Burden of congenital rubella syndrome and potential impact of rubella vaccine introduction in South Africa

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Declaration

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This dissertation includes four articles that have been published in peer-reviewed journals. The protocol for this PhD was approved by the Stellenbosch University Health Research Ethics Committee: HREC Reference number S18/08/177(PhD)

Abstract

Background

Introduction of rubella vaccines into public vaccination schedules of all countries is necessary if global rubella elimination is to be achieved. Rubella is targeted for elimination in five World Health Organization (WHO) regions and several international organizations, under the stewardship of the WHO, are working towards this goal. Although there is no rubella elimination or control target for the WHO Africa region, there has been accelerated introduction of rubella vaccination on the continent. South African government is planning to introduce rubella vaccination in its Expanded Programme on Immunization (EPI) schedule and several epidemiological studies have been conducted to aid preparation of this public health intervention. In the absence of vaccination, rubella is mainly a mild endemic childhood viral illness that is asymptomatic in up to 50% of cases. The most severe consequences of rubella occur when infection occurs during pregnancy. These include miscarriages, stillbirths, intra-uterine growth restriction and congenital rubella syndrome. Rubella vaccines are therefore intended to prevent rubella and associated complications. In South Africa, rubella vaccines are not part of the EPI schedule and there is limited information on the epidemiology of rubella and its complications. In addition, the South African government has to cover the cost of introducing rubella vaccination. Therefore, the aim of this research project was to characterize the epidemiology of rubella and congenital rubella syndrome in South Africa, to assess the potential impact of introducing rubella vaccination in the EPI schedule.

Methods

Four different studies were carried out as part of this PhD project: a cross-sectional descriptive study, a sero-survey, a mathematical modelling study and a systematic review.

Results

The findings of a newly established CRS surveillance system to provide data on disease trends in the absence of rubella vaccination are presented in the first research component. We provided baseline data on laboratory-confirmed CRS that will enable planning and monitoring of RCV implementation in the South African EPI program. Ninety-eight percent of mothers of infants with CRS were young women 14 to 30 years old, indicating a potential immunity gap in this age group for consideration during introduction of RCV. In the second research component, we present results of testing on residual samples collected from public health facilities to identify immunity gaps in various age groups and genders. The bulk of individuals susceptible to rubella are children under sixteen years old and about 20% of individuals 16 to 49 years old are susceptible to rubella. In multivariable logistic regression, age and province of residence were found to be associated with rubella susceptibility.Webuilt on a previously published mathematical model adapted to the South African context in the third research component and provide insights into optimal scenarios for RCV introduction into the South African public immunization schedule. We simulated a number of scenarios that combined infant vaccination with vaccination of older individuals. Routine vaccination at 12 months of age coupled with

vaccination of nine-year-old children was associated with the lowest RCV cost per CRS case averted for a similar percentage CRS reduction. Interestingly, at 80% RCV coverage, all vaccine introduction scenarios could achieve rubella and CRS elimination in South Africa.In the final research component, we systematically reviewed mathematical modelling studies to identify the most effective approach for countries introducing RCV into their public immunization schedules. There were variations in the manner in which individual studies reported outcomes. However, we found that better outcomes are obtained when rubella vaccination is introduced into public vaccination schedules at coverage figures of 80%, as recommended by WHO, or higher.

Conclusion

The results from these different studies support the implementation of a strategy involving infant vaccination in combination with vaccination of older individuals. Further research projects are required to provide more detail on the burden of CRS and the economic impact of RCV introduction into the EPI schedule.

Opsomming

Agtergrond

Om rubella-entstowwe in openbare inentingsskedules van alle lande in te stel, is nodig om wêreldwye eliminasie van rubella te bereik. Rubella word geteiken vir uitskakeling in vyf streke van die Wêreldgesondheidsorganisasie (WGO) en verskeie internasionale organisasies, onder toesig van die WGO, werk daaraan. Alhoewel daar geen eliminasie- of beheerdoelwit vir rubella vir die WGO-Afrika bestaan nie, is daar 'n vinnige instelling van inenting teen rubella op die vasteland. Die Suid-Afrikaanse regering is van plan om rubella-inenting in te stel in sy program vir uitgebreide immunisering (EPI), en verskeie epidemiologiese studies is gedoen om die voorbereiding van hierdie ingryping in die gesondheid te help. In die afwesigheid van inenting, is rubella hoofsaaklik 'n ligte endemiese virussiekte by kinders wat in tot 50% van die gevalle asimptomaties is. Die ernstigste gevolge van rubella kom voor wanneer infeksie tydens swangerskap voorkom. Dit sluit miskrame, doodgeboortes, groeibeperking binne die baarmoeder en aangebore rubella-sindroom in. Inenting teen rubella is dus bedoel om rubella en gepaardgaande komplikasies te voorkom. In Suid-Afrika maak rubella-entstowwe nie deel uit van die EPI-skedule nie en is daar beperkte inligting oor die epidemiologie van rubella en die komplikasies daarvan. Daarbenewens moet die Suid-Afrikaanse regering die koste dek vir die instelling van rubella-inenting. Daarom was die doel van hierdie navorsingsprojek om die epidemiologie van rubella en aangebore rubella-sindroom in Suid-Afrika te karakteriseer, om die potensiële impak van die instelling van rubella-inenting in die EPI-skedule te bepaal.

Metodes

Vier verskillende studies is uitgevoer as deel van hierdie PhD-projek; 'n beskrywende deursnee-studie, 'n sero-opname, 'n wiskundige modelleringstudie en 'n sistematiese oorsig.

Resultate

Die bevindinge van 'n nuutgestigte CRS-bewakingstelsel om inligting oor siektetendense te verskaf in die afwesigheid van inenting teen rubella word in die eerste navorsingskomponent aangebied. Ons het basisdata gegee oor CRS wat deur laboratorium bevestig is, wat die beplanning en monitering van RCV-implementering in die Suid-Afrikaanse EPI-program moontlik maak. Agt-en-negentig persent van moeders van babas met CRS was jong vroue van 14 tot 30 jaar oud, wat dui op 'n moontlike immuniteitsgaping in hierdie ouderdomsgroep vir oorweging tydens die bekendstelling van RCV. In die tweede navorsingskomponent bied ons die resultate aan van die toetsing van residuele monsters wat van openbare gesondheidsinstellings versamel is om immuniteitsgapings in verskillende ouderdomsgroepe en geslagte te identifiseer. Die grootste deel van die individue wat vatbaar is vir rubella is kinders jonger as sestien jaar en ongeveer 20% van individue tussen 16 en 49 jaar oud is vatbaar vir rubella. In meerveranderlikke logistieke regressie is gevind dat ouderdom en provinsie geassosieer word met rubella vatbaarheid. Gebou op 'n voorheen gepubliseerde wiskundige model wat aangepas is vir die Suid-Afrikaanse konteks in die derde navorsingskomponent en bied insigte in optimale scenario's vir RCV-bekendstelling in die Suid-Afrikaanse openbare inentingskedule. Ons het 'n aantal

scenario's gesimuleer wat baba-inenting kombineer met inenting van ouer persone. Roetine-inenting op 12-maande-ouderdom, tesame met die inenting van nege-jarige kinders, is geassosieer met die laagste RCV-koste per CRS-geval wat afgeweer is vir 'n soortgelyke persentasie CRS-vermindering. Interessant genoeg, met 80% RCV-dekking, kan alle inenting-inleidingscenario's rubella en CRS-uitskakeling in Suid-Afrika bereik. Daar was variasies in die wyse waarop individuele studies die uitkomste gerapporteer het. Ons het egter gevind dat beter resultate behaal word wanneer rubella-inenting in openbare inentingsskedules bekendgestel word teen 'n dekkingsyfer van 80%, soos aanbeveel deur die WGO, of hoër.

Afsluiting

Die resultate van hierdie verskillende studies ondersteun die implementering van 'n strategie rakende baba-inenting in kombinasie met inenting van ouer individue. Verdere navorsingsprojekte is nodig om meer besonderhede te gee oor die las van CRS en die ekonomiese impak van die bekendstelling van RCV in die EPI-skedule.

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Dedication

To my GOD and Creator who blessed me abundantly and saw me through this PhD journey.

My children: Yanis, Latifa, Quenzy, Priss and Jean-Paul,

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List of Published Articles

Citation	Journal	Thesis Chapter
Motaze NV, Manamela J, Smit S, Rabie H, Harper K, duPlessis N, Reubenson G, Coetzee M, Ballot D, Moore D, Nuttall J, Linley L, Tooke L, Kriel J, Hallbauer U, Sutton C, Moodley P, Hardie D, Mazanderani AH, Goosen F, Kyaw T, Leroux D, Hussain A, Singh R, Kelly C, Ducasse G, Muller M, Blaauw M, Hamese M, Leeuw T, Mekgoe O, Rakgole P, Dungwa N, Maphosa T, Sanyane K, Preiser W, Cohen C, Suchard M. Congenital Rubella Syndrome Surveillance in South Africa Using a Sentinel Site Approach: A Cross-sectional Study. Clin Infect Dis. 2019 May 2;68(10):1658-1664. doi: 10.1093/cid/ciy758. PMID: 30203002; PMCID: PMC6495013	Clinical Infectious Diseases	2
N. V. Motaze, L. Makhathini, S. B. Smit, C. G. Adu-Gyamfi, M. Fortuin, C. S. Wiysonge & S. M. Suchard (2020): Rubella seroprevalence using residual samples from the South African measles surveillance program: a cross-sectional analytic study, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1738834	Human Vaccines & Immunotherapeutics	3
Motaze, N.V.; Edoka, I.; Wiysonge, C.S.; Metcalf, C.J.E.; Winter, A.K. Rubella Vaccine Introduction in the South African Public Vaccination Schedule: Mathematical Modelling for Decision Making. Vaccines 2020, 8, 383. https://doi.org/10.3390/vaccines8030383	Vaccines	4
Motaze, N.V.; Mthombothi, Z.E.; Adetokunboh, O.; Hazelbag, C.M.; Saldarriaga, E.M.; Mbuagbaw, L.; Wiysonge, C.S. The Impact of Rubella Vaccine Introduction on Rubella Infection and Congenital Rubella Syndrome: A Systematic Review of Mathematical Modelling Studies. Vaccines 2021, 9, 84. https://doi.org/10.3390/vacciness9020084	Vaccines	5

List of Abbreviations

Abbreviation	Full meaning
AFRO	Africa Regional office
CDC	Centers for Disease Control and Prevention
CRS	Congenital rubella syndrome
EMRO	Eastern Mediterranean Regional Office
EPI	Expanded Programme on Immunization
GAVI	The Vaccine Alliance
GVAP	Global Vaccine Action Plan
MR	Measles and rubella
MMR	Measles, mumps and rubella
MMRV	Measles, mumps, rubella and varicella
NAGI	National Advisory Group on Immunization
NDOH	National Department of Health
NICD	National Institute for Communicable Diseases
NITAG	National Immunization Technical Advisory Group
PAHO	Pan American Health Organization
RCV	Rubella-containing Vaccines
SEAR	World Health Organization South-East Asia Region
WHO	World Health Organization
WPRO	Western Pacific Regional Office

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CHAPTER ONE
Introduction

1.0. About this chapter

In this chapter, we outline the history, pathogenesis, diagnosis, clinical presentation and management of rubella along with its complications, especially CRS. We then describe the burden of disease of rubella and CRS, providing details specific to South Africa. We also provide an overview of rubella vaccines including global efforts geared towards introducing rubella vaccination in all countries worldwide. We mention study designs that can be used to characterize the epidemiology of rubella and the impact of introducing rubella vaccination in the public immunization schedule of South Africa. We also briefly discuss the place of these types of studies in contributing to decision-making regarding rubella vaccine introduction.

The candidate performed the literature review, wrote the first draft of this chapter and revised subsequent drafts following comments from the supervisors and reviewers.

1.1. Background

Vaccines protect individuals from infections but their intended action on communities is to result in adequate levels of herd immunity , a concept first described by Topley and Wilson in 1923 [1], which refers to the protection of susceptible individuals conferred by a certain proportion of immune individuals in the group [2]. Vaccines are considered one of the most cost-effective health care interventions to date [3,4]. Variolation or inoculation procedures conducted by Edward Jenner for preventing smallpox in the 18th century became very popular and are perceived to have paved the way for modern vaccinology [5]. However, the concept and practice of inoculation was practiced in China as far back as 1000 AD [6]. Advances in science over time led to improved methods of manufacturing and administering vaccines for preventing infectious diseases.

Rubella-containing vaccines (RCVs) were first approved in 1969 [7,8] and were successful in controlling large outbreaks in Europe and North America. These outbreaks were followed by several cases of congenital rubella syndrome (CRS), which consists of birth defects in children born to women infected with rubella early in pregnancy. Subsequently, the number of rubella and CRS cases declined in these regions and globally as uptake of vaccination by countries increased. Evidence of the success of vaccination is the successful elimination of rubella and CRS in 2009 in the Pan American Health Organization (PAHO) region. Subsequently, other World Health Organization (WHO) regions established rubella elimination targets[9] and are working towards achieving these targets in a bid to replicate the success of PAHO. Along with elimination of measles and neonatal tetanus, rubella elimination is one of the measures of success of the Global Vaccine Action Plan (GVAP) [10] .

The WHO Africa Regional office (AFRO) does not currently have a rubella and CRS elimination or control target although some Sub-Saharan countries have rubella vaccines in their public immunization schedules. In South Africa, rubella vaccination is not part of the Expanded Programme on Immunization (EPI) schedule and will likely be administered as a combination with measles vaccine in the near future. According to the public immunization schedule of South Africa, measles vaccines are administered to children at six months and one year [11]. The possibility of switching from the vaccine containing only measles to RCVs that include rubella saves costs that might be associated with cold chain, medical supplies and other programmatic costs that accompany introduction of a new vaccine.

In line with WHO recommendations, measles vaccine coverage should be maintained at a minimum of 80% before RCVs are introduced [12]. This cut-off value has been found to be robust in terms of avoiding the negative impact of increasing average age of infection for rubella with vaccination of infants [13]. An increased average age of infected individuals for a childhood infection is often inconsequential. However, unlike most vaccine-preventable childhood infections, CRS which is the most severe outcome of rubella infection occurs following infection in women of reproductive age. This is a dilemma with which countries introducing RCVs are faced; the vaccine which is intended to prevent infections has the potential to cause significant harm.

Several low-income countries in te WHO Africa region have introduced rubella vaccination into their EPI schedules with support from The Vaccine Alliance (GAVI) [14]. South Africa is planning to introduce rubella vaccination in its public vaccination program but is not eligible for GAVI funding. Therefore, careful examination of available evidence is crucial to support vaccine introduction and costs of vaccine introduction have to be taken into consideration in addition to scenarios that achieve rapid rubella elimination or control targets. Results of each research project outlined in this dissertation contribute to the body of knowledge on a specific aspect of rubella epidemiology and projected impact of introducing RCV into the EPI schedule of South Africa.

1.2. Literature review

Rubella virus

The first clinical description of rubella was made in the 18th century by German physicians, which is the reason it is referred to as German measles [8,15]. Given the nature of the rash in patients, the word “rubella” which means “little red” in Latin [16], was used when referring to infected individuals who were initially thought to be presenting with an alternative manifestation of measles [8].

Rubella virus was first isolated from human tissues in 1962 [17]. The rubella virus is an enveloped RNA virus [18] which has a nucleocapsid and an envelope containing glycoproteins E1 and E2 [19]. The E1 glycoprotein is the main target for antibody responses [20]. The epitope and mechanism of these neutralization antibodies has only been recently described [21]. This

rubella E1 protein is a fusion protein that is similar to those in other viruses such as alphaviruses and flaviviruses. However, distinct characteristics separate the E1 protein in rubella virus from this protein in the other viruses of the *Togaviridae* family.

Rubella virus belongs to the *Togaviridae* family [22] and is the only member of the *Rubivirus* genus within this family [23]. Only one serotype of rubella exists [24] with two main clades identified: clade 1 having 10 genotypes and clade 2 having 3 genotypes [25]. By May of 2020, about 6600 sequences had been submitted to WHO's genotyping database (http://www.who-rubella.org), with fewer genotypes detected during recent years: 5 in 2016 and 2 in 2018 [12]. Genotypes 1B, 1E and 2B were reported in South Africa between 2007 and 2009 [25].

Due to limited collection of samples from patients with rubella, data for genetic analysis is sparse and certain regions are under-represented [23]. Collecting samples from rubella cases in countries that have not yet introduced rubella vaccination and still have a relatively high number of cases could contribute to the body of knowledge regarding molecular characterization of rubella viruses.

Epidemiology of rubella

Prior to development of RCVs, rubella was a global infectious disease [26] and there were intermittent outbreaks occurring every 5-9 years [12] although disease patterns varied with setting. Since there were no licensed rubella vaccines, the only control measures were efforts to limit person-to-person contact. Significant resources were invested to develop safe and efficacious vaccines in order to prevent rubella.

In the year 2000, 670,894 rubella cases were reported globally, with Europe reporting the highest number of cases (621,039) and AFRO the smallest number (865) [27]. It is likely that limited rubella surveillance activities resulted in the small number of reported cases in AFRO given the small number of countries with RCV in their public vaccination schedules. The number of reported rubella cases reported worldwide decreased to 94,030 in 2012, with the Western Pacific region (WPRO) reporting the highest number of cases (44,275) and PAHO the fewest (21) [27]. In 2016, a total of 22,361 rubella cases were reported, representing a 97% decrease compared to 2000 [28]. These achievements were only possible as a result of RCVs that were introduced in an increasing number of countries, with the end goal being to eliminate rubella globally.

As WHO regions reinforced their rubella prevention efforts, there were varying degrees of success achieved. The first region to eliminate rubella was PAHO in 2009 [29]. By 2016, 66% of countries in the WHO European region had eliminated rubella [30] and in WPRO 29% of countries had eliminated rubella [31]. Elimination of rubella was defined as the interruption of endemic rubella virus transmission in a country for a period $\geq$ 12 months in the presence of high-quality surveillance [29,32]. Ideally, rubella elimination should be targeted but some regions, such as the WHO South-East Asia region (SEAR), has set control targets rather than elimination targets [33]. Although uptake of rubella vaccination rapidly increased in AFRO, there is neither an elimination nor control target for rubella in this region [9]. Nonetheless, there are ongoing surveillance programs for rubella and CRS.

In 1996 there were an estimated 110,000 CRS cases in countries that had not yet introduced RCV [34]. The highest number of cases occurred in South East Asia with about 46,000 cases (uncertainty interval: 1,016-168,910), followed by Africa with about 22,000 (uncertainty interval: 6,127–51,472) and the Western Pacific region with about 12,634 (uncertainty interval: 1,545–21,396)[26]. These were mainly regions in which uptake of rubella vaccination was poor. In the early 2000s, over 100,000 CRS cases were thought to occur each year [35] and CRS incidence was estimated to vary from about 0.1-0.2/1000 live births during endemic periods to about 0.8-4/1000 live births during epidemics [36–41].

Samples collected from suspected measles cases in South Africa are tested for both measles and rubella at the regional reference laboratory situated in the National Institute for Communicable Diseases (NICD). The NICD coordinates surveillance of notifiable medical conditions (NMCs) in South Africa, with measles, rubella and CRS being on the list of NMCs [42]. A total of 1496 rubella cases were detected in 2019 [43] which is higher than the 817 cases detected in 2016 [44] but lower than the 2512 cases in 2017 [45].There was no surveillance for CRS in South Africa by the end of 2015, which is when AFRO updated surveillance guidelines for rubella and CRS [46]. CRS cases reported were mainly diagnosed in referral health facilities [47]. In the absence of RCV in the routine immunization schedule, it became imperative for a comprehensive surveillance system to be established to provide estimates of CRS burden. Together with the existing rubella surveillance CRS surveillance will enable assessment of the impact of RCVs when they are eventually introduced into the EPI schedule.

Transmission of rubella virus

Rubella virus is the only member of the *Togaviridae* family which is not transmitted by arthropods [15,21]. Humans are the only known host for rubella [15] so only human-to-human transmission is responsible for disease spread which often follows a seasonal pattern [23]. The incubation period ranges from 12 to 23 days [7,15] and infected individuals usually develop a maculopapular rash on the face and neck 14-17 days after infection [48]. Infected individuals who cough or sneeze expel respiratory droplets containing infective viral particles that infect susceptible individuals. Infection can also occur through direct contact with objects carrying infective material [23] but the respiratory route is the predominant transmission route. Children and adults with rubella can excrete the virus from 7 days prior to onset of rash to 12 days after appearance of rash [15]. This period of viral shedding can be much longer in infants with CRS who can excrete virus through the respiratory route for several months [49].

The basic reproduction number (Ro), which is the number of secondary cases that can occur when an infected individual is introduced into a completely susceptible population, was estimated to be as low as 2 [50] or as high as 12 [51]. A more recent study of Ro in African countries estimates values ranging from 3.3 (credible interval: 3.0-3.7) in Burkina Faso to 7.9 (credible interval 7.7-8.1) in South Africa [13]. Pathogen-specific characteristics as well as social and environmental factors influence Ro. Therefore, Ro can differ from one country to another and between different regions within a single country. Estimates of Ro are critical when considering RCV introduction because depending on the vaccination coverage and birth rate, there might be an increase of decrease in CRS incidence for different values of Ro. There was an

increase in CRS incidence in Greece following introduction of rubella vaccination in the routine immunization schedule at low coverage levels [52]. Following detailed assessment of available evidence, WHO recommended a minimum coverage of 80% for routine immunization and supplementary immunization activities when introducing RCVs [53]. This threshold was found to be robust for a wide range of scenarios including varying figures of Ro and birth rates [13].

Pathogenesis of rubella

When respiratory droplets from an individual infected with rubella virus reach the upper respiratory tract of a susceptible individual, the virus multiplies in the mucosa before spreading to regional lymph nodes [7]. Viremia occurs about five to seven days later [15], a process during which the virus enters the blood stream and is transported to all organs of the body, where it causes cell damage or cell death depending on the type of tissue [7]. If infection occurs during pregnancy, the virus reaches the placenta and crosses over to the fetus [26]. Rubella interferes with organ formation leading to organ defects and the inflammatory processes resulting from infection of fetal tissue lead to organ enlargement.

