***negligible risk application*** *was reviewed by* College of Human Sciences Research Ethics Committee, in compliance with the Unisa Policy on Research Ethics and the Standard Operating Procedure on Research Ethics Risk Assessment.

The proposed research may now commence with the provisions that:

1. The researcher(s) will ensure that the research project adheres to the values and principles expressed in the UNISA Policy on Research Ethics.
2. Any adverse circumstance arising in the undertaking of the research project that is relevant to the ethicality of the study should be communicated in writing to the College Ethics Review Committee.
3. The researcher(s) will conduct the study according to the methods and procedures set out in the approved application.

University of South Africa
Preller Street, Muckleneuk Ridge, City of Tshwane
PO Box 392 UNISA 0003 South Africa
Telephone: +27 12 429 3111 Facsimile: +27 12 429 4150
www.unisa.ac.za

Annexure B: Ethics Approval from Lesotho

LESOTHO

Ministry of Health
P.O. Box 514
Maseru 100

Category of Review:
[] Initial Review
[x] Continuing Annual Review
[ ] Amendment/Modification
[ ] Reactivation
[ ] Serious Adverse Event
[ ] Other _____

REF: ID07-2022 Renew 01
Date: May 03, 2023
To:
Dr Thabelo Makhupane,
Principal Investigator
Expanded Programme on Immunization (EPI)
Ministry of Health

Dear **Dr. Makhupane**

Re: Rubella Epidemiology in Lesotho after Vaccine Introduction: A review of Measles and Rubella Case-Based Surveillance

This is to inform you that the Ministry of Health Research and Ethics Committee reviewed and **APPROVED** the above named protocol for renewal and hereby authorizes you to continue the study according to the activities and population specified in the protocol. Departure from the approved protocol will constitute a breach of this permission

This approval includes review of the following attachments:
[x] Other materials: Request for renewal including progress report dated March 2023

This approval is **VALID** until 04th May, 2024.

We are looking forward to having an annual progress report and a final report at the end of your study. If you have any questions, please contact the Research and Ethics Committee at reumoh@gmail.com (or) 59037919/58800246

Yours sincerely,

DR. 'NYANE LETSIE
Director General Health Services

DR. JILL SANDERS
Co-Chairperson National Health Research & Ethics Committee (NH-REC)

Annexure C: Letters requesting permission to conduct the study

PERMISSION LETTER

Research title: Rubella prevalence in Lesotho using measles and rubella case-based surveillance data.

Researcher:

(Thabelo Makhupane)

Request for permission to conduct research at the Ministry of Health, Lesotho.

23rd September 2022

Dr Makhoase Ranyali
Family Health Division
Ministry of Health, Lesotho
Email: makhoaser@yahoo.co.uk
Tel: (266) 58844544

Dear Dr Ranyali,

I, Thabelo Makhupane am doing research with Professor Habedi, a professor in the Department of Health Studies towards a Master of Public Health degree at the University of South Africa. We are requesting permission to review data captured in the measles and rubella case-based surveillance system.

The aim of the study is to evaluate the effect of the introduction of a rubella containing vaccine on the occurrence of rubella in Lesotho.

The Expanded Program on Immunization (EPI) under the Family Health Division of the Ministry of Health has been selected because it is the only unit within the Ministry of Health that conducts surveillance of vaccine preventable diseases like rubella.

The study will entail the review of measles and rubella case investigation forms and laboratory results for the period January 2018 to December 2022. Variables like age, sex, district of residence and year of notification will be captured for all rubella cases. No information that can identify cases will be collected.

This study will be funded by the principal researcher.

The study will be beneficial in determining the impact of rubella vaccination and will also identify populations that remain at risk of rubella and congenital rubella syndrome that should be targeted for vaccination.

This study will be retrospective in nature. There will be no direct human participant involvement and no potential risk to respondents.

The results of this study will be shared with the EPI program and will also be disseminated to other stake holders through the Ministry of Health Research Forum.

Yours sincerely

_____

Dr Thabelo Makhupane
Principal Researcher

LESOTHO

Ministry of Health

P.O. Box 514

Maseru

30th August 2023

Dr Thabelo Makhupane
Principal Investigator
Ministry of Health

Dear Dr Makhupane,

Re: Approval to use measles and rubella case-based surveillance data for research.

This is to inform you that permission has been granted to utilize measles and rubella case-based surveillance data for research with the understanding that the conditions stipulated by the Ministry of Health Research and Ethics committee are adhered to.

I look forward to reading the report at the end of the study.

Yours Sincerely,

Dr Makhoase Ranyali
Family Health Division
Ministry of Health, Lesotho
Email: makhoaser@yahoo.co.uk

Annexure D: Data collection instrument

DATA COLLECTION TOOL 1

Research title: Rubella prevalence in Lesotho using measles and rubella case-based surveillance data.