Clinical presentation of rubella infection

Rubella mostly causes mild symptoms in infected individuals [54] although arthritis, encephalitis and thrombocytopenia are well known complications [48]. Subclinical disease can occur in up to 50% of cases [23], suggesting that the several infected individuals may not be identified and go on to infect susceptible contacts. After an incubation period lasting 12 to 23 days, a maculopapular rash appears on the face before spreading to the rest of the body. In some patients, there is a prodromal phase characterized by malaise, fever, cough, conjunctivitis, headache and sore throat [15]. Given the non-specific clinical presentation and the possibility of subclinical disease, a history of contact with an infected individual can be helpful in making a diagnosis.

Clinical presentation of CRS

CRS was initially linked to maternal rubella infection by Normal McAlister Gregg, an Australian ophthalmologist, who reported an unusual series of congenital cataracts that he and his colleagues documented [55]. After several reports were published in Australia and other countries linking maternal rubella infection to congenital defects [56–58], CRS was established as a complication of rubella. The most severe effects of rubella infection occur when a pregnant woman is infected during the first trimester of pregnancy. The consequences could be adverse pregnancy outcomes such as miscarriages, intra-uterine fetal death or CRS. Babies born with CRS usually present with a multitude of signs and symptoms including: cataracts, microphthalmia, glaucoma, patent ductus arteriosus, pulmonary stenosis, microcephaly, hepatomegaly, splenomegaly, thrombocytopenic purpura, deafness and mental retardation [7,15,26].

Laboratory diagnosis of rubella infection

There are two main laboratory methods routinely used for diagnosing rubella infection: serology and molecular testing. Serological tests include detection of rubella-specific immunoglobulin M (IgM) and immunoglobulin G (IgG).

A positive IgM test usually indicates acute or recent infection with rubella virus [23]. However, certain individuals could have persisting IgM antibodies for up to three years following vaccination [59]. Furthermore, positive rubella IgM results have been demonstrated in cases infected with measles or parvovirus B19 [60]. Additional testing for rubella IgG avidity has been suggested in order to refine the diagnosis [60,61]. Although rubella infection or vaccination often confer life-long immunity [12], rubella reinfection with a positive IgM has been reported [62].

IgG testing is usually interpreted as a measure of previous exposure to rubella. Two consecutive IgG tests can be carried out in an individual and a four-fold increase in titer is considered as evidence of rubella infection [63]. This sequential IgG testing is mostly used for diagnosing CRS rather than rubella infection in children and adults. A single IgG test can provide information of the immunity status of an individual or population. Serological surveys that involve IgG testing are used to identify immunity gaps for vaccination planning purposes.

Molecular tests include detection of rubella-specific RNA by real time (RT) polymerase chain reaction (PCR) with or without virus isolation through viral culture. Virus isolation is laborious and helpful in identifying the rubella genotype so that circulating strains can be documented and novel strains identified. However, PCR is an efficient molecular diagnostic method.

Treatment of rubella and CRS

There is no specific antiviral treatment for rubella infection. The aim of medical treatment is to relieve symptoms. Pregnant women diagnosed with rubella in the first trimester can be offered medical termination of pregnancy if possible in the local setting. Similar to rubella infection of children and adults, there is no antiviral treatment for neonates and infants diagnosed with CRS. Surgical operations are carried out for cardiac and ocular defects when possible. Surgery is followed by appropriate postoperative follow-up. Given that several organs are affected in CRS cases, a multidisciplinary approach should be adopted. Isolation of CRS cases is also a key intervention because of abundant shedding of rubella virus for prolonged periods of time; possibly up to 12 months [61].

Rubella vaccines

Several rubella vaccines were developed and tested in the late 1960s [64–66] but the first vaccine was licensed in 1969 [7]. Although rubella vaccination did not form part of the initial group of vaccines in the EPI recommended by the WHO in 1974 [67], there have been considerable efforts to prevent rubella and CRS. However, timing of RCV introduction has been linked to economic development with higher income countries introducing rubella vaccination earlier than countries with lower incomes [35]. By the year 2000, 99 countries had introduced RCV in their EPI schedules and this number increased to 132 in 2012 [27]. Further increases in uptake of RCV resulted in a total of 173 countries introducing the vaccine by the end of 2019 [68]. Out of 21 countries that did not include RCV in their public immunization programs by the end of 2019, 16 were in AFRO while 5 were in the Eastern Mediterranean Region (EMRO) [12].

Vaccines usually lead to a decrease in disease occurrence but rubella vaccines pose a very singular problem. Introduction of rubella vaccine at low coverage has been documented to cause transient increases in incidence of congenital rubella syndrome in Costa Rica [69] and Greece

[52]. It is also important to vaccinate both males and females since selective vaccination of girls and women leaves males susceptible, leading to continued transmission [27,70].

There are currently three combinations of rubella and other vaccines: measles and rubella (MR); measles, mumps and rubella (MMR); measles, mumps, rubella and varicella (MMRV) [8,11]. Given these combinations with measles vaccines, countries introducing RCV are subjected to minimal additional costs for cold chain requirements and programmatic costs. The previously administered measles vaccine would simply be substituted for the RCV. The RCV would be administered to individuals of the same age groups as the previous measles vaccine.

The publication of the WHO rubella position paper in 2011[53] coincided with a pivotal transition from steady state to accelerate rubella control and CRS prevention[27]. This was followed by the formulation and adoption of the GVAP [10] by all member states at the World Health Assembly in 2012. A coordinated drive to eliminate rubella globally led to a sharp increase in the number of countries that introduced RCV in their EPI schedules, leading to further decreases in reported rubella and CRS cases. Countries differ in their vaccine introduction strategies and vaccination coverages which might lead to differences in rubella and CRS incidence. Geographical distribution of populations, contact patters and age structure also influence disease transmission, especially for childhood diseases such as rubella.

In South Africa, RCVs are administered in the private health sector and only the MMR combination is available [11]. The South African government is planning to introduce RCV in the EPI schedule and engagements with the National Advisory Group on Immunization (NAGI), the country's National Immunization Technical Working Group (NITAG), are ongoing. Following a literature review, possible strategies for introducing RCV had been suggested [71] but the National Department of Health (NDOH) has not yet decided on what strategy to adopt and in what year RCVs will be introduced. However, the most current available evidence will guide final decision on what vaccine schedule to adopt.

Mathematical models

Epidemiological studies are divided into two main groups: classical epidemiology (observational and interventional studies) and dynamical or mechanistic epidemiology (mathematical modelling) [72]. Classical epidemiological studies explore relationships between exposures and individuals or groups of individuals, assuming these individuals are independent. On the contrary, dynamical epidemiology applies mathematics to understand how interactions in biological systems influence disease transmission.

Mathematical models divide individuals in a population into compartments, such as susceptible, infected and recovered for an SIR model, were first detailed by Kermack and McKendrick in the 1920s [73]. Several models using this approach were subsequently developed for a variety of infectious diseases. For models of rubella infection dynamics, compartments are chosen to correspond with disease stages. These include: maternal immunity (M), susceptible (S), infected or exposed but non-infectious (E), infectious (I), recovered (R), and vaccinated (V). A combination of these compartments are used by different authors depending on the model design, mostly with the aim of simulating vaccine introduction scenarios.

Some modelling approaches were used to estimate epidemiological parameters for rubella dynamics such as the force of infection [74,75] or the basic reproductive number [13,76]. Due to the non-linear nature of infection dynamics, mathematical modelling has emerged as a robust method of evaluating the effects of vaccination [77] and was included in the rubella research agenda by WHO in 2004 [78]. Several aspects of rubella infection dynamics have been explored in low-income [34,79] and high-income [50,80] settings. The knowledge gained is used to continuously design new models that improve understanding of infection dynamics and disease control measures.

For childhood infections such as rubella, vaccinating only children results in a reduced force of infection among adults [81] resulting in an increase in the average age of infection. Contact patterns drive spread of infectious diseases and have been shown to vary with age [82]. Consequently, necessary cautionary action must be taken when introducing rubella vaccines to avoid increasing incidence of CRS. A variety of vaccine introduction strategies have been explored by age-structured mathematical models to inform rubella vaccine introduction in various countries [83–89]. Countries planning RCV introduction could learn from these experiences.

In South Africa where RCV are not part of the EPI schedule, models have previously been used to estimate CRS incidence [90] and explore the effects of varying RCV coverage at sub-national level [87]. Building on a previously published modelling approach [91,92], the impact of introducing RCVs in the South African EPI schedule was simulated. The choice of scenarios explored was informed by consultations with NAGI. These model outputs, in combination with other data sources (surveillance, sero-surveys and economic evaluation studies), should provide a solid basis for policy-making.

Evidence synthesis

Decisions regarding the health of individuals or the public should be based on the best available evidence. Individual studies address specific questions on a given topic in a specific study population. Combining findings of individual studies addressing a particular research question enables researchers to obtain robust results. By conducting a meta-analysis, samples from individual studies are combined to obtain a larger sample size and the end result is a more precise estimate [93,94]. It is worthwhile noting that the approach in mathematical modelling does not allow for meta-analysis, but this does not exclude the possibility of a robust systematic review of modelling studies with relevant findings.

Systematic reviews of randomized controlled trials (RCTs) have long been recognized as producing the highest level of evidence for healthcare interventions [95,96] and are therefore at the top of the evidence pyramid. A new evidence pyramid has recently been proposed [97] that takes methodological limitations into consideration rather than strictly classifying strength of evidence according to study design. Therefore, there is room for integration of evidence from mathematical modelling into the evidence pyramid. With the understanding that results of studies have broad consequences on guidelines for health care, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was formulated to guide classify levels of evidence and strengths of recommendation [98]. Evidence from RCTs starts off as high

quality evidence following the GRADE approach and the rating of quality of evidence can be downgraded according to specific criteria. On the contrary, evidence based on observational studies start off with a low quality rating and can subsequently be upgraded [99].

While the methods for systematic reviews of classical epidemiological studies and integration of their findings with GRADE have been well developed, systematic reviews of mathematical modelling are relatively new. The process of obtaining evidence by considering results of several studies addressing the same study question should apply irrespective of the design of the individual studies and this includes dynamical epidemiology studies. Published systematic reviews of mathematical modelling studies have addressed diverse research topics including vaccines for tuberculosis [100], mosquito-borne pathogen transmission [101], HIV host dynamics [102], and progression of sexually transmitted infections [103].

1.3. Rationale

Several countries in AFRO have introduced rubella vaccination into their routine immunization schedules, supported by funding from GAVI. South Africa is not eligible for GAVI funding and has to cover the cost of RCV introduction.

In the Southern African Development Community (SADC), South Africa is the only country yet to introduce RCVs. The NDOH is currently planning RCV introduction and has engaged with the National Advisory Group on Immunization (NAGI), which is the equivalent of the National Immunization Technical Advisory Group (NITAG) for the country. Several strategies for vaccine introduction are considered, with the aim of choosing one that would achieve elimination of rubella and CRS with minimal cost to the South African government.

This PhD project applied various methodological approaches to provide evidence for supporting the decision-making process of the NDOH in South Africa.

1.4. Aim and objectives

The aim of this research project was to characterize the epidemiology of rubella and congenital rubella syndrome in South Africa to assess the potential impact of introducing rubella vaccination in the national Expanded Programme on Immunization schedule.

The objectives were to:

- Establish a national surveillance system for reporting cases of congenital rubella syndrome in South Africa.
- Determine the proportion of individuals susceptible to rubella in South Africa.
- Model the impact on rubella and CRS incidence of introducing RCVs into the South African public vaccination schedule.
- Systematically review mathematical modelling studies that simulate RCV introduction to identify the most effective vaccination strategies.

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CHAPTER TWO
Congenital rubella syndrome surveillance in South Africa

2.0. About this chapter

In this chapter, we present a sentinel site surveillance program for CRS in South Africa and describe characteristics of detected CRS cases and their mothers. We were unable to provide national estimates of prevalence/incidence but the clinical characteristics of cases and differences in timeliness of diagnosis as well as provincial reporting could help improve detection of CRS cases. The age distribution of the mothers of CRS cases provides insights into the immunity gap amongst females of reproductive age. This study was published in Clinical Infectious Diseases and the full citation is**:** *Motaze NV, Manamela J, Smit S, Rabie H, Harper K, duPlessis N, Reubenson G, Coetzee M, Ballot D, Moore D, Nuttall J, Linley L, Tooke L, Kriel J, Hallbauer U, Sutton C, Moodley P, Hardie D, Mazanderani AH, Goosen F, Kyaw T, Leroux D, Hussain A, Singh R, Kelly C, Ducasse G, Muller M, Blaauw M, Hamese M, Leeuw T, Mekgoe O, Rakgole P, Dungwa N, Maphosa T, Sanyane K, Preiser W, Cohen C, Suchard M. Congenital Rubella Syndrome Surveillance in South Africa Using a Sentinel Site Approach: A Cross-sectional Study. Clin Infect Dis. 2019 May 2;68(10):1658-1664. doi: 10.1093/cid/ciy758. PMID: 30203002; PMCID: PMC6495013.* The paper is available online at: https://doi.org/10.1093/cid/ciy758. Below is the author list with their respective affiliations:

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The candidate played the principal role in the conceptualization of this study, development of the protocol, collection and analysis of the data and writing of the manuscript and submission to the journal.

2.1. Abstract

Background
Congenital rubella syndrome (CRS) includes disorders associated with intrauterine rubella infection. Incidence of CRS is higher in countries with no rubella-containing vaccines (RCV) in their immunization schedules. In the World Health Organization African region, RCVs are being introduced as part of the 2012-2020 global measles and rubella strategic plan. This study aimed to describe the epidemiology of confirmed CRS in South Africa prior to introduction of RCVs in the immunization schedule.

Methods
This was a descriptive study with 28 sentinel sites reporting laboratory-confirmed CRS cases in all nine provinces of South Africa. In the retrospective phase (2010 to 2014), CRS cases were retrieved from medical records and in the prospective phase (2015 to 2017) clinicians at study sites reported CRS cases monthly.

Results
There were 42 confirmed CRS cases in the retrospective phase and 53 confirmed CRS cases in the prospective phase. Most frequently reported birth defects were congenital heart disease and cataracts. The median age of mothers of CRS cases was 21 years in the retrospective phase (range: 11 to 38 years) and 22 years in the prospective phase (range: 15 to 38 years).

Conclusion
Baseline data on laboratory-confirmed CRS will enable planning and monitoring of RCV implementation in the South African EPI program. Ninety-eight percent of mothers of infants with CRS were young women 14 to 30 years old, indicating a potential immunity gap in this age group for consideration during introduction of RCV.

2.2. Introduction

Background

Congenital rubella syndrome (CRS) includes a range of disorders associated with congenital rubella infection (CRI) following maternal rubella infection, especially in the first trimester of pregnancy. Birth defects include cataracts, glaucoma, hearing impairment, congenital heart defects, microcephaly and pigmentary retinopathy. Intra-uterine rubella infection can also result in miscarriage or stillbirth. Although some signs of CRS are apparent during the neonatal period, onset of other disorders after the age of 2 years has been described [1]. Laboratory tests for CRS in suspected cases include: rubella immunoglobulin M (IgM) in cord blood or in the serum of the infant, immunoglobulin G (IgG) and Polymerase Chain Reaction (PCR). Maternal rubella infection frequently goes unnoticed since there often is no rash [2]. Treatment for CRS is limited to management of symptoms because there is no available antiviral therapy and diagnosis is made in the newborn when tissue damage has already occurred during intra-uterine life.

There were about 105,000 (95% CI:54,000-158,000) CRS cases globally (based on mathematical modelling) in 2010, decreasing from about 119,000 (95% CI:72,000-169,000) in 1996 [3]. This decrease was attributed to introduction of rubella-containing vaccines (RCV) in several countries. The World Health Organization (WHO) region of the Americas successfully eliminated indigenous transmission of rubella virus in 2009 [4] by implementing an effective strategy that included: introducing RCV into routine vaccination schedules with very high coverage (>95%), carrying out mass campaigns and integrating measles surveillance with rubella and CRS surveillance. The WHO European region also implemented a similar strategy with the objective of eliminating rubella and CRS [5]. Elimination of rubella and CRS is achievable in Africa, building on the lessons learned from these experiences.

The main objective of rubella vaccination is to prevent CRS but if high vaccine coverage is not maintained, there can be a paradoxical increase in CRS incidence [6,7]. This paradoxical increase is attributed to a decrease in circulating rubella in childhood such that individuals reach adolescence and adulthood while being susceptible to rubella infection. Subsequent infection during the first trimester of pregnancy then leads to CRS. The WHO, in its Global Vaccine Action Plan and Global measles and rubella strategic plan 2012-2020 aims to achieve measles and rubella elimination in at least five WHO regions by 2020 [8,9]. The WHO Africa region has not yet set an elimination target for CRS [8]. Seven sub-Saharan countries had introduced RCV by 2014[10] and 14 by 2017 [11] through assistance from the Global Alliance for Vaccines and Immunization (GAVI) [12]. The EPI schedule in South Africa does not currently include RCV but rubella vaccines are administered in private health care facilities [13]. Rubella vaccines have high immunogenicity and confer long-lasting protection [14], while having a favorable safety profile [15]. No CRS cases were reported when RCVs were inadvertently administered around the period of conception [16]. Achieving rubella and CRS elimination requires vaccination of children as well as females and males of reproductive age [17] with RCVs; a strategy that has been shown to be cost-effective [18].

Introduction of RCV into the routine immunization schedule requires careful planning and WHO has outlined a number of activities that should be carried out. These activities can lead to CRS elimination over varying periods of time and include wide age range immunization campaigns, integration of rubella and measles surveillance, vaccination of older populations to fill immunity gaps and CRS surveillance [19,20]. Since the rubella vaccine will be given in combination with the measles vaccine, coverage figures for measles vaccine can be used to estimate projected coverage of RCV. The WHO recommends a minimum measles vaccine coverage of 80% at district and national levels before RCV introduction [8,20]. It is imperative to maintain this high coverage in all districts since disparities in vaccination coverage might lead to localized increases in CRS incidence [21,22].

Data on rubella surveillance in South Africa has been published for 2000-2010 [21], 2016 [23] and submitted for 2017 [24]. Rubella surveillance was discontinued for a period of time during 2013-2014. Males and females were equally affected and most rubella cases were aged between one and 12 years. There is a consistent seasonal pattern throughout all these years with annual increase in cases during the last three months of the year.

Previous publications on CRS in South Africa included case reports and mathematical modelling studies [2,21,25]. A recent study conducted from 2008 to 2011 reported on CRI in one province of South Africa [26] but there has been no national CRS surveillance program.

Objectives

The aim was to describe the epidemiology of laboratory-confirmed CRS in South Africa from 2010 to 2017. Specific objectives were to enumerate laboratory-confirmed CRS cases in sentinel public health facilities, describe birth defects found in laboratory-confirmed CRS cases and describe characteristics of mothers of laboratory-confirmed CRS cases in terms of age and rubella vaccination history.

2.3. Methods

This was a descriptive cross-sectional study with two phases. In the retrospective phase, we obtained data from case files of laboratory-confirmed CRS cases diagnosed from 2010 through 2014. In the prospective phase, study sites reported laboratory-confirmed CRS cases monthly from 2015 through 2017.

We included infants who met our case definition for laboratory-confirmed CRS. A laboratory-confirmed CRS case was defined as any infant aged less than 12 months with a positive laboratory test (rubella IgM, two rubella IgG serology tests four weeks apart with titers that do not drop at the expected rate of a two-fold decline per month or PCR), and who presented with at least one of the following: cataracts, congenital glaucoma, congenital heart disease, hearing impairment, pigmentary retinopathy, purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease. We adapted the case definition used by United States of America's Centers for Disease Control and Prevention (CDC)[27].

We included 28 clinical sites selected that were referral hospitals in major cities of each province. In the South African health system cases are referred from primary health care facilities through to tertiary hospitals following a tiered system. Cases reported by more than one hospital were only recorded once in the database. Focal persons were pediatricians, neonatologists or pediatric infectious disease specialists at these study sites (see Supplementary material 1). Participating laboratories were those at the National Health Laboratory Service (NHLS) virology departments at Groote Schuur Hospital, Tygerberg Hospital (TH), Steve Biko Academic Hospital (SBAH), Dr George Mukhari Academic Hospital (DGMAH) and Inkosi Albert Luthuli Central Hospital (IALCH). The NHLS in South Africa has a network of laboratories that perform testing for all health facilities in the public health sector. The selected laboratories carry out rubella testing for patients at sentinel sites. In addition to these laboratories, some samples were sent to the National Institute for Communicable Diseases (NICD) for testing.

All participating laboratories are accredited by the South African National Accreditation System (SANAS) according to the standard ISO15189. Infants with compatible clinical syndromes were tested either by serology, or rubella PCR on urine, or both according to clinical request. Different commercial assays were used for serology testing at the different laboratories: automated platforms, either the Architect (Abbott, Germany) or Elecsys (Roche, Germany) were used at DGMAH, IALCH, SBAH and GSH. Commercial m-capture ELISAs, either Vitek (BioMerieux, France) or or Enzygnost (Siemens, Germany) were used to detect rubella IgM at GSH, TH and NICD laboratories.

Rubella PCR was performed at GSH, TH and NICD using in house assays, based on primers from Bothma et al [28].

In the retrospective phase, we extracted positive rubella serology or molecular tests between 2010 and 2014 in patients aged 12 months or less from the laboratory information system of the NHLS. We retrieved data from the medical records in the hospital archives and completed the case investigation form (CIF) (see Supplementary material 2). Medical records were searched electronically at three sites (Tygerberg, Universitas and Peolnomi hospitals) while manual searching was done at all other study sites.

In the prospective phase (2015 to 2017), each designated focal person received an e-mail on a monthly basis (see Supplementary material 3) for reporting of confirmed CRS cases (including zero reporting) and completion of the CIF if applicable. Although not part of the initial plan for monthly reporting, clinicians who did not respond for a number of months were contacted through a phone call to make sure no CRS cases were missed at the study site. Participant information was captured and stored in a Microsoft Excel 2010 database that was accessible only to the epidemiologists at the Centre for Vaccines and Immunology. The database was updated monthly and imported into Stata (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) for descriptive analysis. Continuous variables were reported using medians and ranges while categorical variables were reported using absolute numbers and percentages.

Ethical considerations

All nine provincial ethics committees as well as the management of participating hospitals and university research ethics committees that cover the tertiary hospitals approved the study.

2.4. Results

We identified 95 laboratory-confirmed CRS cases from 28 sites situated in all nine provinces of South Africa (Table 1), 77 diagnosed by IgM serology, 17 by PCR and one by serial IgG serology. There were 42 cases in the retrospective phase and 53 cases in the prospective phase. Participant characteristics are summarized in Table 2.

Maternal characteristics

The age of mothers of CRS cases ranged from 14 to 38 years in the retrospective phase with a median of 21 years. In the prospective phase, maternal age ranged from 15 to 38 years with a median of 22 years (see Supplementary material 4). None of the mothers reported ever having received RCV. In the retrospective phase none of the mothers had laboratory-confirmed rubella while 2 (4%) in the prospective phase had laboratory confirmed rubella infection during the index pregnancy. Six (14%) mothers in the retrospective phase and six (11%) in the prospective phase reported having a rash during pregnancy. Data on maternal rash was unavailable for 34 (81%) mothers in the retrospective phase and 34 (64%) in the prospective phase.

Distribution of reported CRS cases across provinces in South Africa

The Western Cape Province reported the highest number of cases in both study phases with 19 cases in the prospective phase and 22 in the retrospective phase. No CRS cases were reported in North West province (see Supplementary material 5).

Table 1: CRS cases reported at sentinel surveillance sites, South Africa, 2010-2017

Province & study site	Retrospective phase (N=42)					Prospective phase (N=53)			
	2010	2011	2012	2013	2014	2015	2016	2017	Site Total
Eastern Cape Province									
Cecilia Makiwane Hospital	0	0	0	0	0	2	0	0	**2**
Frere Hospital	0	0	0	0	0	2	0	0	**2**
Free State Province									
Pelonomi Hospital	0	0	0	0	0	1	0	2	**3**
Universitas Hospital	0	2	0	1	1	5	0	0	**9**
Gauteng Province									
Charlotte Maxeke Johannesburg Hospital	0	0	0	0	0	0	1	0	**1**
Chris Hani Baragwanath Hospital	0	0	0	0	0	0	1	0	**1**
Dr George Mukhari Academic Hospital	0	0	0	0	0	0	1	1	**2**
Kalafong Hospital	0	0	0	0	0	0	1	0	**1**
Rahima Moosa Mother and Child Hospital	0	0	0	0	0	0	1	0	**1**
Steve Biko Academic Hospital	0	0	0	1	2	0	2	3	**8**
KwaZulu-Natal Province									
Inkosi Albert Luthuli Central Hospital	0	1	1	2	1	2	0	0	**7**
King Edward VIII Hospital	0	0	0	0	3	0	0	0	**3**
Prince Mshiyeni Memorial Hospital	0	0	0	0	1	1	0	0	**2**
Greys Hospital	0	0	0	0	0	0	0	0	**0**
Limpopo Province									
Mankweng Hospital	0	0	0	0	1	0	0	1	**2**
Pietersburg Hospital	0	0	0	0	2	3	0	1	**6**
Mpumalanga Province									
Rob Ferreira Hospital	0	0	0	0	0	1	0	0	**1**
Witbank Hospital	0	0	0	0	1	1	0	0	**2**
Northern Cape Province									
Kimberley Hospital	0	0	0	0	0	1	0	0	**1**
Dr Harry Surtie Hospital	0	0	0	0	0	0	0	0	**0**
North West Province									
Job Shimankana Tabane Provincial Hospital	0	0	0	0	0	0	0	0	**0**
Klerksdorp/Tshepong Hospital	0	0	0	0	0	0	0	0	**0**
Mafikeng Provincial Hospital	0	0	0	0	0	0	0	0	**0**
Western Cape Province									
Groote Schuur Hospital	1	2	0	0	1	0	0	0	**4**
Mowbray Maternity Hospital	0	0	0	0	0	1	0	0	**1**
New Somerset Hospital	0	0	0	1	2	1	0	0	**4**
Red Cross War Memorial Children's Hospital	3	3	2	1	3	9	1	0	**22**
Tygerberg Hospital	1	1	1	0	0	7	0	0	**10**
Total per year	**5**	**9**	**4**	**6**	**18**	**37**	**8**	**8**	**95**

Birth defects in CRS cases

The most common birth defect was congenital heart disease and the least common were pigmentary retinopathy and radiolucent bone diseases (Table 3). There were 18 CRS cases with one or more abnormalities not included in the case definition with the most frequent being bicytopenia (4 cases) and microphthalmos (3 cases). Each of the following defects were found in only single cases: bicuspid aortic valve, hydrops fetalis, hypospadias with single umbilical artery, cerebral atrophy with cortical blindness and cerebral palsy, hydrocoele, supra-umbilical hernia with dilated renal pelvis, myxomatous tricuspid and mitral valves, cleft palate, coloboma of iris, colpocephaly, rubella keratitis and Williams syndrome.

Age at CRS diagnosis

The age at diagnosis in the retrospective phase ranged from 0 to 11 months with 14 (33%) cases diagnosed within four weeks of delivery. In the prospective phase, age at diagnosis ranged from 0 to 11 months with 27 (51%) cases diagnosed within four weeks of birth (see Supplementary material 6).

Mortality among CRS cases

At the time data was captured on the CIFs, three (7%) cases in the retrospective phase were reported to have died and 20 (48 %) were still alive. In the prospective phase, eight (15%) cases were reported to have died and 39 (74%) were alive. The proportion of cases with no data on mortality was 45% in retrospective phase and 11% in the prospective phase.

Surveillance adequacy indicator

In order to track reporting by study sites in the prospective phase, e-mails were sent to each clinician on a monthly basis. Five sites had a 0% response rate for all three years of the prospective phase. Eight sites had a 100% response rate for at least one year of the prospective phase (see Supplementary material 7). For clinicians in KwaZulu-Natal province, monthly reporting started in 2016 due to delayed ethics approvals.

Table 2: Infant and maternal characteristics of CRS cases identified at sentinel surveillance sites, South Africa, 2010-2017

	Retrospective phase: 2010-2014 (N=42)	Prospective phase: 2015-2017 (N=53)
	Infant	
Age group n (%)		
0 to 1 month	14 (33%)	27 (51%)
2 to ≤3 months	18 (43%)	18 (34%)
4 to ≤6 months	9 (22%)	6 (11%)
6 to 11 months	1 (2%)	2 (4%)
Unknown	0(0%)	0(0%)
Sex n (%)		
Females	16 (38%)	28 (53%)
Males	26 (62%)	25 (47%)
Gestational age n (%)		
Preterm	13 (31%)	18 (34%)
Term	17 (40%)	29 (55%)
Unknown	12 (29%)	6 (11%)
Mortality		
Alive	20 (48%)	39 (74%)
Died	3 (7%)	8 (15%)
Unknown	19 (45%)	6 (11%)
	Maternal	
Age (median(range))	21 years (14-38)	22 years (15-38)
Reported n (%)	23 (55%)	40 (75%)
Unknown n (%)	19 (45%)	13 (25%)
Parity n (%)		
1	18 (43%)	20 (38%)
2-7	14(33%)	18 (34%)
Unknown	10 (24%)	15 (28%)
Rubella vaccination n (%)		
Yes	0 (0%)	0 (0%)
No	0 (18%)	11 (21%)
Unknown	42 (82%)	42 (79%)
Rash during pregnancy		
Yes	6 (14%)	6 (11%)
No	2 (5%)	13 (25%)
Unknown	34 (81%)	34 (64%)

Note. Unknown refers to cases that had no information available in the medical records.

Table 3: Clinical signs as per case definition of CRS cases identified at sentinel surveillance sites, South Africa, 2010-2017

Clinical characteristic n (%)	**2010-2014 (N=42)**	**2015-2017 (N=53)**
Congenital Heart Disease		
Yes	30 (71%)	43 (81%)
No	3 (7%)	3 (6%)
Unknown	9 (22%)	7 (13%)
Cataract		
Yes	22 (52%)	28 (53%)
No	8 (19%)	15 (28%)
Unknown	12 (29%)	10 (19%)
Glaucoma		
Yes	1 (2%)	2 (4%)
No	15 (36%)	20 (38%)
Unknown	26 (62%)	31 (58%)
Hearing Impairment		
Yes	5 (12%)	3 (6%)
No	6 (14%)	2 (4%)
Unknown	31 (74%)	48 (90%)
Hepatosplenomegaly		
Yes	16 (38%)	26 (49%)
No	6 (14%)	17 (32%)
Unknown	20 (48%)	10 (19%)
Jaundice		
Yes	3 (7%)	10 (19%)
No	7 (17%)	26 (49%)
Unknown	32 (76%)	17 (32%)
Meningoencephalitis		
Yes	2 (5%)	7 (13%)
No	11 (26%)	24 (45%)
Unknown	29 (69%)	22 (42%)
Mental Retardation		
Yes	9 (21%)	2 (4%)
No	4 (10%)	4 (8%)
Unknown	29 (69%)	47 (88%)
Microcephaly		
Yes	10 (24%)	23 (43%)
No	11 (26%)	14 (27%)
Unknown	21 (50%)	16 (30%)
Pigmentary retinopathy		
Yes	0 (0%)	2 (4%)
No	14 (33%)	14 (26%)
Unknown	28 (67%)	37 (70%)
Purpura		
Yes	3 (7%)	13 (24%)
No	8 (19%)	28 (53%)
Unknown	31 (74%)	12 (23%)
Radiolucent bone disease		
Yes	0 (0%)	5 (9%)
No	6 (14%)	16 (30%)
Unknown	36 (86%)	32 (61%)

2.5. Discussion

The number of laboratory-confirmed CRS cases varied from four in 2012 to 37 in 2015 and a total of 95 laboratory-confirmed CRS cases were detected between January 2010 and December 2017. The Western Cape Province reported the highest number of CRS cases when compared to other provinces. The most frequent anomalies, according to our case definition, in both phases of the study were congenital heart disease and cataracts while the least common were hearing impairment and radiolucent bone disease. Most mothers of CRS cases, were between 14 and 30 years of age.

The higher number of reported cases in the prospective phase compared to the retrospective phase could be explained by increased awareness following discussions with clinicians at the start of the study. Since laboratory testing of CRS cases was initiated by the clinician's suspicion, increased awareness of the study might have led to a higher index of suspicion among clinicians. The drop in reported cases between 2015 and 2017, however, suggests limited influence of clinician awareness on detection of CRS cases. The fewer number of cases in the retrospective phase of the study could be explained by challenges in record keeping since medical records of many patients could not be retrieved.

The higher number of reported CRS cases in the Western Cape does not imply a higher CRS burden in that province. Differences in the diagnosis and referral processes as well as the presence of a highly specialized referral pediatric hospital in Cape Town could explain this finding.

Several studies have reported varying frequencies of congenital abnormalities in CRS case [7] [29] usually occurring in combinations [30]. However, in the individual case it is not possible attribute every anomaly observed to rubella virus [31]. Birth defects such as cataracts and congenital heart disease are frequently observed early after birth while hearing impairment and developmental delay are usually diagnosed in late infancy. Many cases may therefore be diagnosed in specialist clinics when the children are over the age limit for our case definition (12 months). As infants approach one year of age, laboratory confirmation becomes challenging since a negative rubella test result does not exclude CRS [32] but the infant would be excluded from our study. Interestingly some identified CRS cases had additional symptoms that are not part of standard case definitions.

The number of deaths reported among CRS cases differed between study phases Differences in in-hospital CRS mortality between study phases could be explained by challenges in follow-up of cases and obtaining data from medical records. Infants with CRS are at higher risk of severe morbidity and mortality [2] [7] [33] and following these cases prospectively would enable more accurate estimates of survival.

None of the mothers of CRS cases reported having received rubella vaccine. A rash during pregnancy was reported by mothers in the prospective and retrospective phases. History of rash was not available in most cases in the prospective and retrospective phases. Rubella infection frequently presents without a rash [34] and in many cases, the mother may have forgotten a rash

in early pregnancy. The presence of rash is often a key element that raises suspicion and leads to identification of rubella in pregnancy.

Most mothers in our study were aged between 14 and 30 years. About 27% of the general female population of South Africa is in this age range [35] while 70.7% of pregnant women included in the antenatal Human immunodeficiency Virus survey are within 15 to 30 years of age [36]. The age distribution of mothers of CRS cases is an indication of the susceptible adult female population of child-bearing age in public health facilities in South Africa. Immunity testing among adolescents and adults of both genders could complement data on susceptibility to rubella.

This study had a number of strengths: All cases were laboratory confirmed and the sentinel sites were dispersed nationally in all provinces. Both the clinicians and virology laboratories that test for rubella were involved in case finding. This two-way flow of information on potential CRS cases ensured a high probability of identifying cases from the study sites. Lastly, active communication was maintained with the clinicians at study sites to ensure regular reporting and document zero reporting. The absence of responses to e-mails sent to a number of clinicians prompted phone calls that served as an alternative method of communication. The main limitation of the study is due to the fact that we could not include CRS cases diagnosed at health facilities which were not sentinel sites. Another limitation relates to difficulties in obtaining patient data, especially in the retrospective phase of the study. We could not calculate CRS incidence because there was no suitable denominator for an incidence estimate. Some of the CRS cases reported by the sentinel sites were referred from other health facilities, often situated in different health districts or provinces. Since some CRS cases were diagnosed at health facilities that were not sentinel sites, using the birth cohort at sentinel sites would over-estimate incidence while using the national birth cohort in South Africa would under-estimate CRS incidence. There may also have been underreporting due to our case definition being limited to infants less than one year of age.

2.6. Conclusion

The number of laboratory-confirmed CRS cases in South Africa ranges from four cases in 2012 to 37 cases in 2015 in the absence of public rubella vaccination. The identified CRS cases predominantly presented with severe signs and symptoms that could be diagnosed early by clinicians. The ages of 98% of mothers of the CRS cases ranged from 14 to 30 years. An immunity gap exists amongst women in this age group that should be considered when identifying target age groups for RCV introduction. Continuous CRS surveillance will enable monitoring of the impact of rubella vaccination once introduced into the South African EPI schedule.

Our findings highlight the need for a rubella control programme in South Africa. Optimal timing for implementation depends on ability to exceed 80% vaccine coverage, using measles vaccination coverage at one year of age as a proxy. South Africa should strengthen routine immunization coverage in preparation for RCV implementation.

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CHAPTER THREE

Rubella seroprevalence in South Africa

3.0. About this chapter

In this chapter, we focus on obtaining details regarding the immunity profile of the South Africans who make use of the public health sector. We carried out rubella IgG testing on residual samples from the measles surveillance program. Only samples that tested negative for measles and rubella IgM were included. Health facilities all over the country collect samples from suspected measles cases and these samples are sent to the NICD for testing. The proportion of negative rubella IgG results in different age groups imply different levels of immunity to rubella and can be used when deciding on target age groups for rubella vaccination. This study was published in Human Vaccines & Immunotherapeutics (https://www.tandfonline.com/doi/full/10.1080/21645515.2020.1738834). This study was published in Human Vaccines & Immunotherapeutics and the citation is: *N. V. Motaze, L. Makhathini, S. B. Smit, C. G. Adu-Gyamfi, M. Fortuin, C. S. Wiysonge & S. M. Suchard (2020): Rubella seroprevalence using residual samples from the South African measles surveillance program: a cross-sectional analytic study, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1738834* Below is the list of authors and their affiliations:

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The candidate played the lead role in the conceptualization of this study, development of the protocol, analysis of the data and writing of the manuscript and submission to the journal.

3.1. Abstract

Introduction
South Africa is yet to introduce rubella-containing vaccines (RCV) into its routine immunization schedule. Selecting the target population when introducing RCV should take into account the ages of susceptible individuals in the population. We aimed to determine the seroprevalence of antibodies to rubella and characterize immunity gaps among individuals of all ages in South Africa.

Methods
We tested for rubella immunoglobulin G (IgG) antibodies with a commercial enzyme-linked immunosorbent assay. We used residual samples collected from 2016 through 2018 as part of the national measles surveillance program. We only tested samples that were negative for measles and rubella immunoglobulin M (IgM) and explored the association between rubella susceptibility (IgG negative) and predictor variables (year of sample collection, age, sex and province of residence) using logistic regression analysis.

Results
We obtained results for 6057 records. Rubella susceptibility was highest among Individuals aged zero to 11 months (81.9%), followed by children one to five years old (71.5%), six to 10 years old (40.9%) and 11 to 15 years old (31.25) while the smallest proportion of susceptible individuals was among those 16 to 49 years old (19.9%). Females were less likely to be susceptible to rubella compared to males (OR=0.79 (95%CI: 0.71-0.87), P<0.001) in unadjusted analysis but this effect was not observed after adjusting for age and province. In multivariable logistic regression, age (OR= 6.24(4.52 – 8.63), P<0.001) and province of residence (OR= 0.97 (95%CI: 0.95 – 0.99), P=0.01) were associated with rubella susceptibility

Conclusion
In the absence of rubella vaccination in the Expanded Program on Immunization in South Africa, the bulk of individuals susceptible to rubella are children under sixteen years old. About 20% of individuals 16 to 49 years old are susceptible to rubella. This susceptibility gap must be born in mind during RCV introduction.

3.2. Introduction

The Global Measles and Rubella Strategic plan 2012-2020 aimed to eliminate measles and rubella in at least five World Health Organization (WHO) regions by the end of 2020 (1). A midterm review suggested that these elimination goals were not likely to be achieved due to several challenges culminating in a shortage of resources for the execution of the plan (2). A number of WHO regions, including Africa, do not have a target for rubella elimination, although many countries have successfully introduced rubella-containing vaccines (RCV) in their Expanded Program on Immunization (EPI) schedules (3). One of the recommendations

highlighted in the midterm review involved achieving and maintaining high levels of population immunity to measles and rubella through vaccination (2).

Measles vaccination is already part of the EPI schedule in South Africa, however, RCV are only available in the private sector (4). There are several commercially available combinations of RCV, all of which contain the measles vaccine (5). The availability of combination vaccines provides an opportunity to incorporate RCV into already existing measles vaccination activities that entail routine vaccination of infants and supplementary immunization activities (SIAs) targeting older individuals. The WHO recommends introducing RCV when countries achieve at least 80% coverage for measles routine vaccination and/or SIAs (6). Countries that introduced RCV in this manner have experienced considerable reductions in rubella incidence (7).

In its guidance document on introduction of RCV, the WHO points out the importance of reviewing the rubella susceptibility profile of the population and targeting a wide age range of individuals during the initial introductory vaccination campaign (8). Identifying age groups of susceptible individuals is therefore important in order to target them during this initial mass campaign. Seroepidemiological studies are used to characterize rubella immunity in populations from results of immunoglobulin G (IgG) testing. The rubella IgG test is unable to distinguish antibodies obtained from passive transfer during pregnancy from antibodies that develop following vaccination or following infection with rubella virus. Furthermore, as an individual acquires rubella antibodies, there is an increase in antibody titers up to a maximum level followed by a decrease in titers. Depending on what time a sample is collected, results might differ in the same individual. Distinguishing between antibodies following vaccination and infection depends on the availability of data on vaccination history in settings where RCV are used. In settings where there is no mass vaccination against rubella, the presence of rubella antibodies can be assumed to be secondary to infection in the majority of cases.

Several serological studies have characterised rubella susceptibility or immunity in different population subgroups in Sub-Saharan Africa (9–11) and in other WHO regions (12–14). When planning RCV introduction, serosurveys provide insight into the population subgroups that should be targeted for vaccination and provide data for modelling rubella transmission dynamics (15–17) including estimation of the burden of congenital rubella syndrome (CRS). Individuals of reproductive age are of particular interest since susceptibility to rubella in this age group has a direct impact on occurrence of CRS, which is the main target of the RCV. Assessing immunity in pregnant women can provide insight into rubella immunity among individuals of reproductive age. Rubella seroprevalence estimates vary in different settings. In Iran, rubella seroprevalence ranged from about 89% among women below 25 years of age to 85% among children under-five, dropping to 81.4% in 11-15 year olds with the highest figures (98.8%) among 21-25 year olds (18). Another Iranian study among pregnant women found that 96% of participants were immune to rubella (14). In Germany, 87.6% of children below 17 years of age were immune to rubella (12) with the age group of 3 to 6 year olds having the highest proportion of immune individuals. A systematic review including several studies in Sub-Saharan Africa (9) reported rubella seroprevalence among individuals of reproductive age ranging from 65% in Sudan to 98% in Nigeria.

An analysis of residual specimens collected from individuals of all age groups in public and private health facilities all over South Africa reported rubella immunity in 93.8% of females aged 12 to 49 years (19). Another study reported rubella immunity in over 95% of pregnant women in the Western Cape province (20). Although these studies report high proportions of immunity to rubella among individuals of reproductive age, it is not certain if rubella infection dynamics remained unchanged over time given that those studies were conducted a decade ago. In order to provide more recent estimates on rubella susceptibility, we aimed to investigate all age groups as the South African government considers introducing RCV.

3.3. Methods

Sampling

In this cross-sectional analytic study, we performed rubella immunity testing on residual samples collected in 2016, 2017 and 2018. We included residual samples from measles surveillance that were collected in public facilities and that tested negative for both measles and rubella IgM. Blood samples for measles surveillance are collected from any patient who presents with rash and fever in addition to at least one of the following symptoms; conjunctivitis, coryza or cough. These samples can be considered to represent the general population since they come from patients in all health districts of the nine provinces in South Africa. Gauteng province has the smallest surface area and the highest population density while the least densely populated is Northern Cape province which has the largest surface area. Johannesburg is the economic hub of the country and is situated in Gauteng province and each province has at least one urban city with rural and semi-rural areas. With the private sector catering for about 15% of the population (21), the public health sector represents about 85% of the South African population and offers free health care services.

Rubella IgG testing

We tested for the presence of rubella IgG with a test that uses an indirect enzyme-linked immunosorbent assay (ELISA) method (Platelia™, Bio-Rad, Marnes-la-Coquette, France). We determined the presence and concentration of IgG antibodies to rubella by comparing the optical density (OD) of the sample to the concentration in International Units per milliliter (IU/ml) of the calibrators of the standard curve. The Platelia™ Rubella IgG test is standardized to WHO International Standard RUBI 1-94.

We considered a negative (titer < 10 IU/ml) result as indicative of absence of immunity to rubella and a positive result (titer ≥ 15 IU/ml) as indicative of immunity to rubella. We interpreted an equivocal result (titer from 10 IU/ml to ≤ 15 IU/ml) as inconclusive since we could not obtain a second sample for testing two weeks after the first sample as per the manufacturer's specifications.

Statistical analysis

We summarized categorical data using numbers and percentages and skewed continuous data with medians and ranges. We reported equivocal results when reporting descriptive statistics and

subsequently excluded them in all further analyses. The ages of individuals were divided into strata corresponding to individuals below the target for routine immunization (0 to 11 months), individuals who could be targeted for mass vaccination activities (1 to 5 years, 6 to 10 years and 11 to 15 years), individuals of reproductive age (16 to 49 years) and older individuals (50 years and above).