Researcher:

(Dr Thabelo Makhupane. Email: makhupanethabelo@gmail.com. Tel: +266 50645471)

IDENTIFICATION

Case number _____

District _____ Health facility/outreach site_____

Patient residence/village_____

Date of birth _____/_____/_____ Age Years_____ Months _____Sex _____

Where the child lived 2 weeks prior to rash onset:

Country_____ District_____

Town/Village_____

NOTIFICATION OF INVESTIGATION

Date seen _____ /_____ /_____

Date notified _____ / _____ /_____ Date case investigated____ /_____/_____

HISTORY

Date of rash onset ____ /_____ /___. Date of last measles -rubella (MR) vaccination ____/____/_____

Number of valid MR doses (including one given during SIA) ☐

BLOOD SPECIMEN

Date specimen received at lab_____ /_____ /____Date specimen collected ____ /___/___

Specimen condition: 1= adequate ☐ Date specimen sent to lab _____ /___/___
2= Inadequate Date lab tested blood _____ /____/_____

Results Rubella IgM 1= Positive
2= Negative
3= Indeterminate
4= Unavailable ☐

Date Results sent to Clinician_____ /_____ /_____

DATA COLLECTION TOOL 2

Research title: Rubella prevalence in Lesotho using measles and rubella case-based surveillance data.

Researcher:

(Dr Thabelo Makhupane. Email: makhupanethabelo@gmail.com. Tel: +266 50645471)

DISTRICTS	POPULATION ESTIMATES				
	2018	2019	2020	2021	2022
Maseru					
Berea					
Leribe					
Butha-Buthe					
Mokhotlong					
Thaba-Tseka					
Mafeteng					
Mohale's Hoek					
Quthing					
Qacha's Nek					
Total					

DISTRICTS	MEASELS-RUBELLA IMMUNIZATION COVERAGE				
	2018	2019	2020	2021	2022
Maseru					
Berea					
Leribe					
Butha-Buthe					
Mokhotlong					
Thaba-Tseka					
Mafeteng					
Mohale's Hoek					
Quthing					
Qacha's Nek					
Total					

Annexure E: Letter of Statistician

9th October 2023

To whom it may concern

This letter serves to certify that the data analysis for the dissertation titled: **Rubella prevalence in Lesotho using measles and rubella case-based surveillance data** by Thabelo Makhupane was performed using SPSS version 28 with the assistance of the research support consultant from the School of Interdisciplinary Research and Graduate Studies in the College of Graduate Studies at the University of south Africa.

Kind Regards
PL Masondo

University of South Africa
College of Graduate Studies
Preller Street, Muckleneuk Ridge, City of Tshwane
PO Box 392 UNISA 0003 South Africa
www.unisa.ac.za/cgs

Annexure F: Certificate of language editor

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CERTIFICATION OF EDITING

WHOM IT MAY CONCERN

I Dr Rethabile Possa -Mogoera, the director of Mapheello African Languages Services hereby confirm that I performed text editing on the thesis of Thabelo Makhupane titled Rubella Prevalence in Lesotho Using Measles and Rubella Case-Based Surveillance Data. I attended to the following:

1. Grammatical accuracy and spelling

2. Stylistic consistency

3. General logic and argumentation

4. Technical correctness of references and quotations.

I did not judge the argument in itself, and I also did not check the sources for correct quotations and arguments.

Yours faithfully

Dr Rethabile Possa-Mogoera

10 Trinity crescent , Parklands North, Milnerton , 7441
Tel: 078 916 2814 / 061 607 1633 **Email:**mapheello.alser@gmail.com
TRANSLATION - INTERPRETING - EDITING - TRANSCRIBING - TUTORING

Annexure G: Turnitin Receipt

turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

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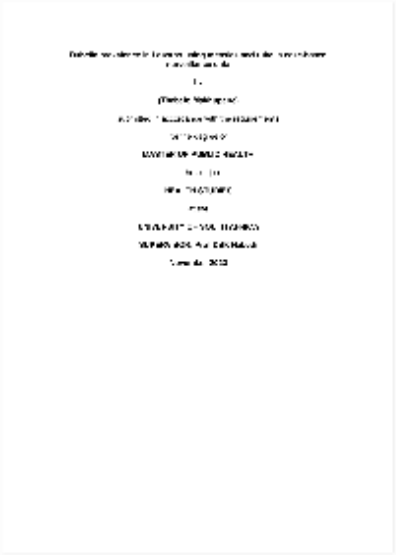

Annexure H: Similarity Index Percentage Report

Rubella prevalence in Lesotho using measles and rubella case-based surveillance data.

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