We calculated 99% confidence intervals for proportions of susceptible individuals. We explored the association between rubella susceptibility and predictor variables (age, sex and province of residence) using univariable and multivariable logistic regression analyses. We applied a stepwise backward automatic method for the multivariable logistic regression and a p-value of 0.05 to select variables that remained in the final model. We cleaned and analyzed the data using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Ethical considerations

The Human Research Ethics Committee at Stellenbosch University approved the study (Reference number S18/08/177(PhD)). All participant data were available only to the study team and stored on password-protected computers.

3.4. Results

We retrieved 6216 eligible samples and obtained 6057 rubella IgG results. The sample volume was insufficient for 75 records while 82 had equivocal results. Gauteng province had the highest number of samples tested while Free State province had the fewest. Participant ages ranged from one month to 104 years with a median age of 5 years (Table 1). Overall 43% of individuals were immune (IgG positive) while 57% were susceptible (IgG negative)

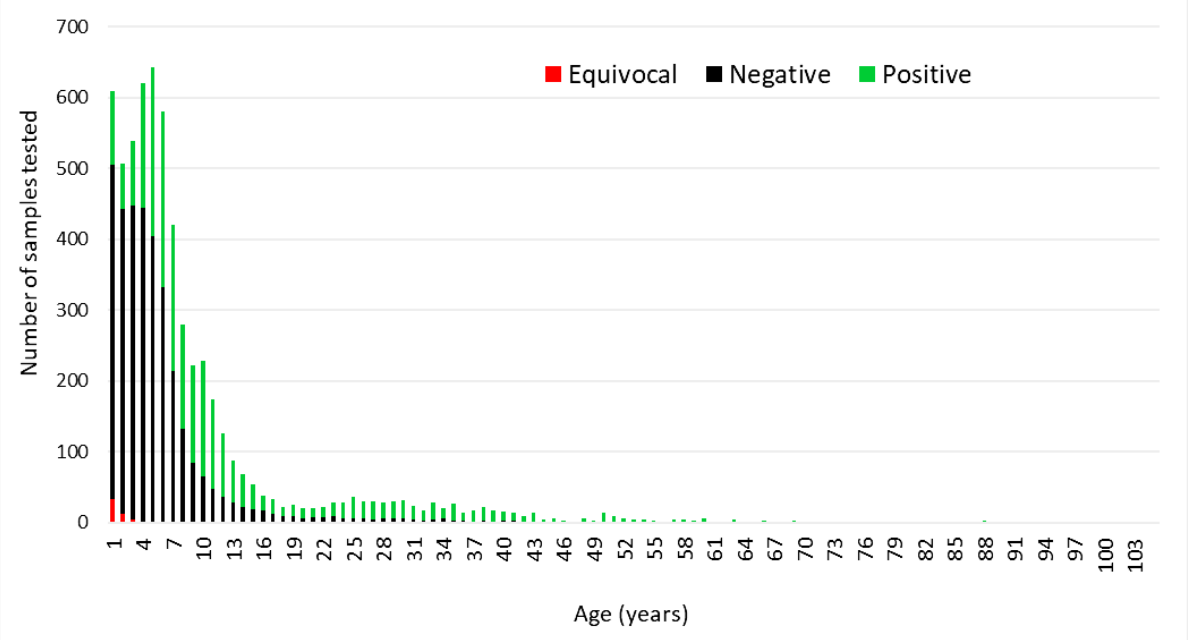


Figure 1: Results of rubella IgG testing by age in years for records with known age (n=6021)

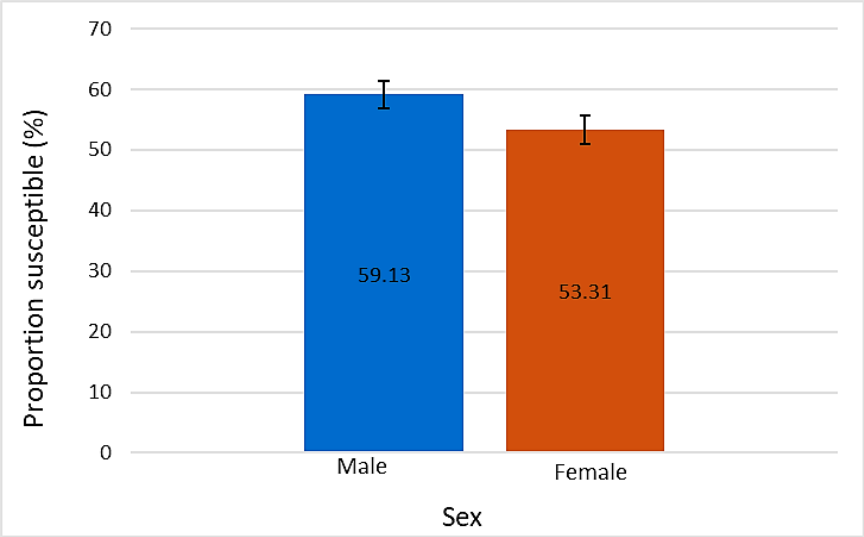


Figure 2: Proportion of rubella susceptible (IgG negative) individuals among males and females. Error bars represent 99% confidence intervals.

Individuals between 1 and 5 years of age represented the majority of participants and about 67% (55/82) of equivocal results were in this age group (Figure 1). Rubella susceptibility was highest among Individuals aged zero to 11 months (81.9%), followed by children one to five years old (71.5%), six to 10 years old (40.9%) and 11 to 15 years old (31.25) while the smallest proportion of susceptible individuals was among those 16 to 49 years old (19.9%).

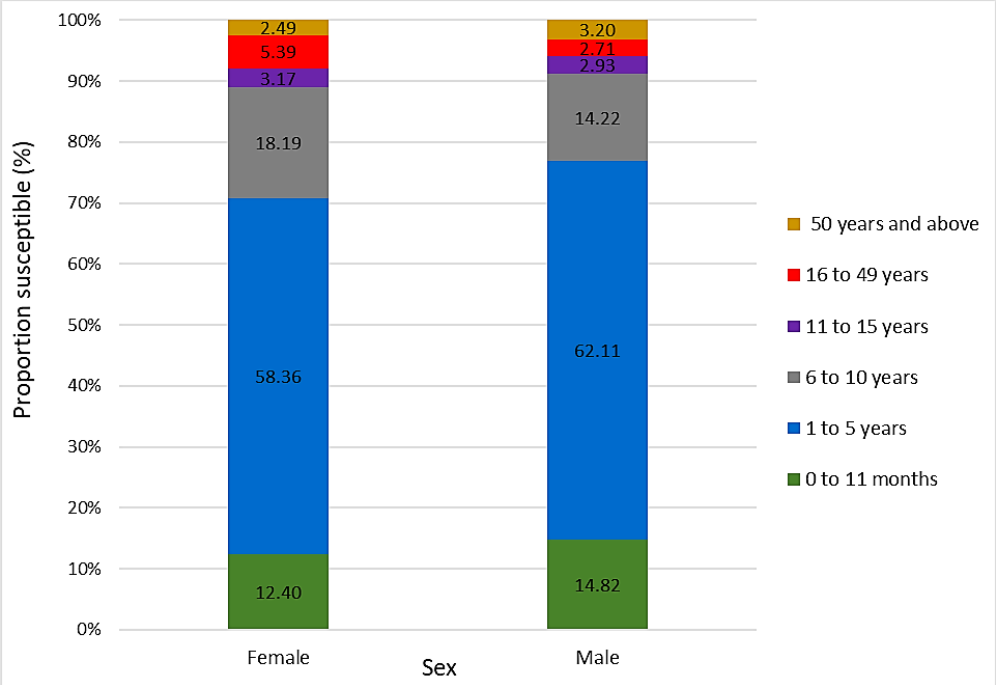
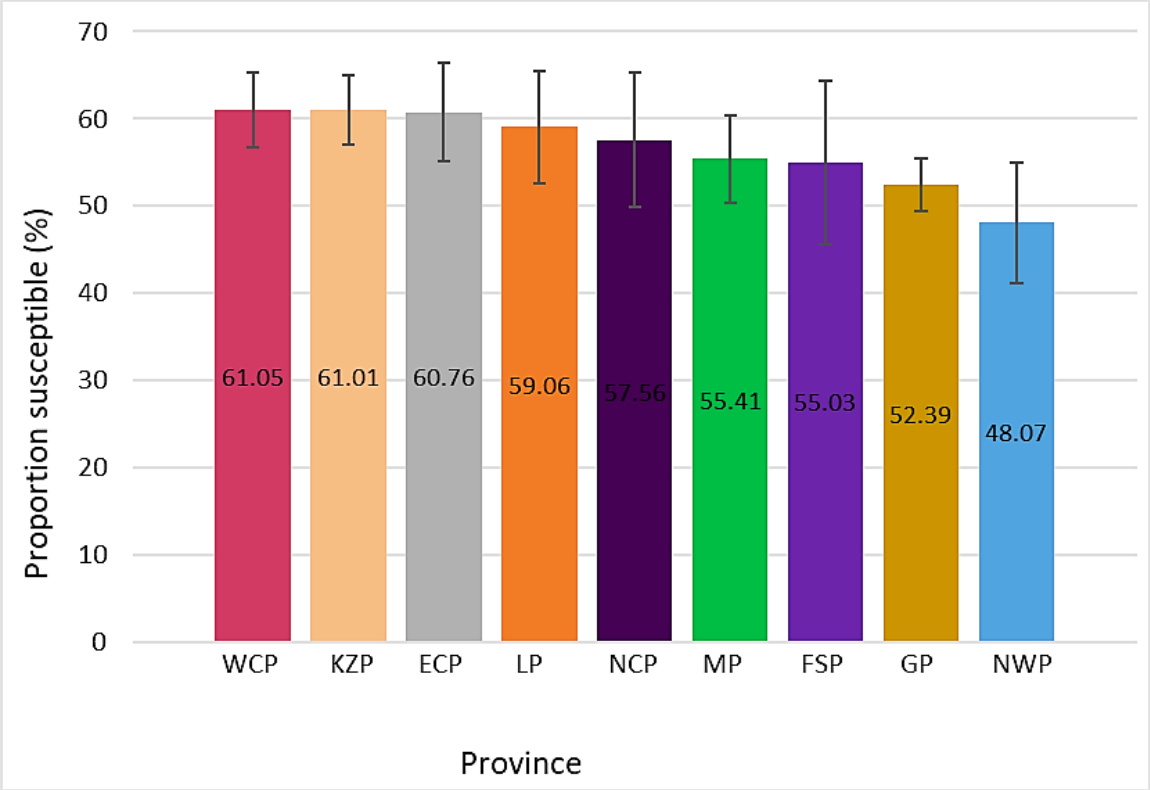


Figure 3: Proportion of rubella susceptible (IgG negative) individuals in each age group among males and females.



**** WCP= Western Cape Province, KZP= KwaZulu-Natal Province, ECP= Eastern Cape Province, LP= Limpopo Province, NCP= Northern Cape Province, MP= Mpumalanga Province, FSP= Free State Province, GP= Gauteng Province, NWP= North West Province***

Figure 4: Proportion of rubella susceptible (IgG negative) individuals for each province. Error bars represent 99% confidence intervals.

The proportion of susceptible individuals was higher amongst males (59.13%, 99%CI: 56.84-61.39) compared to females (53.31%, 99%CI: 50.86-55.75) (Figure 2). Most susceptible individuals were 1 to 5 years old among males (62.11%) and females(58.36%), while the smallest proportion of susceptible individuals was the 16 to 49 years old age group for males (2.71%) and those 50 years and above (2.49%) for females (Figure 3). Women of reproductive age (16-49 years) represented 5.39% of susceptible females.

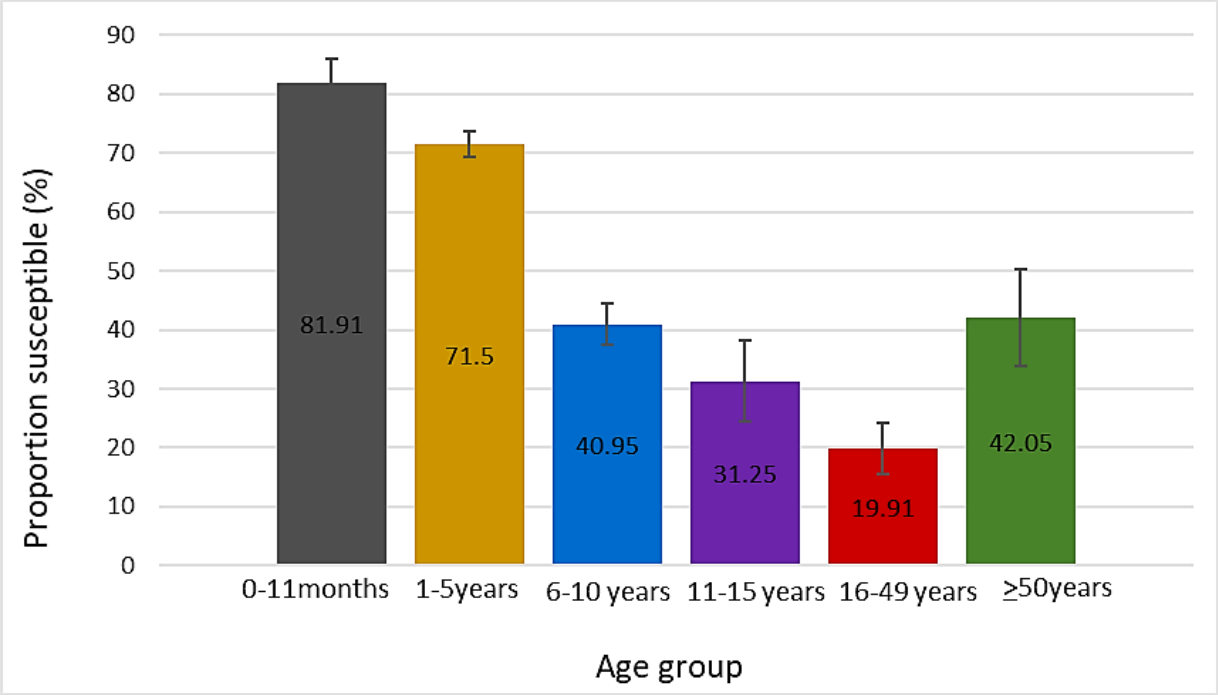


Figure 5: Proportion of rubella susceptible (IgG negative) individuals by age group. Error bars represent 99% confidence intervals.

Figure 4 shows the proportion of susceptible individuals in each province in descending order. Susceptibility ranged from 48.07%, in North West province to 61.05% in Western Cape province. The proportion of susceptible individuals decreased with increasing age group except for individuals 50 years and above (Figure 5). The highest proportion of susceptible individuals were children aged 0 to 11 months (81.91%) while individuals 16 to 49 years old had the lowest (about 19.91%).

Risk factors associated with rubella susceptibility

Table 2 shows the results of unadjusted (univariable) and adjusted (multivariable) logistic regression analyses. In unadjusted analysis female individuals were less likely to be susceptible compared to men (OR = 0.79, 95%CI: 0.71 – 0.87) but after adjusting for age group and province of residence, this association was no more observed (OR = 0.91, 95%CI: 0.81 – 1.01). Province of residence and age group were associated with rubella susceptibility in both unadjusted and adjusted analyses.

Table 1: Demographic characteristics of samples included from 2016 through 2018 (N=6216)

Variable	Category	n (%)
Sample collection year	2016	1332 (21.43)
	2017	2973 (47.83)
	2018	1911 (30.74)
Gender	Male	3211 (51.66)
	Female	2877 (46.28)
	Unknown	128 (2.06)
Province	Eastern Cape	511 (8.22)
	Free State	193 (3.11)
	Gauteng	1890 (30.42)
	KwaZulu-Natal	1029 (16.56)
	Limpopo	390 (6.28)
	Mpumalanga	674 (10.85)
	Northern Cape	274 (4.41)
	North West	372 (5.99)
	Western Cape	881 (14.18)
	Unknown	2 (0.03)
Age group	0 – 11 months	626 (10.07)
	1 to 5 years	2920 (46.98)
	6 to 10 years	1333 (21.44)
	11 to 15 years	340 (5.47)
	16 to 49 years	681 (10.96)
	$\geq$ 50 years	278 (4.47)
	Unknown	38 (0.16)

Table 2: Unadjusted and adjusted logistic regression analyses

Variable	Rubella IgG result: n (%)		Unadjusted		Adjusted	
	susceptible	Immune	OR (95% CI)	p- value	OR (95% CI)	p-value
Gender (n=5931)				**<0.001**		**0.086**
Male	1491 (53.31)	1306 (46.69)	**Ref**	**Ref**	**0.95 (0.84 - 1.06)**	**Ref**
Female	1853 (59.13)	1281 (40.87)	**0.79 (0.71-0.87)**	**<0.001**		**0.41**
Province (n=6057)				**<0.001**		**0.01**
Eastern Cape	302 (60.76)	195 (39.24)	**0.99 (0.79 - 1.24)**	**0.92**	**0.99 (0.77 - 1.28)**	**0.96**
Free State	104 (55.03)	85 (44.97)	**0.78 (0.57 – 1.07)**	**0.13**	**0.76 (0.53 - 1.08)**	**0.12**
Gauteng	955 (52.39)	868 (47.61)	**0.70 (0.59–0.83)**	**<0.001**	**0.74 (0.62 - 0.89)**	**0.002**
KwaZulu-Natal	618 (61.01)	395 (38.99)	**0.99 (0.83 – 1.20)**	**0.98**	**0.93 (0.76 - 1.14)**	**0.48**
Limpopo	225 (59.06)	156 (40.97)	**0.92 (0.72 – 1.18)**	**0.51**	**0.82 (0.63 - 1.08)**	**0.15**
Mpumalanga	369 (55.41)	297 (44.59)	**0.79 (0.65 – 0.97)**	**0.03**	**0.77 (0.62 – 0.97)**	**0.03**
Northern Cape	174 (48.07)	188 (51.93)	**0.87 (0.66 – 1.14)**	**0.31**	**1.03 (0.76 – 1.41)**	**0.85**
North West	156 (57.56)	115 (42.44)	**0.59 (0.46– 0.76)**	**<0.001**	**0.68 (0.52 – 0.90)**	**0.01**
Western Cape	522 (61.05)	333 (38.95)	**Ref**	**Ref**		**Ref**
Age group (n=6021)				**<0.001**		**<0.001**
0 – 11 months	471 (81.91)	104 (18.09)	**6.24 (4.52 – 8.63)**	**<0.001**	**6.20 (4.42 – 8.70)**	**<0.001**
1 to 5 years	2050 (71.50)	817 (28.50)	**3.46 (2.67 – 4.47)**	**<0.001**	**3.44 (2.62 – 4.53)**	**<0.001**
6 to 10 years	541 (40.95)	780 (59.05)	**0.96 (0.73 – 1.25)**	**0.74**	**0.94 (0.70 – 1.25)**	**0.65**
11 to 15 years	105 (31.25)	231 (68.75)	**0.63 (0.45 – 0.88)**	**0.01**	**0.62 (0.43 – 0.88)**	**0.01**
16 to 49 years	131 (19.91)	527 (80.09)	**0.34 (0.25 – 0.47)**	**<0.001**	**0.36 (0.26 – 0.49)**	**<0.001**
≥ 50 years	111 (42.05)	153 (57.95)	**Ref**	**Ref**		**Ref**

** Rubella susceptibility (IgG negative) is the outcome variable with age, sex and province of origin as predictor variables.*

3.5. Discussion

We present a cross-sectional snapshot of current immunity levels in South Africa, showing that about 57% of individuals are susceptible to rubella. We found a decrease in the proportion of susceptible individuals with increasing age. Age group, sex and province were associated with rubella susceptibility in unadjusted analyses but only province of residence and age group remained associated with rubella susceptibility in multivariable analysis.

Several studies in Sub-Saharan Africa have described the predominance of rubella infections in children (22–25) and a recent analysis of rash-based surveillance data in South Africa revealed similar results (26). Rubella infections occurring in childhood result in most individuals being immune by the time they are adolescents or adults. This translates to decrease in susceptibility with increasing age. This natural process of immunization leaves out a number of individuals who age into the reproductive age group while being susceptible. Introducing RCV should address this immunity gap, conditional on achieving coverage figures that are high enough.

Rubella susceptibility among individuals of reproductive age is an indication of the risk of CRS. Our estimates of rubella susceptibility are lower than those reported in individuals of reproductive age (9,10) and among pregnant women (11,27) in other Sub-Saharan countries prior to RCV introduction. This could be due to lower virus circulating in South Africa as a result of rubella vaccination in the private sector (4), or due to differences in study design, especially the community-based sampling framework used in several of these studies. The unexpectedly high susceptibility among individuals aged 50 years and older could be explained by the small number of samples obtained from individuals in this age group, leading to biased estimates.

We observed an association between age and rubella susceptibility, which is a finding that is similar to several studies (10,12,13,27). This could be due to the nature of contacts between younger individuals that favor transmission of infections such as rubella when compared to contacts between older individuals (28). Increased susceptibility to rubella among younger individuals coupled with evidence of increased rubella incidence in this age group (22–24,26) justifies targeting children below 15 years old (29) for mass vaccination during RCV introduction rather than just infants in routine immunization activities. Following rubella vaccine introduction into the routine EPI schedule, the average age of infection is likely to increase and a similar study will be required in future to assess population immunity and adapt vaccination strategies to minimize the risk of CRS.

Although men were more likely to be susceptible to rubella in unadjusted analysis, we found no association between gender and susceptibility to rubella in adjusted analysis. Although females of reproductive age could be vaccinated as part of specific CRS control measures (6), omitting males from vaccination activities could lead to a persistence of viral circulation which will eventually pose a risk to susceptible pregnant women.

The association between susceptibility to rubella and province of residence has limited impact on vaccine introduction since countries do not selectively introduce RCV in certain provinces leaving out others. The provinces with the highest proportion of susceptible individuals are among the most populated in South Africa (30). However, Gauteng province, which has the highest number of individuals and is the smallest province in terms of surface area has the second lowest proportion of susceptible individuals. This suggests that there are different drivers of rubella transmission in various provinces.

We did not match the age structure of our sample to that of the general population of South Africa since most samples for measles surveillance were collected from children. Most of the individuals in our sample were children under 10 years of age and it could be argued that this predominance of children influenced our estimates. Although we did not match the distribution of the South African population in terms of age and sex, the country has a predominantly young population with similar numbers of individuals in 5-year population sub-groups between 0 and 34 years of age. Regarding sex, the proportion of females is slightly greater than that of males (51% vs. 49%) (30). Blaizot et al (31) compared sampling structures and sample sizes for estimating epidemiological parameters from serological data for a number of infectious diseases, including rubella. They found that using our sampling approach which predominantly includes children would provide similar estimates compared to a sampling approach that represented the

country's population age structure or a sample with similar numbers of individuals from all age groups.

Our study has two limitations. Firstly, we used residual sera from individuals at public health facilities. This institution-based sampling could have influenced our results since it reflects health-seeking behavior of individuals included in the study. However, the facilities from which our samples were obtained include peripheral clinics and hospitals. Another limitation relates to the fact that samples from private health facilities were not included in the analysis. Given that RCV are available in the private sector, it is unclear to what extent the susceptibility profile of individuals using private health care differs from those using public health facilities.

The main strength of our study is the national representativeness of our sample. Given that we included samples from all provinces, our estimates are a reliable reflection of the situation in the general population. Another factor that contributes to the robustness of our results is the large sample size including residual sera from three consecutive years. This enabled us to report rubella seroprevalence with 99% confidence intervals thereby increasing the precision of our estimates.

3.6. Conclusion and recommendations

In the absence of rubella vaccination in the Expanded Program on Immunization in South Africa, the bulk of individuals susceptible to rubella are children under sixteen years old. About 20% of individuals 16 to 49 years old are susceptible to rubella. This has an impact on the risk of congenital rubella syndrome since this group comprises most females of reproductive age. Age group and province of residence are associated with susceptibility to rubella. Although vaccine introduction is not likely to be a selective process with respect to provinces, any rollout strategy should be cognizant of the age-specific susceptibility profile.

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CHAPTER FOUR

Simulating rubella vaccine introduction in South Africa

4.0. About this chapter

In this chapter, we built on a published age-structured deterministic rubella transmission model that had been previously used to simulate rubella vaccine introduction in several countries. We adapted the model to the South African context and simulated different scenarios (informed by discussions with relevant stakeholders) for RCV introduction into the EPI schedule with a 30 year time horizon. In addition to rubella and CRS incidence, we obtained values for the effective reproductive number over time, which gives an estimate of the risk of outbreaks. We calculated the cost associated with each scenario by considering only the additional cost of the combination vaccine with respect to the currently administered measles vaccine. Knowing that the basic reproductive number is one of the key model inputs, we used a value that was previously estimated as the default and carried out sensitivity analysis using extreme values from other countries on the African continent. The findings from the simulations could be helpful to the South African government when choosing a RCV introduction strategy. This study was published in Vaccines. This study was published in Vaccines and is accessible at: https://doi.org/10.3390/vaccines8030383 .The full citation is: *Motaze, N.V.; Edoka, I.; Wiysonge, C.S.; Metcalf, C.J.E.; Winter, A.K. Rubella Vaccine Introduction in the South African Public Vaccination Schedule: Mathematical Modelling for Decision Making. Vaccines 2020, 8, 383.* Here is the list of authors with their respective affiliations:

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4.1. Abstract

Background: age structured mathematical models have been used to evaluate the impact of rubella-containing vaccine (RCV) introduction into existing measles vaccination programs in several countries. South Africa has a well-established measles vaccination program and is considering RCV introduction. This study aimed to provide a comparison of different scenarios and their relative costs within the context of congenital rubella syndrome (CRS) reduction or elimination. Methods: we used a previously published age-structured deterministic discrete time rubella transmission model. We obtained estimates of vaccine costs from the South African medicines price registry and the World Health Organization. We simulated RCV introduction and extracted estimates of rubella incidence, CRS incidence and effective reproductive number over 30 years. Results: compared to scenarios without mass campaigns, scenarios including mass campaigns resulted in more rapid elimination of rubella and congenital rubella syndrome (CRS). Routine vaccination at 12 months of age coupled with vaccination of nine-year-old children was associated with the lowest RCV cost per CRS case averted for a similar percentage CRS reduction. Conclusion: At 80% RCV coverage, all vaccine introduction scenarios would achieve rubella and CRS elimination in South Africa. Any RCV introduction strategy should consider a combination of routine vaccination in the primary immunization series and additional vaccination of older children.

Keywords: rubella; congenital rubella syndrome; rubella-containing vaccine; vaccine introduction strategies; age-structured rubella transmission model

4.2. Introduction

Rubella is a mild viral infection in children and adults but can lead to birth defects in infants born to women infected during pregnancy. These birth defects, known as congenital rubella syndrome (CRS), include transient and permanent sequelae [1]. Rubella-containing vaccines (RCV) have been in use since the late 1960s and this has led to successful elimination of rubella and CRS in many countries [2]. There is however a transient risk of increasing CRS incidence if vaccination coverage with RCVs is less than 80% because this inadequate coverage leads to reduced transmission in childhood resulting in increased number of females attaining the reproductive age group while being susceptible to rubella [3–5].

The World Health Organization (WHO) recommends introducing RCVs in countries that are aiming for measles elimination by concomitant administration of vaccines against measles and rubella [6]. Available combinations of RCV include measles-rubella (MR), measles-mumps-rubella (MMR), and measles-mumps-rubella-varicella (MMRV) vaccines. Given the goal of achieving elimination in 10 to 20 years, the WHO recommends an initial mass vaccination campaign, or supplementary immunization activities (SIAs), targeting individuals 9 months to 14 years of age, followed by introducing RCV into the routine vaccination program with regular SIAs every four to five years [6] to reach children missed by routine vaccination. This strategy is financially supported by Gavi, the Vaccine Alliance, for Gavi eligible countries. The opportunity to incorporate the RCV vaccine into existing measles immunization programs comes with substantial cost-savings relative to the more usual situation where a completely different vaccine has to be introduced, as a different target population, delivery scheme and other program mechanisms need to be developed.

A number of guiding principles have been formulated to assist countries planning RCV introduction in their public vaccination schedule [7] beyond the wide age range for SIAs coupled with routine vaccination (generally via combination with measles). Recommended steps include development of integrated surveillance for rubella and measles, follow-up SIAs, filling immunity gaps in older populations, and CRS surveillance [8].

Several countries in the WHO Africa region have introduced RCV into their Expanded Program on Immunization (EPI) schedule [9] as part of the measles-rubella elimination strategy. According to the current WHO measles and rubella strategic plan 2012-2020, measles is targeted for elimination by 2020, but the WHO African (AFRO) region has not yet set a target for rubella elimination [10]. In the current EPI schedule of South Africa, measles vaccine is given at six months and 12 months of age [11]. Introduction of RCVs is being considered and careful planning is therefore required in order to maximize benefits of the intervention.

Mathematical modelling has played an important role in the development of public health policy for rubella. This is in part because the nuanced and age-dependent nature of the burden of rubella infection requires a dynamical framework in projecting its epidemiology. In fact, delays to wide-spread introduction of RCV stemmed from mathematical models of the potential impact of vaccination introduction on the burden of CRS from the 1980s [12,13]. Further, mathematical models combined with serological surveys have been key to evaluating the burden of CRS, since the manifestation of this syndrome is hard to disentangle from many other potential aetiologies in resource poor settings [14]. Indeed, estimates of CRS incidence per 100,000 live births in Africa in the 90s obtained by applying mathematical models to age profiles of serology ranged between 104 (25 to 246) [15] and 115 (55 to 231) [14] in 1996. These estimates were similar for 2000; 116 (55 to 232) and 2010; 116 (56 to 235) [14].

Recently, age-structured mathematical models designed to reflect contemporary ranges of human demography have been used to re-evaluate the impact of RCV introduction into existing measles programs [16] . The basic model was further refined to more closely reflect particular settings (requiring country-specific estimates of population age distribution, birth rate, age-specific fertility rates, contact patterns, and existing vaccination strategies) to develop context-specific recommendations for RCV introduction in African and Asian countries [17,18], including South Africa [19] . This latter analysis suggested that introduction of the vaccine was likely to result in a reduction of the burden of CRS, with negligible impacts of spatial variability in vaccination coverage and transmission; but did not formally address the question of the added value of introduction of the vaccine.

In this paper, we simulate rubella infection in South Africa using an age-structured rubella transmission model. We explore the effects of a number of vaccine introduction scenarios on patterns of rubella infection and CRS incidence, extending the range of scenarios beyond those explored by Metcalf et al. [19] to evaluate combination of RCV with Human papilloma virus vaccination, different scheduling for SIAs as well as a range of different SIA target age ranges. We provide the first comparison of costs of these scenarios (RCV cost relative to the cost of measles vaccination alone) within the context of CRS reduction or elimination over different periods of time [6]. This work can be used to guide the decision-making process when the government of South Africa introduces RCV into the public vaccination schedule.

4.3. Methods

Age-Structured Rubella Model

To explore the impact of introduction of RCV into South Africa, we used a previously published deterministic discrete time age-structured model [16,20] which is characterized by a matrix capturing transitions between epidemiological states (maternally immune (M), susceptible (S), infected (I), recovered (R), and vaccinated (V)) and between age groups (Supplement 1 Figure S1). Individuals in the maternally immune (M) compartment are children born to mothers who are immune to rubella and passively acquire immunity. Susceptible (S) individuals are those who lose maternal immunity or are born susceptible and at risk of becoming infected (I). Infected individuals recover by the next time step moving into the recovered (R) compartment. The vaccinated (V**)** compartment represents individuals who receive RCV and are successfully immunized. The time step used in the model was ~16 days, as this corresponds to the generation time of rubella. See supplement 1 for model details.

One of the key model inputs is the basic reproductive number (R_0), which is the average number of secondary infections resulting from a typical infectious person in a totally susceptible population. The value of R_0 used in this model was 7.9 and was obtained from a previously published modelling study estimating R_0 for 40 African countries[21]. We proceeded to run simulations with different estimates for R_0 in a sensitivity analysis. The highest estimate used was an R_0 of 12 which was estimated in Ethiopia [22] and the lowest estimate estimated in Burkina Faso was 3.3 [21]. The nature of interactions between individuals influences transmission of infectious diseases. This was represented in the model as a function for seasonal amplification [23–25] and age-specific mixing based on estimated age-dependent social contact [26] and non-modelled heterogeneities [27]. Duration of maternal immunity [28] and vaccine efficacy [29] were estimated from published literature. Demographic data over time for South Africa were obtained from projections by the United Nations (UN) Population Division [30]. See supplement 1 for model parameter details.

Preventing CRS is the main reason for administering rubella vaccination, given the mild nature of infection among children and adults. We therefore assessed the impact of vaccine introduction on both rubella and CRS incidence over time for all scenarios. To estimate the burden of CRS, we combined rubella age-specific incidence generated by the model with an age-related fertility profile for South Africa obtained from the UN Population Division 2015 estimates [30].

Vaccine Introduction Scenarios

We explored vaccine introduction scenarios that reflect options that might be implemented in South Africa (Table 1). The measles vaccine is currently administered at six months and 12 months

as part of the EPI schedule in South Africa. Previously, country-wide SIAs were organized every four to five years but in recent years, SIAs are only organized as measles outbreak control measures in affected districts or provinces. On the contrary, RCVs are currently available in South Africa but only in the private health sector, which caters for about 15% of the population. We therefore fixed RCV coverage in our simulations to 15% prior to introducing the vaccine in the EPI schedule. The WHO recommends an initial SIA, targeting a wide age range of individuals, with the concurrent introduction of RCV into the routine EPI schedule [6]. We simulated rubella disease dynamics for 55 years (1995 to 2050) by first simulating endemic rubella disease dynamics (from 1995 to 2019) before initiating vaccine introduction (from 2020 onwards). Analyses covered three time horizons (10 years, 20 years, and 30 years) following RCV introduction to encompass various time frames required for CRS elimination using different RCV introduction strategies [6].

Rubella containing vaccines if introduced into the South African EPI program will be in combination with measles vaccine. Estimates of coverage for the second dose of routine measles vaccination [31] according to the South African government differ from those of WHO (79% versus 53% in 2017, 75% versus 50% in 2018). To encompass the emergent properties of a range of potential coverage values and target ages for routine immunization (9 or 12 months), we considered an array of scenarios reflecting different levels of coverage for routine vaccination achieved by 12 months, ranging from 60% to 95%. We also considered one scenario in which a dose of RCV was administered to boys and girls at the same age as the human papillomavirus (HPV) vaccine. The HPV vaccine is administered each year to nine year-old girls in schools in South Africa. It is reasonable to assume that this approach could be considered in an attempt to cover the adolescent population in the absence of SIAs. For all RCV introduction scenarios, including SIAs, we set the coverage of RCV during SIAs at 80% because this is the minimum coverage recommended by WHO [6]. We also set the coverage of RCV at 80% at the time of co-administration with HPV vaccine in order to be consistent with RCV coverage for individuals who are above the age for the primary series of RCV.

Table 1. Possible scenarios for rubella-containing vaccine (RCV) introduction in South Africa.

Scenario	Routine Vaccination in Expanded Program on Immunization (EPI)	Target Age Group for Routine Vaccination	Target Age Group for Initial Mass Campaign	Follow-Up Mass Campaigns	
				Target Age Group	Timing
1	No RCV in EPI				
2	RCV introduction	1 year	No initial campaign	No follow-up campaign	N/A
3	RCV introduction	1 year	1 to 14 years	No follow-up campaign	N/A
4	RCV introduction	1 year	1 to 14 years	1 to 4 years	One follow-up campaign 5 years after initial campaign
5	RCV introduction	1 year	1 to 14 years	1 to 4 years	Six follow-up campaigns every 5 years after initial campaign for 30 years
6	RCV introduction	1 year and 9 years	No initial campaign	No follow-up campaign	N/A

Evaluating Costs of RCV Introduction

We evaluated costs relating to introducing the RCV from the perspective of the South African government as additional cost per dose of RCV compared to the current practice of administering measles-only containing vaccine. In the absence of detailed information, we assumed that no additional program costs are associated with introduction of the RCV vaccine, due to a direct substitution of the RCV with measles-only containing vaccine. Thus, for rubella, focusing on additional (undiscounted) costs relative to the measles baseline should be appropriate to guiding the investment case for rubella vaccine introduction.

The price per dose of the measles vaccine currently used in South Africa (10 doze vial) in South African Rands (ZAR), is ZAR 29.13 [32]. For RCVs, we estimated price per dose for MR (ZAR 38.00 per dose) and MMR (ZAR 81.00 per doze) based on prices reported for the Pan American Health Organization (PAHO) in the Market Information for Access to Vaccines database [33]. PAHO prices are usually within 10% of vaccine prices in South Africa (personal communication with the national cold chain manager). We assume that a multi-year contract will be signed such that the price of the RCV remains the same for the duration of the simulations. To obtain additional costs of RCV introduction, the difference in price per dose between the RCVs (MR and MMR) and the measles vaccine was multiplied by the total number of persons vaccinated under each scenario. Total numbers of persons vaccinated under each scenario were estimated by applying expected coverage estimates to corresponding target populations obtained from the UN population estimates [34]. The number of CRS cases averted in each scenario was obtained by subtracting the number of CRS cases in that scenario from the number of CRS cases in scenario 1.

For each scenario, we calculated the number of RCV doses per CRS case averted by dividing the total number of RCV doses used by the total number of CRS cases averted. The corresponding cost per CRS case averted was obtained by dividing additional RCV costs by CRS cases averted. These estimates were obtained for MR and MMR using 60% coverage representing the worst case scenario, 80% coverage representing the WHO recommended minimum coverage for RCV introduction and the 95% coverage level representing the best case scenario.

Evaluating DALYs Averted by RCV Introduction

To assess total undiscounted disability-adjusted life years (DALYs) averted by the introduction of RCV, we estimated the number of CRS cases averted from 2020 to 2050 (as the difference in CRS cases between each RCV scenario and the no RCV scenario) and applied this to undiscounted DALYs lost per CRS case. DALYs lost per CRS case were obtained from an existing study reporting DALYs lost for a range of countries using disability weights from the 1990 and 2010 Global Burden of Disease (GBD) study [35]. For the purposes of this paper, we use estimates of DALYs lost reported for upper middle-income countries (World Bank classification for South Africa) using 2010 GBD disability weights.

Evaluating Impact on Outbreak Risk

An important measure of the success of vaccination programs is the degree to which they can sustain elimination and (even transiently) prevent outbreaks [36]. The effective reproductive number (R_E) is the average number of secondary cases resulting from the introduction of one infectious person into a population containing some individuals who are not susceptible to the infection [37]. Estimates of R_E have been used to inform timing of vaccination interventions for preventing disease outbreaks [38], and to determine the likelihood for disease outbreaks in populations if an infectious case was introduced [39].The endemic nature of rubella in the absence of RCV and the subsequent change in number of susceptible individuals with an introduction of

RCV could result in a change in R_E over time. A value for R_E greater than one implies rubella outbreaks can occur and values less than 1 mean that the infection goes into extinction. Values of R_E over time were extracted from the simulations to understand the impact of various scenarios on estimated time to rubella elimination and periods when there was a rebound in R_E from values below 1 to values greater than 1. These fluctuations in R_E associated with different scenarios will inform vaccination activities which should be implemented even after perceived short-term elimination is achieved to avoid possible rebound in rubella incidence. We extracted and presented values of R_E for the entire period during which the simulations were run. The effective reproduction number (R_E) was estimated from the model output using the next generation method [40].

4.4. **Results**

Rubella Incidence

Figure 1 represents the typical patterns we see across the 6 vaccination campaigns. In the absence of rubella vaccination in the public sector (scenario 1), rubella remains endemic with annual peaks in incidence (Figure 1A). There is a decrease in the incidence of rubella over time due to declining birth rates which decreases the rate at which individuals become infected in the population resulting in an increase in the average age of infection (Figure 1). For all scenarios with a mass campaign (scenarios 3, 4, and 5), there is a sharp decrease in rubella incidence (Figures 1C,D,E). For these same scenarios, we see an increase in the average age of infection; however, this is only among very few to no rubella cases, so is not meaningful when evaluating the impact of vaccination. For scenarios with RCV introduction without mass vaccination (scenarios 2 and 6), there is a gradual decrease in rubella incidence as well as a gradual increase in average age of infection (Figure 1B,F). The higher average age of infection with decreased rubella incidence results from higher relative numbers of rubella in individuals of older age groups compared to cases in children that substantially reduce following vaccine introduction.

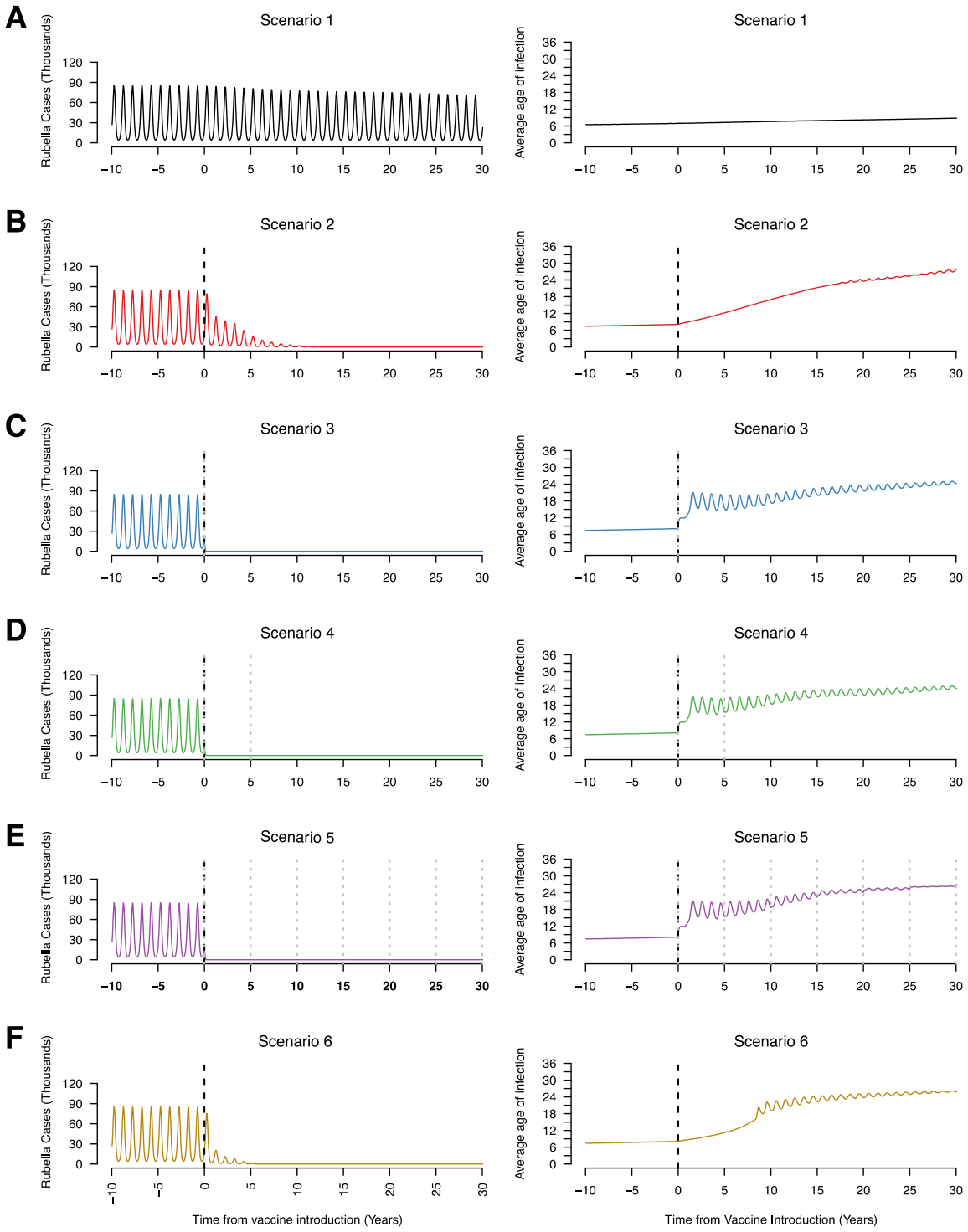

Figure 1. Time series of the annual number of rubella infections (in thousands) and average age of infection for scenario 1 (**A**), scenario 2 (**B**), scenario 3 (**C**), scenario 4 (**D**), scenario 5 (**E**), and scenario 6 (**F**), assuming 80% RCV coverage in routine and campaigns if relevant to the scenario. The vertical black dotted line represents the year of RCV introduction (year zero) and the grey dotted lines represent supplementary immunization activities (SIAs).

CRS Incidence

Without RCV introduction, CRS incidence (CRS cases per 100,000 live births) increased steadily over time as a result of rising average age of infection (black line, Figure 2A). Introduction of RCVs in the EPI schedule along with an initial mass campaign leads to rapid reduction in the incidence of CRS while this reduction was much slower when RCVs were introduced without an initial mass campaign (Figure 2C,D,E versus Figures 2B,F). In scenario 2, CRS incidence initially drops following introduction of RCV and subsequently begins to increase; the timing of increase vary with RCV coverage levels. Lower levels of RCV coverage lead to a shorter time to a recrudescence of CRS cases following an observed initial decrease (Figure 2B). In scenarios 3 and 4, low RCV coverage (60%) leads to a decrease in the incidence of CRS cases followed by a slight recrudescence of cases after 20 years (Figure 2C,D). This was not observed for scenario 5 even with RCV coverage levels as low as 60% due to the frequent campaigns occurring every five years and obtaining 80% coverage (Figure 2E). For scenario 6, there was also no recrudescence of CRS incidence regardless of RCV coverage but the decrease in CRS incidence was faster than scenario 2 and slower compared to scenarios 3, 4 and 5 (Figure 2F). A reduction in CRS incidence to less than 1 per 100,000 live births was achieved and sustained for RCV coverage values of 80% and above for all scenarios. The time to CRS elimination was shortest and did not vary with R_0 for scenarios 3 through 5 at 80% RCV coverage (Supplement 1). For scenario 6, CRS elimination following RCV introduction was quicker with a higher values of R_0 and time to CRS elimination was shorter in scenario 6 compared to scenario 2 (Supplement 2).

CRS Cases Averted

The number for CRS cases averted in scenarios 2–6 compared to scenario 1 over different time horizons (10 years, 20 years, and 30 years) is shown in Figure 3. The number of CRS cases averted was consistently smallest for scenario 2 regardless of vaccine coverage. The highest incremental number of cases averted was observed between 60% coverage and 80% coverage. There is little difference in CRS cases averted between scenarios 3, 4, and 5 for 80% RCV coverage compared to scenarios where RCV coverage was 95%. For scenario 6, there were fewer CRS cases averted compared to scenarios 3, 4, and 5 but more cases averted compared to scenario 2.

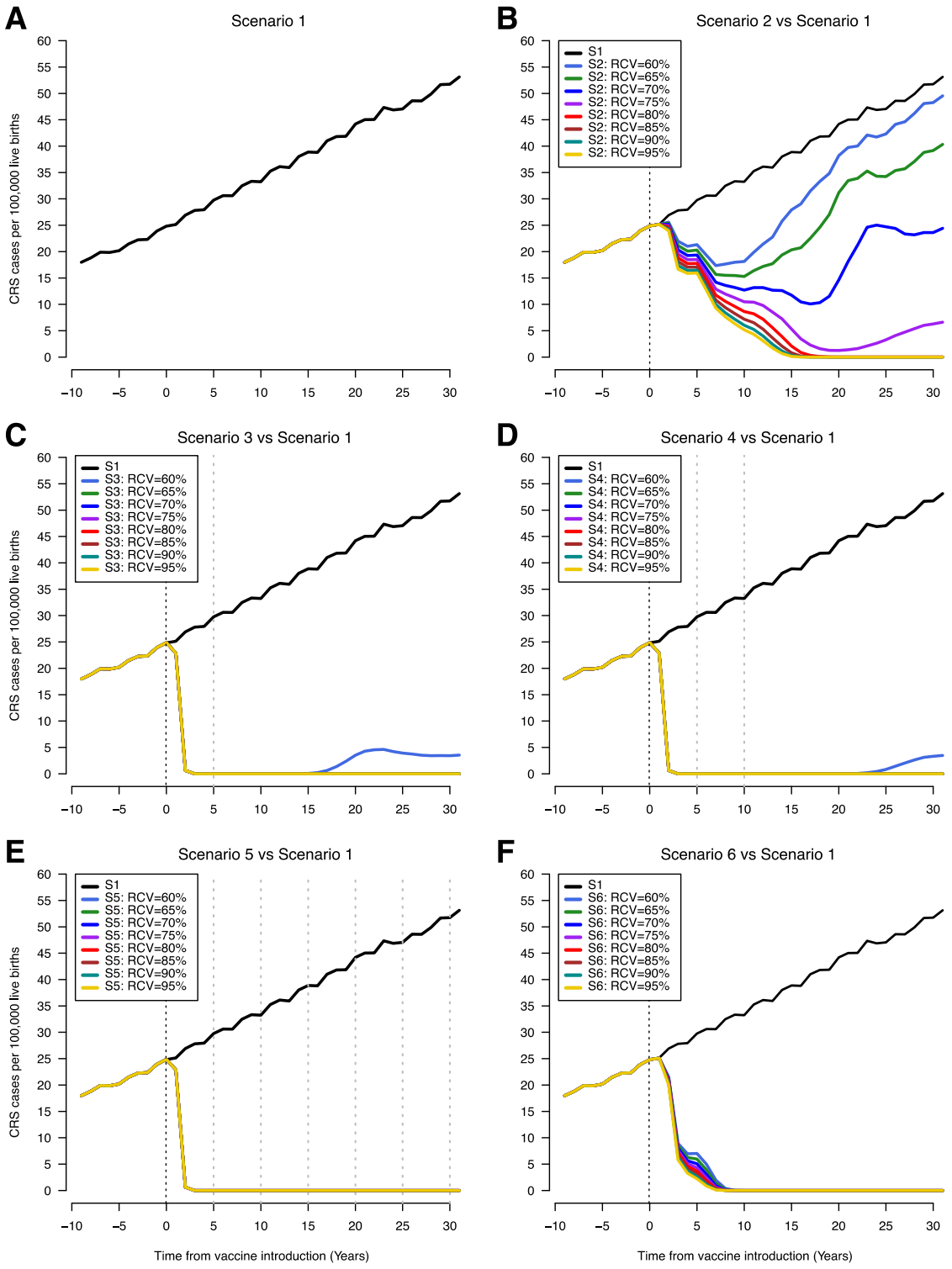

Figure 2. Time series of congenital rubella syndrome (CRS) incidence (CRS cases per 100,000 live births) showing scenario 1 (**A**) and comparing scenario 1 with scenarios 2–6 (**B–F**). The vertical black dotted line indicates year of RCV introduction (year zero) and the grey dotted lines represent SIAs. The x-axis shows time from 10 years prior to RCV introduction to 30 years after RCV introduction. CRS incidence estimates overlap on the plots for different RCV coverages, so that only the line for 95% coverage appears on the graph (RCV coverages 65–95% years 0–30 (**C** and **D**), RCV coverages 60-95% years 0–30 (**E**), and RCV coverages 60–95% years 8–30 (**F**)). (S1 = scenario 1, S2 = scenario 2, S3 = scenario 3, S4 = scenario 4, S5 = scenario 5, S6 = scenario 6).

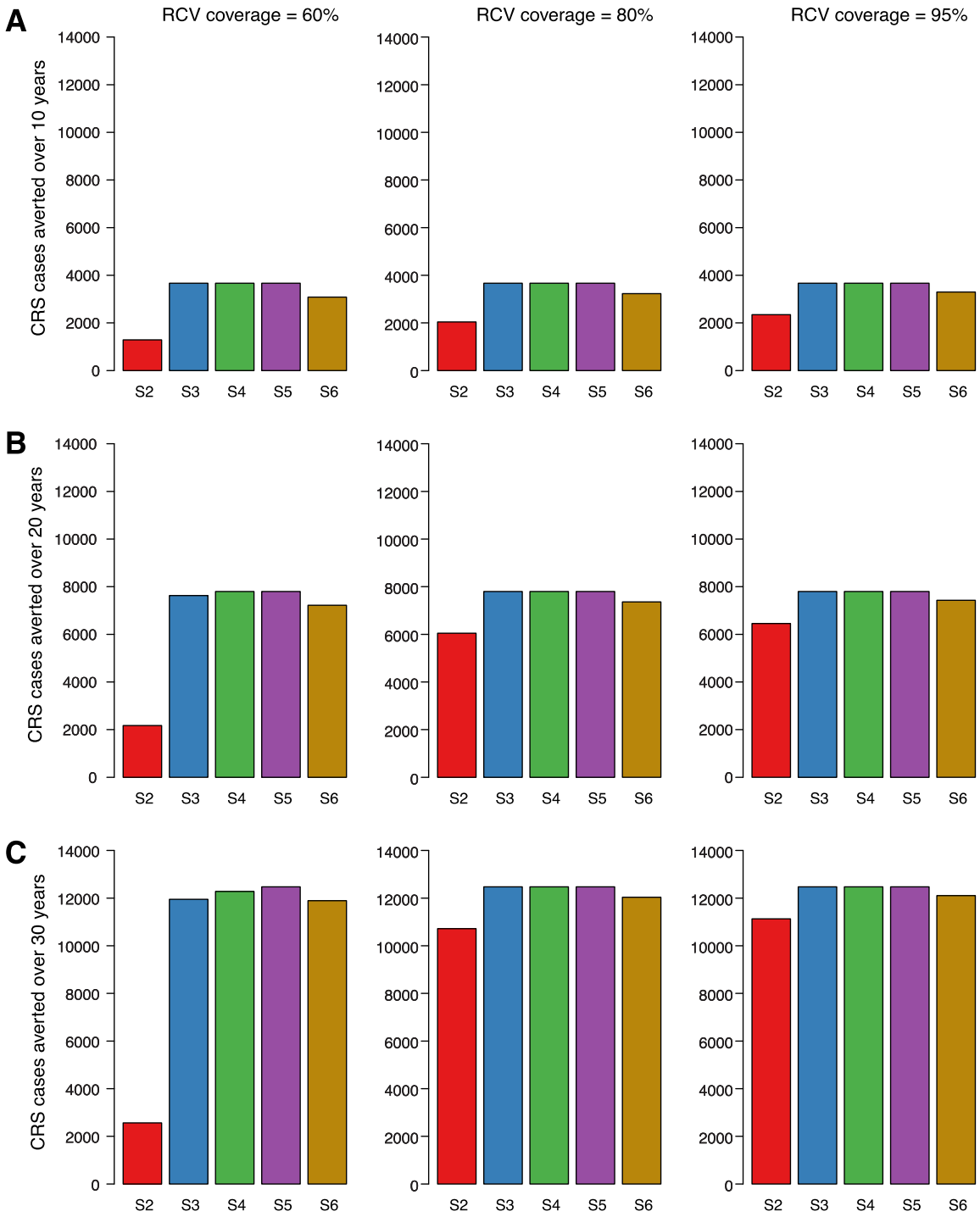

Figure 3. Cumulative number of CRS cases averted for scenarios 2 through 6 compared to scenario 1 over three time horizons post vaccine introduction. Each row of figures represents a different time horizon; 10 years (**A**), 20 years (**B**), and 30 years (**C**). Each column represents a different level of vaccination coverage for routine doses (60%, 80%, and 95%) from left to right, while maintaining coverage at 80% for vaccines administered outside the routine schedule. Scenarios 2 through 6 were each compared to scenario 1 and represent the bars in each plot (S2 = scenario 2 vs. scenario 1, S3 = scenario 3 vs. scenario 1, S4 = scenario 4 vs. scenario 1, S5 = scenario 5 vs. scenario 1, S6 = scenario 6 vs. scenario 1).

Efficiency of RCV to Reduce CRS Cases

We present comparisons of the percentage reduction in CRS cases with the number of RCV doses per CRS case averted and the corresponding additional vaccine cost per CRS case averted (Figure 4). The cost of the MR (Figure 4A) vaccine is lower than of the MMR vaccine (Figure 4B), as such the cost per CRS case averted is also lower. As observed above, the highest percent reduction in CRS cases is observed in scenarios 3, 4, and 5 within all coverage levels and across time horizons (Figure 3). At higher levels of coverage (80–95%), scenarios 3, 4, and 5 have the highest number of doses per case averted and consequently, the highest RCV cost per case averted. However, at the lowest coverage level (60%), scenario 6 is observed to have the lowest number of doses per CRS case averted and the lowest RCV cost per case averted across all study time horizons. Within each study scenario, number of doses and cost per CRS averted increases with coverage. An exception is observed in scenario 2 where at 60% coverage, a higher number of doses and cost per case averted is observed compared to 80% and 95%. This can be explained by re-emerging CRS cases observed at lower levels of coverage in scenario 2 approximately 5 years post-RCV introduction (Figure 2A). When RCV cost per case averted is compared to the additional benefits of each scenario (represented here as percent CRS reduction), scenario 6 (at 60% coverage) is observed to have the least RCV cost at a high percent reduction in CRS cases across all time horizons.

The relationship between RCV and CRS cases averted across the scenarios and vaccination coverages described above is qualitatively similar to the relationship between RCV and undiscounted DALYS averted (Supplement 2). The maximum DALYs averted in any scenario is 285,611 based on 12,472 CRS cases averted (Supplement 3).

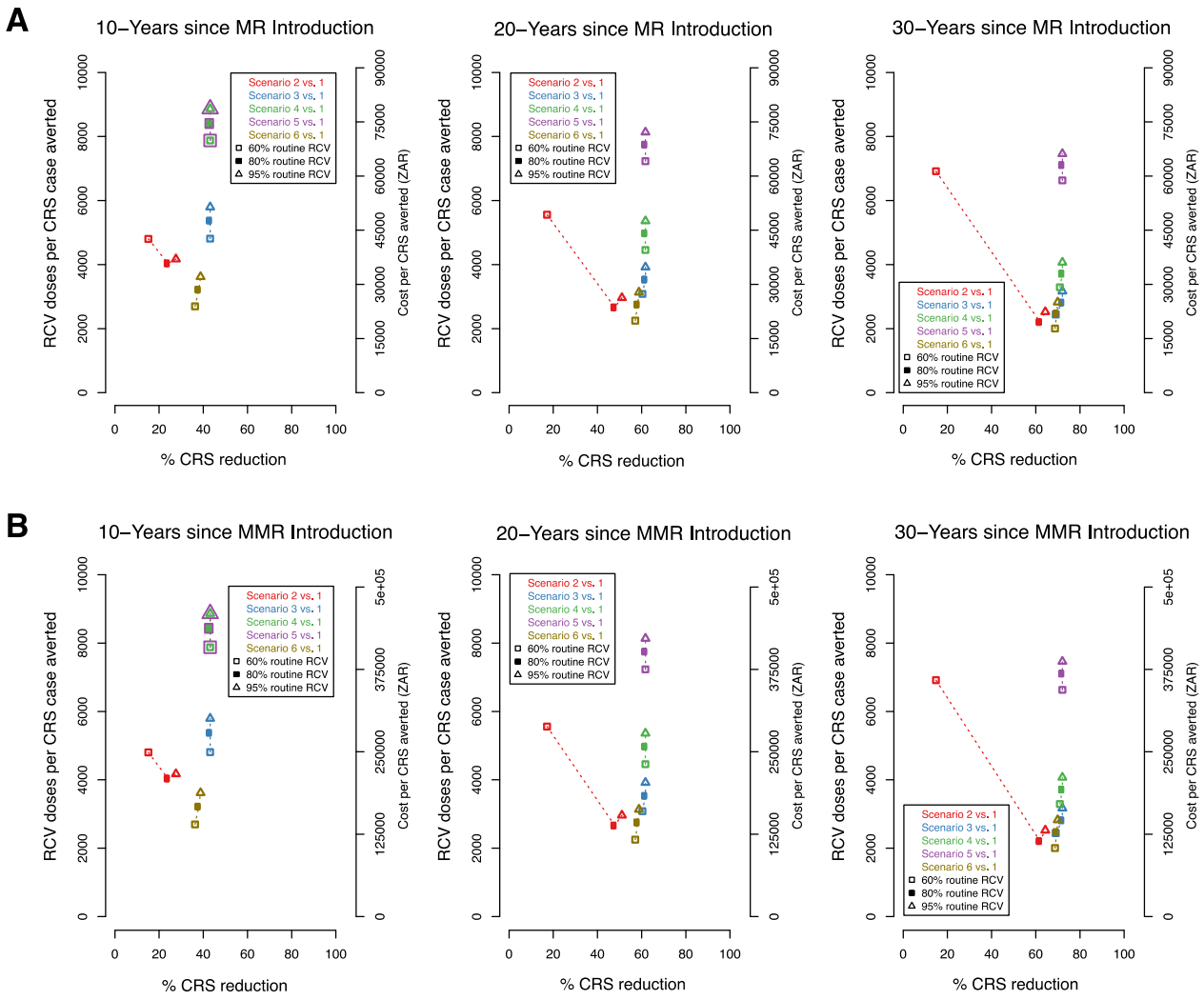

Figure 4. The percent reduction in CRS cases by the number of RCV doses (left y-axis) and cost (right y-axis) per CRS cases averted over three time horizons (10, 20, 30 year). Each figure compares the percent reduction in CRS cases for scenarios 2–6 to scenario 1 (represented by colours) for three RCV coverages (60%, 80%, 95% represented by shapes). Cost is evaluated based on the measles-rubella (MR) (**A**) and measles-mumps-rubella (MMR) (**B**) vaccine. At the 10 year horizon in both 4A and 4B, the numbers corresponding the scenario 4 and 5 overlap and have been represented as overlapping points.

Effective Reproductive Number (R_E)

We present values of R_E for all scenarios, maintaining RCV coverage at 80% (Figure 5). For scenario 1 (absence of RCV introduction) the value of R_E fluctuates around 1.2 which consistent with the periodic peaks in rubella cases described in South Africa [19]. In scenario 6, R_E drops to values below one over about 5 years and stays below one over the entire simulation period. In scenario 5, R_E dropped immediately and remained below one over the entire simulation period. In scenarios 3, 4, and 5, the drop in R_E was followed by a brief rebound before a subsequent decrease as a result of accumulating susceptible individuals. The drop in R_E to below 1 was much slower in scenario 2 (over 13 years) and this represents a prolonged period during which outbreaks could occur. The result that R_E drops and stays below one is robust to routine coverage level for all scenarios so long as RCV coverage is 65% or higher (Supplement 4). At 60% coverage, the R_E drops below one and then increases slowly eventually crossing above one in scenarios 2, 3, and 4 (Supplement 4). At 80% RCV coverage, R_E drops and remains at values below one for all

scenarios, although this drop is immediate for scenarios 3 through 5 and gradual for scenarios 2 and 6. The time required for R_E to drop below one was inversely related to R0 values and was longer for scenario 2 compared to scenario 6 (Supplement 5).

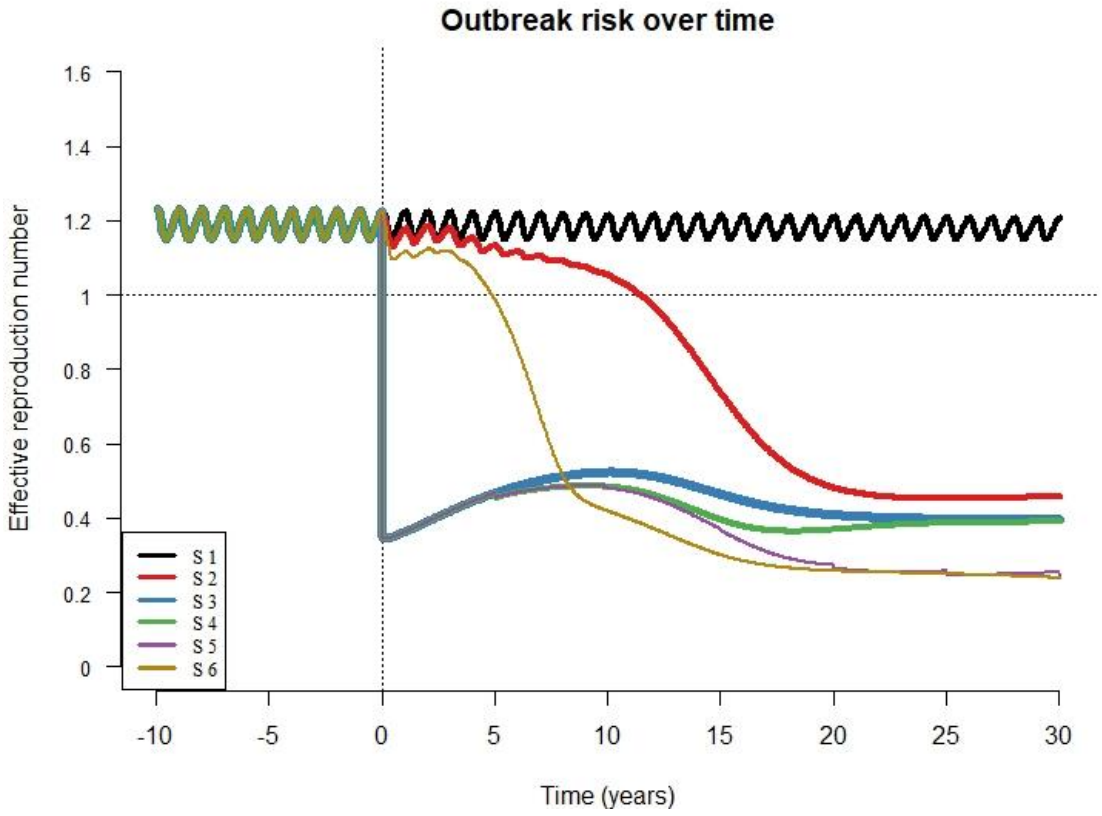

Figure 5. R effective (R_E) over time for all scenarios (S1 = scenario 1, S2 = scenario 2, S3 = scenario 3, S4 = scenario 4, S5 = scenario 5, S6 = scenario 6) with vaccine coverage for both routine immunization and campaigns (if relevant to the scenario) set at 80%. The X axis shows time from 10 years prior to RCV introduction to 30 years after RCV introduction. The vertical dotted line represents the year of RCV introduction and the horizontal dotted line represents the value for the effective reproductive number above which outbreaks are likely to occur.

4.5. Discussion

The incidence of CRS is used as a measure for evaluating the effectiveness of rubella vaccination strategies and CRS elimination is a major milestone of RCV introduction. Different vaccine introduction strategies achieve CRS elimination over various periods of time depending on the vaccination coverage achieved and target age groups for vaccination [6]. In the absence of RCV introduction into the EPI schedule, CRS incidence increased steadily over the simulation period. A previous modelling study used results of rubella antibody testing and estimated that CRS incidence in South Africa for 2005 ranged from 16 to 69 CRS cases per 100,000 live births. When exploring the effect of varying RCV coverage levels (60% through 95%) on CRS incidence, our study shows that a reduction in CRS incidence to less than 1 per 100,000 live births can be achieved and sustained when RCV coverage was at least 80% for all scenarios.

Our results show that introducing RCV into the EPI schedule without mass campaigns or SIAs (scenarios 2 and 6) leads to a slower decrease in rubella cases and CRS incidence over time compared to an abrupt decrease observed in scenarios with SIAs. Introducing the vaccine into the routine EPI program protects infants and reduces rubella virus circulation but leaves unprotected individuals of reproductive age who remain susceptible to rubella infection and subsequently CRS. On the other hand, RCV introduction accompanied by a mass campaign targeting individuals up to 15 years of age (scenarios 3–5) results in an immediate reduction of rubella and CRS incidence. This is due to greater reduction in rubella virus circulation in the population and although individuals above 15 years of age are not vaccinated, the reduction in viral circulation and subsequently rubella cases is sufficient to lead to elimination of CRS.

The average age of infection for rubella shifts from the younger to the older age groups following RCV introduction as rubella incidence declines. Prior to RCV introduction, the bulk of rubella infections occur in childhood consistent with a lower average age of infection. A decrease in the number of infections in the younger age group targeted by RCVs results in older individuals bearing a higher relative burden of rubella infection.

Overall, cumulative CRS cases averted was highest in scenarios with higher number of mass campaigns (scenarios 5, followed by scenario 4 and finally scenario 3). The number of CRS cases averted in scenario 6 was lower than in scenarios 3 through 5, but higher than in scenario 2. This suggests that in the absence of mass campaigns, targeting children of specific age groups might be a reasonable alternative. When vaccination coverage are low, we show that reduction in rubella virus circulation can be achieved by vaccinating individuals up to 15 years of age, accompanied with multiple SIA every 5 years (scenario 5). This is sufficient to lead to CRS elimination at coverage levels as low as 60%. However, it is advisable for governments to aim for at least the 80% threshold recommended by WHO, or better still, 95% coverage which is required for measles elimination since the combined vaccine will be used. Achieving high levels of vaccine coverage is important when considering other RCV introduction scenarios due to a possible re-emergence of CRS cases. In 2, 3, and 4, CRS incidence rises above 1 per 100,000 births a few years after RCV introduction when coverage levels are lower than 80%. For scenario 5 in which several SIAs occur after the initial RCV introduction, CRS elimination is sustained even with the lowest vaccine coverage simulated (60%). Interestingly, in all RCV introduction scenarios, the incidence of CRS remain below pre-vaccine incidence estimates irrespective of RCV coverage. This implies that all of the RCV introduction scenarios evaluated in this analysis result in lower annual CRS incidence rate compared to the current situation in South Africa of not having a RCV within the national EPI program. Nonetheless, the WHO recommends that RCV should be introduced when countries meet the 80% threshold and highlights the importance of mass campaigns targeting older children in addition to routine vaccination of infants, not only at introduction of RCV but also as regular follow-up mass campaigns.

Mass campaigns have high budget implications. We found that although scenarios 4 and 5 have the highest percent reduction in CRS cases, the costs associated with both scenarios are higher compared to other scenarios. Conversely, the lowest cost per case averted is observed in scenario 6 (vaccinating only infants and nine year olds with no SIAs or mass campaigns) when coverage levels are low at 60%. However, this does not account for additional costs associated with managing re-emergent CRS cases, 5–10 years post introduction of RCV. Therefore, the additional benefits (CRS cases averted) observed in each scenario need to be weighed against additional RCV costs and CRS management costs in an economic evaluation to inform the most cost-effective scenario that can be implemented in South Africa.

In South Africa, the human papillomavirus vaccine is administered to school-going girls at nine years of age [11] and this is an attractive option for reducing rubella susceptibility (and hence reduction in CRS incidence) in adolescent females. Implementing a RCV dose for nine-year-old children would require scaling up of the school vaccination program to account for both girls and boys, a move that would require additional resources since this would be an annual intervention. We simulated this option and it resulted in lower RCV cost for a comparable percentage CRS reduction compared to all other scenarios. It is important to note however, we assumed that all children age nine years old are enrolled and therefore eligible for the vaccine. Enrolment less than 100% will result in a lower impact of RCV on CRS incidence in this scenario. The additional RCV cost alone (compared to the cost of the current measles vaccine) might not be adequate to assess the cost-effectiveness of this strategy; however, it does provide a preliminary insights into the comparative costs of the vaccination scenarios modelled.

The cost of RCV increased with increasing target age group for SIAs. This was inversely proportional to the CRS burden since the higher number of vaccinated individuals inversely correlates with the number of susceptible individuals with resulting decrease in CRS incidence. Routine vaccination coupled with vaccination of nine years old children (scenario 6) achieved reductions in CRS cases at the least vaccine costs per CRS case averted compared to the other scenarios modelled. Scaling up HPV vaccination in schools to include boys for the RCV component appears to be a sustainable option. South Africa is a middle-income country and is not eligible to receive Gavi funding so the costs of RCV introduction will be entirely borne by the national government. The estimates of vaccine cost from the government perspective indicate higher costs with increasing target age for mass campaigns but the increasing cost corresponds to decreasing CRS incidence. A trade-off will have to be made by decision makers regarding this. For RCV, most of the added cost (when compared to the current measles vaccine) is tied to the additional cost of the rubella component of the vaccine since routine measles vaccination is an established program and mass campaigns can be organized, but with additional costs. Although vaccine wastage and other program-related costs were not estimated, it is likely that vaccine wastage from a 10-dose RCV formulation will not change from current levels of the measles vaccine. Further considerations will have to be made if any formulation other than the 10 dose vial is used.

Keeping RCV coverage for routine immunization and SIAs at 80%, the effective reproduction number (R_E) dropped sharply from values fluctuating around 1.2 in the pre-vaccine era to less than 1 following vaccine introduction except for scenarios 2 and 6 in which R_E dropped to values below one over several years. This delay could lead to surges in rubella cases and eventually CRS cases. With the exception of scenario 5, scenarios with an initial SIA are associated with a rise in values of R_E after the initial drop. The rebound increase in R_E reflects growth in the susceptible population as a result of accumulation of successive fractions of the birth cohort that are unvaccinated each year. As a result, subsequent mass campaigns cover some of these missed individuals, as is the case in scenarios 4 and 5, causing the value of R_E to drop followed by a progressive rise. High RCV coverage levels should be maintained to keep R_E below 1, thereby avoiding rubella outbreaks that could lead to CRS cases.

Strengths and Limitations

A major strength of this paper is the fact that the age-structured model has been used to inform national RCV introduction strategies in several countries. Secondly, the choice of scenarios simulated and model inputs were informed by sources relevant to the local setting which enables better estimations. Lastly, the approach used to estimate additional vaccine introduction costs of

RCV compared to monovalent measles vaccine can be applied to other countries with a similar immunization schedule for measles and rubella. The main limitation of this study is the fact that the model produces outputs for the entire South African population and does not account for disparities between geographic units such as provinces or districts. Factors such as contact patterns, birth rates, and vaccine coverage could differ between districts or provinces, leading to variation in local disease dynamics. Additionally, the vaccine scenarios assume individuals in the target age group are accessible and can be vaccinated per the assumed coverage and taking into account vaccine efficacy. Finally, all costs associated with RCV scenarios modelled in this study where not fully accounted for, limiting the use of our results in informing the prioritization of RCV scenarios on the basis of their cost-effectiveness.

4.6. Conclusion

The output from the age-structured model emphasizes on the importance of maintaining a high vaccination coverage when introducing RCVs in the South African EPI schedule. The threshold coverage of 80% should be maintained for all vaccine introduction scenarios to achieve rubella and CRS elimination while attaining 95% could, in addition, lead to measles elimination. The results also support a vaccine introduction strategy that entails a combination of routine RCV vaccination in the primary immunization series and additional vaccination of older children in order to maximize the impact on rubella and CRS. More robust economic evaluation studies would be required to inform the prioritization of RCV introduction strategies in South Africa.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Supplement 1: Model Description; Supplement 2: CRS incidence over time for scenarios 2 to 6 compared to scenario 1 with extreme values of R0; Supplement 3: CRS cases averted and DALYs averted over time for scenarios with RCV compared to no RCV; Supplement 4: Change in effective reproductive number over time for all RCV coverage values; Supplement 5: Change in RE over time for scenarios 2 to 6 compared to scenario 1 with extreme values of R0.

Author Contributions: Conceptualization, N.V.M., C.S.W., C.J.E.M., and A.K.W.; Data curation, C.J.E.M.; Formal analysis, N.V.M., C.J.E.M., and A.K.W.; Funding acquisition, N.V.M., C.S.W., and C.J.E.M.; Methodology, N.V.M., I.E., C.S.W., C.J.E.M., and A.K.W.; Project administration, N.V.M.; Resources, N.V.M.; Supervision, C.S.W., C.J.E.M., and A.K.W.; Visualization, N.V.M., I.E., C.J.E.M., and A.K.W.; Writing—original draft, N.V.M., C.J.E.M., and A.K.W.; Writing—review & editing, N.V.M., I.E., C.S.W., C.J.E.M., and A.K.W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest: The authors declare no conflict of interest.

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CHAPTER FIVE

The impact of rubella vaccine introduction on rubella infection and congenital rubella syndrome: a systematic review of mathematical modelling studies

5.0. About this chapter

In this chapter, we systematically review mathematical modelling studies that simulated introduction of RCVs in countries without rubella vaccination in their public immunization programs. Keeping in mind that there are no published guidelines on the conduct of systematic reviews of dynamical epidemiological studies, we implemented a comprehensive search strategy and followed best practices outlined for systematic reviews of classical epidemiological studies. By exploring individual mathematical modelling studies of rubella vaccine introduction, we sought to identify optimal RCV introduction strategies that have been explored, whether published or unpublished. This manuscript was published in Vaccines and the full citation is: *Motaze, N.V.; Mthombothi, Z.E.; Adetokunboh, O.; Hazelbag, C.M.; Saldarriaga, E.M.; Mbuagbaw, L.; Wiysonge, C.S. The Impact of Rubella Vaccine Introduction on Rubella Infection and Congenital Rubella Syndrome: A Systematic Review of Mathematical Modelling Studies. Vaccines 2021, 9, 84. https://doi.org/10.3390/vaccines9020084*. The article is available online at: https://doi.org/10.3390/vaccines9020084 and here is the list of authors and their affiliations:

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5.1. Abstract

Introduction

Rubella vaccines have been used to prevent rubella and congenital rubella syndrome (CRS) in several World Health Organization (WHO) regions. Mathematical modelling studies have simulated introduction of rubella-containing vaccines (RCV) and their results have been used to inform rubella introduction strategies in several countries. This systematic review aimed to synthesize the evidence from mathematical models regarding the impact of introducing RCVs.

Methods

Systematic review methods for classical epidemiological studies and reporting guidelines were followed as far as possible. A comprehensive search strategy was used to identify published and unpublished studies with no language restrictions. We included deterministic and stochastic models that simulated RCV introduction into the public sector vaccination schedule, with a time horizon of at least five years. Individual-based models and models solely estimating epidemiological parameters were excluded. Outcomes of interest were time to rubella and CRS elimination, trends in incidence of rubella and CRS, number of vaccinated individuals per CRS case averted and cost-effectiveness of vaccine introduction strategies. The methodological quality of included studies was assessed using a modified risk of bias tool and a qualitative narrative was provided given that data synthesis was not feasible.

Results

Seven studies were included from a total of 1393 records retrieved. The methodological quality was scored high for six studies and very high for one study. Quantitative data synthesis was not possible because only one study reported point estimates and uncertainty intervals for the outcomes. All seven included studies presented trends in rubella incidence, six studies reported trends in CRS incidence, two studies reported the number vaccinated individuals per CRS case averted and two studies reported an economic evaluation measure. Time to CRS elimination and time to rubella elimination were not reported by any of the included studies. Reported trends in CRS incidence showed elimination within five years of RCV introduction with scenarios involving mass vaccination of older children in addition to routine infant vaccination. CRS incidence was higher with RCV introduction than without RCV when public vaccine coverage was lower than 50% or only private sector vaccination was implemented. Although vaccination of children at a given age achieved slower declines in CRS incidence compared to mass campaigns targeting a wide age range, this approach resulted in the lowest number of vaccinated individuals per CRS case averted.

Conclusion and recommendation

Vaccination of infants should be combined with vaccination of older children to achieve rapid elimination of CRS. Better outcomes are obtained when rubella vaccination is introduced into public vaccination schedules at coverage figures of 80%, as recommended by WHO, or higher. Guidelines for reporting of outcomes in mathematical modelling studies and the conduct of systematic reviews of mathematical modelling studies are required.

Registration: PROSPERO (CRD42020192638)

Key words: *Rubella, congenital rubella syndrome, rubella-containing vaccines, systematic review, data synthesis*

5.2. Introduction

A systematic review (SR) makes use of predetermined methods to obtain, evaluate and collate available individual studies on a specific research question [1,2]. SRs are deemed as providing the highest level of evidence for health care interventions [3]. When assessing individual studies, comparisons can be made to identify similarities or differences in study characteristics (e.g. setting, design, participants etc.), which influence the applicability of the results to different settings. Meta-analysis (which involves combining results of several individual studies) when appropriate, allows for greater precision since the resulting sample size is larger than that of individual studies.

Five main steps have been suggested for evidence-based practice [4] and SRs [5]. These steps have been widely adopted by researchers to address a variety of research questions. However, the study question of interest determines the design of individual studies that are included. SRs of classical epidemiological studies have been rigorously improved over time with published methodological [2] and reporting approaches [6,7] that are regularly updated. On the contrary,

although there have been several published SRs of mathematical modelling studies, guidelines for their design and implementation have not yet been extensively developed. Examples of study questions addressed by SRs of mathematical modelling include interventions on health care provision in small and large populations [8] and the impact of vaccines on tuberculosis [9] and cervical cancer[10].

Rubella-containing vaccines (RCV) were first introduced in Europe and the USA in 1969 [11], resulting in a decline in the number of rubella infections and cases of congenital rubella syndrome (CRS). Rubella causes mild disease in most children and adult. Severe complications of rubella infections occur mostly in pregnant women and these include miscarriages, stillbirths and CRS. CRS can occur in up to 90% of cases when a pregnant woman gets infected with rubella in the first trimester [12]. Therefore, rubella vaccines not only prevent infection in children and adults but also indirectly protect the foetus.

The global vaccine action plan (GVAP) [13] and the global measles and rubella strategic plan resulted in the establishment of measles and rubella elimination targets for several World Health Organization (WHO) regions [14]. There was subsequently an accelerated roll-out of RCV into the public immunization schedules of countries that did not include rubella vaccination in their national immunization programs. By the end of 2019, only 21 countries did not include RCVs in their public immunization schedules [15]. Different RCV introduction strategies and their impact on rubella and CRS elimination have been outlined by WHO [16]. These included childhood vaccination only or various combinations of childhood and adult vaccination.

Applications of mathematical modelling studies to vaccination strategies are broad. Identifying barriers to achieving elimination of measles [17] and informing vaccine introduction into national public immunization programs [9,18–20] are a few examples. Mathematical modelling studies are referred to as dynamical or mechanistic epidemiological studies while observational and interventional studies (such as cross-sectional, case-control, cohort, randomized controlled trials) are referred to as classical epidemiological studies [21]. A mathematical model uses mathematical statements to represent observations [22]. In general, when the model output solely depends on the inputs, the model is said to be deterministic and when the role of chance is incorporated into the model, the model is said to be stochastic. Using computer software, a mathematical model can be used to simulate or represent a biological process and with advances in technology, there have been advances in the understanding of complex disease processes. Models of rubella transmission dynamics build on current knowledge of pathogen biology and separate the population into compartments depending on disease stage or vaccination status. These compartments could be individuals with maternal immunity (M), exposed individuals who are infected but not yet infectious (E), infected individuals who are infectious (I), previously infected but recovered individuals (R), and vaccinated individuals (V).

In contrast to classical epidemiological studies that deduce conclusions on data collected in the real world, mathematical modelling studies can simulate interventions and estimate their impact. Insights on interventions that would be challenging to implement, such as testing various vaccine introduction scenarios in a given country, can be obtained. Currently, the synthesis of evidence

from mathematical modelling studies has not been as extensive as that of classical epidemiology studies. However, methodically compiling evidence can yield valid findings to inform policy.

Mathematical models have been used to assess the impact of RCV on rubella and CRS elimination in several WHO regions: Costa Rica [23] in the Americas, India [19] in South East Asia and Madagascar [18] and South Africa [20] in Africa. Given the variety of settings and modelling approaches used to evaluate the impact of RCVs, it is important to comprehensively summarize the evidence to inform policy-makers in countries that have not yet introduced RCVs, or guide adjustment of vaccination strategies where RCV are already being used.

Aim and objectives

This study aimed to summarise the evidence from mathematical modelling on RCV introduction scenarios and their impact on rubella transmission dynamics.

The primary objective was to estimate time to CRS elimination following rubella vaccine introduction. Secondary objectives were to describe the main modelling approaches for rubella vaccine introduction, identify vaccine introduction strategies that achieve the most rapid reduction in cases of rubella and CRS, and outline the most cost-effective vaccine introduction strategies.

5.3. Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6]. Given that the PRISMA statement was developed mainly for classical epidemiological studies, we adapted the items of the PRISMA checklist where applicable.

Inclusion criteria

Study design: We included mechanistic or predictive mathematical modelling studies that simulate rubella vaccine introduction into national immunization schedules. We included both deterministic and stochastic models. Scenarios of interest targeted various population age groups and scheduling of vaccination i.e. combining routine doses and mass campaigns.

Participants: Individuals eligible for rubella vaccination of any age in any country

Intervention: Rubella-containing vaccine introduction scenarios

Comparison: No rubella vaccine or different vaccine introduction scenarios

Outcomes: We included studies that reported at least one of the following outcomes of RCVs at a population level: time (in years) to the elimination of CRS, time (in years) to rubella elimination, description of trends in rubella and CRS incidence, number of vaccinated individuals per CRS case averted, and cost-effectiveness of vaccine introduction strategy.

Time horizon: We included studies in which the time horizon from the year of vaccine introduction to the end of the simulation is at least five years. We assumed it is unlikely that any meaningful impact of rubella vaccine introduction will be measurable within a shorter period.

Exclusion criteria

We excluded epidemiological studies with an interventional or observational design. We also exclude mathematical modelling studies that were focused on the estimation of model parameters (e.g. basic reproductive number) and modelling studies in which additional vaccination strategies were tested in a setting that already had public sector vaccination.

Search strategy

A comprehensive search strategy was developed and implemented to obtain published studies in Medline and Scopus. Different combinations of Medical Subject Heading (Mesh) terms were used to maximize the outputs of the electronic search. We reviewed the references of included studies for other potentially eligible studies. We also searched for unpublished studies from conference abstracts and repositories of student theses. We only included studies published between 01 January 2000 and 20 June 2020 (to cover a period of 20 years) and we did not apply any language restrictions.

Study selection and data extraction

Two authors independently reviewed the abstracts of studies retrieved using the search strategy. When the abstracts suggested that the studies met inclusion criteria, full-text articles were reviewed to make a final decision. A data collection tool was developed to extract information on study characteristics, risk of bias and participant, intervention, comparison, outcome and time horizon (PICOT) items from the included studies.

Risk of bias assessment

We assessed the methodological quality of included studies using the risk of bias tool used in previously published studies [8,9,24] (Table 1). This risk of bias tool includes questions on the following criteria: study aims and objectives, population and setting, intervention and comparator, outcome measures, time horizon, modelling methods, parameter ranges and sources, assumptions, uncertainty analyses, model fitting, model validation, presentation of results, discussion and conflict of interest.

The 14 risk of bias criteria consisted of one or more questions addressing specific aspects of the study and were graded as poor (if score = zero), average (if score = one) and good (if score = two). The allocated score for each risk of bias criterion was two if all responses to the questions were “yes”, one if at least one of the responses was “yes”, and zero if none of the responses was “yes”. The scores were added to obtain an overall risk of bias score ranging from zero to 28 for the given study. Based on this score, the methodological quality of included studies was classified as very high (score > 22), high (19-22), medium (14-18) and low (<14). When there was a difference in scoring between authors, the authors arrived at a consensus by discussing the assessment.

Table 1: Risk of bias tool for assessment of included studies

	Criterion (adapted from Fone *et al.* & Caro *et al.)*	Considerations (adapted from Fone et al. and Caro et al.)	Score considerations (0, poor to 2, good)	
1	**Are the aims and objectives clear?**	Are the research questions and modelling objectives clearly defined?	0 Not stated 1 Stated but vague 2 Stated and focussed	Definitions: max 8 points
2	**Is the setting and population clearly defined?**	Does the paper clearly state the setting (e.g. geographical location, high/low TB burden)?	0 Not stated 1 Stated but vague or details missing 2 Stated and focussed	
		In health economics models, has the perspective been stated?		
		Does the paper clearly state the modelled population? (e.g. patient or population group characteristics)		
		Have sub-populations necessary for the research question and setting been modelled?		
3	**Are the intervention and comparators adequately defined?**	Does the paper clearly state the population(s) targeted for vaccination?	0 Not stated or very unclear 1 Stated but details missing 2 Stated and all necessary details stated	
		Does the paper clearly define the vaccine characteristics (e.g. vaccine efficacy, duration of protection, number of doses, waning, timing)?		
		If there is a comparator (no vaccine, baseline or alternative intervention scenario), is it clearly defined?		
4	**Are the outcome measures defined and answer the research question?**	Does the paper clearly define the outcomes of interest?	0 Not stated, very unclear or not suited to research question 1 Stated but details missing or not directly aligned with research question 2 Stated, all necessary details stated, and aligned with research question	
		Do the outcomes correspond to the research question?		
5	**Are the model structure and time horizon clearly described and appropriate for the research question?**	Is the model structure clearly reported and appropriate for the research question?	0 Not appropriate model structure, or poor/no description of model 1 Incomplete description, and/or appropriate in part for research question 2 Complete and reproducible, appropriate structure and time horizon	Model methods: max 4 points
		Does the model reflect current knowledge of disease natural history?		
		Is the time horizon and time step of the model clearly stated and appropriate to the research question (i.e. is it long enough to capture health effects)?		
6	**Are the modelling methods appropriate for the research question and adequately described?**	Were the modelling methods clearly described, and suited to the research question?	0 Not appropriate model structure, or poor/no description of methods 1 Incomplete description, and/or appropriate in part for research question 2 Complete and reproducible, appropriate method	
7	**Are the parameters, ranges and data sources specified?**	Are all parameters and their ranges reported?	0 Poorly reported 1 Some information missing 2 Complete reporting of parameters, ranges and data sources	Model inputs: max 6 points
		Are the data sources for parameters reported?		

8	**Are any assumptions explicit and justified?**	Are all assumptions explicit and justified?	0 Not reported 1 Explicit 2 Explicit and justified	
9	**Is the quality of data considered and is uncertainty explored through uncertainty and/or sensitivity analyses?**	Are data limitations discussed? Are any of the sources known to the reviewer to be inappropriate (e.g. do not match the parameter, are outdated, or known to be poor quality)? Is uncertainty in model structure, parameters and/or assumptions explored through uncertainty and/or sensitivity analyses?	0 No sources or uncertainty 1 Partially addressed, and/or some data inappropriate 2 Fully addressed	
10	**Is the method of fitting described and suitable?**	Is the method of fitting/calibrating the model clearly described? Is the method of model fitting/calibration suitable?	0 Not done, unsuitable method or poor/no description 1 Incomplete description or method not optimal 2 Complete description and suitable methods	Fitting/ validation: max 4 points
11	**Has the model been validated?**	Has an assessment of validity of the results been made by comparing across one or more different model structures, or against a validation data set?	0 Not considered 1 States criteria for validation 2 Validation undertaken	
12	**Have the results been clearly and completely presented, with a range of uncertainty?**	Have the outcome values and their uncertainty ranges for each intervention/scenario been reported? Do the results match the objectives? Are sensitivity analyses clearly reported?	0 Not reported, very unclear or not suited to research question 1 Stated, but ranges or planned sensitivity analyses missing and/or not directly aligned with research question 2 Values and ranges and planned sensitivity analyses reported and aligned with research question.	Results: max 4 points
13	**Are the results appropriately interpreted and discussed in context?**	Does the discussion reflect a fair and balanced interpretation of the results? Are the results of the study discussed in context and is generalisability considered? Are possible biases and limitations discussed?	0 No/poor discussion 1 Some discussion but key points, limitations or context missed 2 Full discussion of key points in context, generalisability considered, limitations discussed	
14	**Are the funding source and conflicts of interest reported?**	Is the funding and the role of the funder clearly stated?	0 No statement of funding or conflicts 1 Funding or conflicts reported 2 Funding and conflict statement	Conflicts: Max 2 points

Data Analysis

We performed a qualitative synthesis of the included studies. The minimum WHO-recommended coverage of RCV is 80% [15] so we used this value as the basis for comparing outcomes reported by different studies in cases where several vaccine coverage values were simulated. If any study did not report outcomes for 80% vaccine coverage, outcome values for the next highest coverage values closest to 80% were reported.

We had planned to derive random-effects pooled predictions of the population-level impact of RCV using the *metaphor* package in R statistical software version 4.0 [25]. We intended to

assign equal weights to all models and estimate the median (along with 10th, 25th, 75th, and 90th percentiles) time to congenital rubella syndrome elimination. We had planned to use univariable and/or multivariable linear meta-regression (depending on the number of included studies) to identify potential sources of heterogeneity among included studies and conduct subgroup analysis for different groups of models (deterministic versus stochastic), different World Health Organization Regions and World Bank country classifications. However, differences in the reporting of outcomes between individual studies did not allow for pooled estimates to be obtained.

Table 2: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	S2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6 & 7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	18
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	16 & 17
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	7 & 8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

Ethical considerations

This systematic review did not include the use of individual participant data. Therefore, we did not seek ethical approval. In line with PRISMA recommendations, the study proposal was registered with PROSPERO (CRD42020192638), an international prospective register of systematic reviews, before conducting the search. The PRISMA checklist is shown in Table 2 below.

5.4. Results

The search strategy retrieved 1393 records and 561 distinct abstracts were assessed for inclusion (Table 3 and 4). We excluded 539 records based on the abstracts and reviewed 22 full text articles. We excluded a further 15 articles and included seven studies in the review (Figure 1).

Only a narrative synthesis was done because of the lack of uncertainty assessment in several included studies.

Table 3: **Search strategy for Scopus (date searched: 19 JUNE 2020)**

	Query	Results
5	(TITLE-ABS-KEY (rubella OR rubellas OR "german measles" OR "three day measles")) AND (TITLE-ABS-KEY (vaccination OR vaccin* OR immuniz* OR immunis*)) AND (TITLE-ABS-KEY (model OR models OR modelling OR modeling OR modelled OR modeled OR "theoretical stud*")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re") OR LIMIT-TO (DOCTYPE , "cp"))	946 document results
4	(TITLE-ABS-KEY (rubella OR rubellas OR "german measles" OR "three day measles")) AND (TITLE-ABS-KEY (vaccination OR vaccin* OR immuniz* OR immunis*)) AND (TITLE-ABS-KEY (model OR models OR modelling OR modeling OR modelled OR modeled OR "theoretical stud*"))	987 document results
3	TITLE-ABS-KEY (model OR models OR modelling OR modeling OR modelled OR modeled OR "theoretical stud*")	13,477,036 document results
2	TITLE-ABS-KEY (vaccination OR vaccin* OR immuniz* OR immunis*)	620,481 document results
1	TITLE-ABS-KEY (rubella OR rubellas OR "german measles" OR "three day measles")	24,817 document results

Table 4: **Search strategy for Pubmed (date searched: 19 JUNE 2020)**

	Query	Results
#4	Search: #1 AND #2 AND #3	447 document results
#3	Search: Models, Theoretical [mh] OR model*[tiab] OR theoretical stud*[tiab]	3,807,970 document results
#2	Search: Vaccination[mh] OR vaccin*[tiab] OR immuniz*[tiab] OR immunis*[tiab]	402,546 document results
#1	Search: Rubella[mh] OR rubella*[tiab] OR german measles[tiab] OR three day measles[tiab]	14,410 document results

Excluded studies

Fifteen studies [26–40] were excluded following review of the full text articles. These studies did not meet one or more inclusion criteria and the study characteristics are shown in Supplement 3.

Included studies

Characteristics of included studies

Seven studies were included and all studies implemented age-structured deterministic models. Two studies were conducted in Africa [18,41], one in Europe [42], and four in Asia [19,43–45]. According to the World Bank classification of countries [46], three studies simulated RCV introduction in lower-middle income countries(India, Madagascar and Vietnam) [18,19,44], three in upper-middle income countries (China, Indonesia and South Africa) [41,43,45] and one in a high-income country (Croatia) [42]. Regarding models' compartments, three studies used MSIRV [18,19,41], three studies used MSEIRV [42–44] and one study used SEIRV [45]. The number of scenarios simulated ranged from three to eight. The characteristics of these included studies are shown in Table 1.

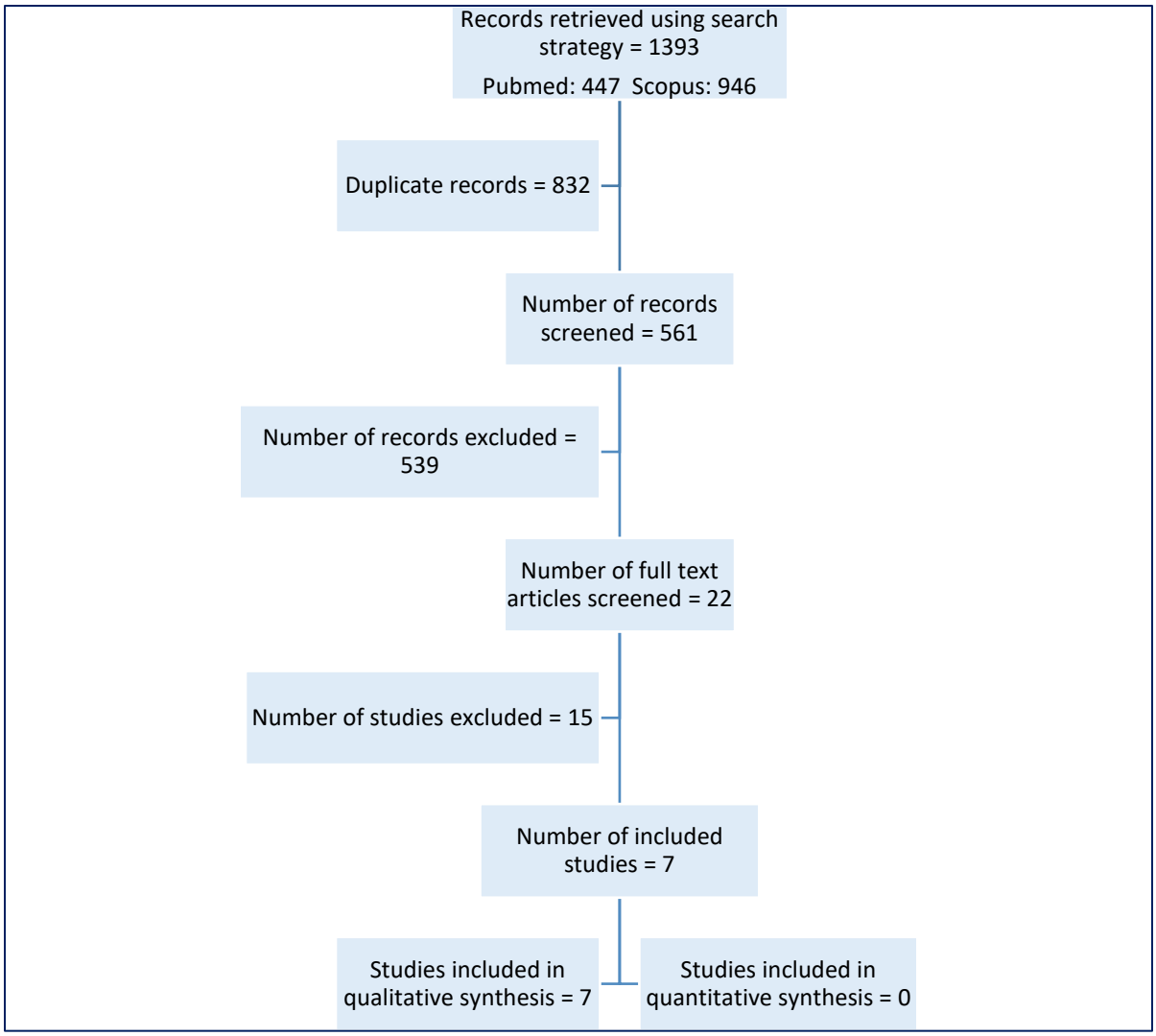
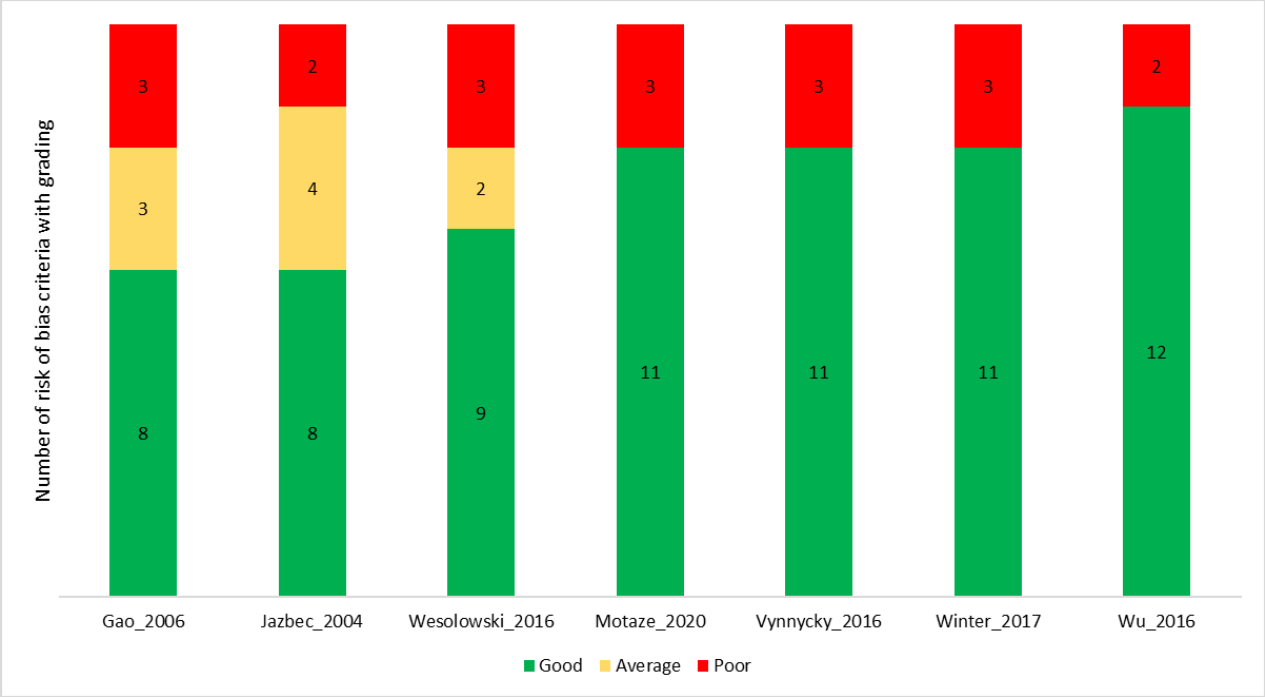


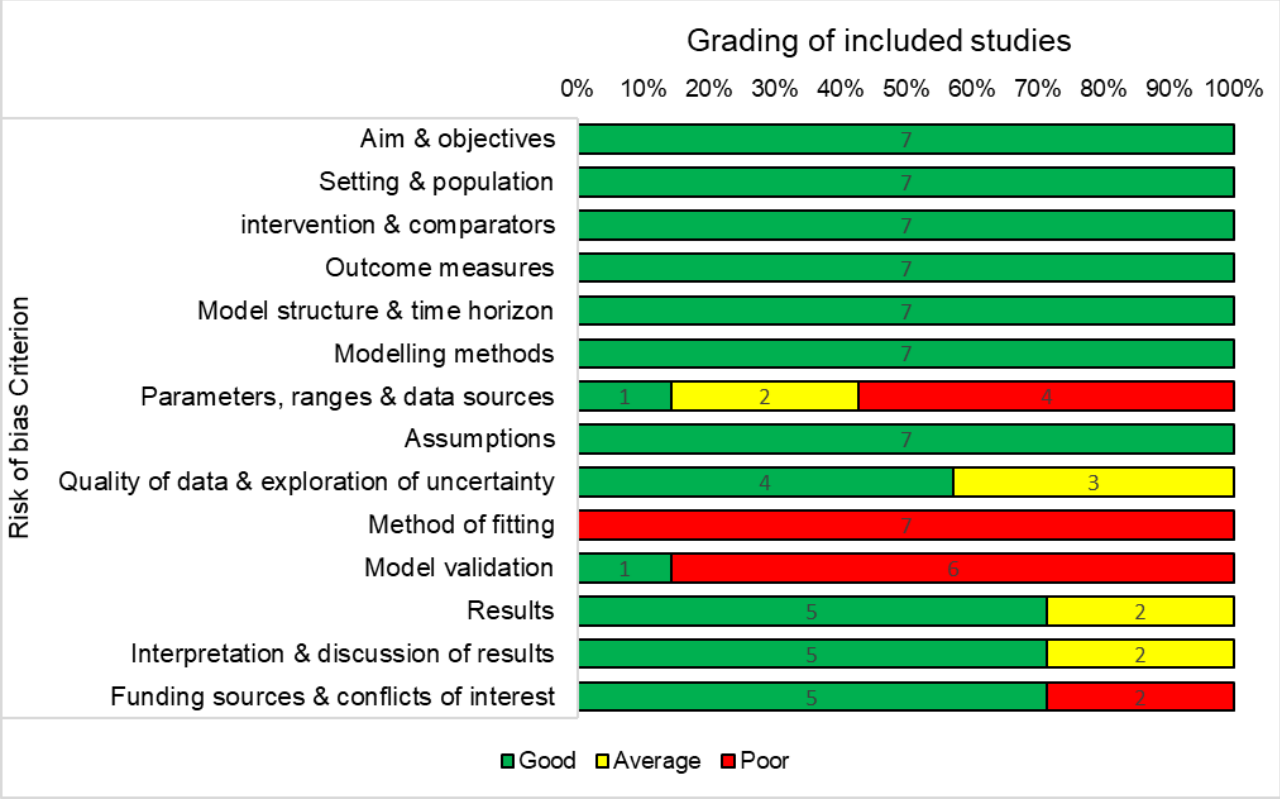
Figure 1: Study flow diagram showing number of records processed at different stages of the review

Risk of bias in included studies

None of the included studies was classified as low or medium with respect to methodologic quality. The methodological quality was high for six studies and very high for one study. The two risk of bias criteria with the lowest scores were method of fitting and model validation. None of the included studies reported the method of fitting and only one study described the validation method used. The highest scores were assigned for aim and objectives, setting and population, intervention and comparators, outcome measures, model structure and time horizon, modelling methods and assumptions. Methodological quality assessments by study and by risk of bias criterion are shown in Figure 2.



a



b

Figure 2: Risk of bias assessment by study (2a) and by risk of bias criterion (2b).

Effect of rubella vaccine introduction

The included studies simulated a variety of vaccine introduction scenarios involving routine infant vaccination and mass campaigns. Some scenarios were simulated by several studies while others were unique to individual studies. Five studies [18,19,41,43,44] simulated national RCV introduction while two studies [42,45] simulated introduction in a limited area within a country. Among the studies that simulated nation-wide vaccine introduction, two studies [18,19] mostly reported outcomes at sub-national level.

Time to elimination of CRS

None of the included studies reported the time from introduction of RCVs to elimination of CRS.

Trends in CRS incidence

Six studies reported on changes in CRS incidence following introduction of RCVs. The number of years to CRS elimination was not specified in the studies but this outcome could be extrapolated from the data on incidence trends within 5-year intervals.

Gao et al. found that compared to no RCV, routine vaccination of 1-year-olds resulted in higher CRS incidence at vaccine coverage figures $\leq$ 50%. When RCV coverage was $\geq$ 70%, CRS incidence was lower with RCVs. At 90% vaccine coverage, rubella elimination was achieved over a period between 15-20 years. When comparing vaccination of 12-year-old girls to no RCV, CRS incidence was lower at all simulated vaccine coverage levels. CRS elimination was not achieved even with 90% vaccine coverage. Trends in CRS incidence were not described for other vaccine introduction scenarios.

Motaze et al. found that CRS incidence was lower for all vaccine introduction scenarios relative to no RCV for all levels of vaccine coverage simulated (60% -95%). With routine vaccination of 1-year-olds CRS elimination was achieved in 15-20 years at RCV coverage $\geq$ 80% and with routine vaccination of 1-year-olds combined with 9-year-olds CRS elimination was achieved in 5-10 years. CRS elimination was achieved for all scenarios involving routine vaccination of 1-year-olds combined with mass vaccination of 1-14-year olds and/or 1-4-year-olds at vaccine coverage figures $\geq$ 65% in 0-5 years.

Vynnycky et al. simulated RCV introduction at a fixed coverage level of 90%, and found that CRS elimination was achieved in under five years for all scenarios involving routine vaccination of 9-month-olds combined with either mass vaccination of 9 months-14 year olds or 15-35-year-old females.

Wesolowski et al. also simulated RCV introduction at a fixed coverage level, but coverage levels differed by region. The incidence of CRS was lower for all vaccine introduction scenarios compared to no RCV. For scenarios involving combinations of routine vaccination and mass campaigns, the effects of mass campaigns targeting individuals above 10 years of age do not differ from targeting 10-year-old children.

Table 4: Characteristics of included studies

Study	Description of target age groups and sex for each vaccine introduction scenario	Setting	WHO region	World Bank gradin g	Previous private sector RCV	Time frame	Classes	Reported outcomes
Gao_2016 [43]	- **scenario 1** : routine vaccination at 1 year (M & F); - **scenario 2**: mass vaccination of 2-14-year-olds (F) and routine 12-year-olds (F); - **scenario 3**: mass vaccination of 2-14-year-olds (F); - **scenario 4**: mass vaccination of 2-14-year-olds (M & F); - **scenario 5**: mass vaccination of 15-40-year-olds (F); - **scenario 6**: routine vaccination of 1-year-old children (M & F) and mass vaccination of 2-14-year-olds (M & F) and 15-40-year-olds (F); - **scenario 7**: routine 1-year-old children (M & F), mass vaccination of 2-14-year-old girls and mass 15-40-year-old women; - **scenario 8**: routine 12-year-olds (F).	China	Western Pacific	Upper-middle Income	Yes	46 years	MSEIR V	-Trends in rubella incidence -Trends in CRS incidence -Number of vaccinated individuals -Number of vaccinated individuals per CRS case averted
Jazbec_2004 [42]	- **scenario 1**: routine vaccination at 1 year (M & F) and at 14 (F); - **scenario 2**: routine vaccination at 1 + 7 years (M & F), and at 14 years (F); - **scenario 3**: routine vaccination at 1 + 12 years (M & F).	Croatia, Tresnjevka municipality	Europe	High-income	No	55 years	MSEIR V	-Trends in rubella incidence
Motaze_2020 [41]	- **scenario 1**: private vaccination only (M & F); - **scenario 2**: private + routine vaccination at 1 year (M & F).; - **scenario 3**: private + routine vaccination at 1 year and start-up campaign for 1-14 year-olds (M & F); - **scenario 4**: private + routine vaccination at 1 year and start-up campaign for 1 - 14 years, followed by one follow-up campaign for 1-4 year-olds (M & F); - **scenario 5**: private + routine vaccination at 1 year and start-up campaign for 1-14 year-olds, followed by follow-up campaigns every 5 years for 1-4 year-olds (M & F); - **scenario 6**: private + routine vaccination targeting 1 year and routine vaccination for 9-year-olds (M & F).	South Africa	Africa	Upper-middle income	Yes	30 years	MSIRV	-Trends in rubella incidence -Trends in CRS incidence -Number of vaccinated individuals per CRS case averted -Economic evaluation measure
Vynnycky_2016 [44]	- **scenario 1**: routine vaccination at 9 months (M & F); - **scenario 2**: catch-up campaign for children 9months - 14years, followed by routine vaccination at 9 months (M & F); - **scenario 3**: catch-up campaign for women aged 15 - 35 years, followed by routine vaccination at 9 months (M & F);	Vietnam	Western Pacific	Lower-middle Income	No	37 years	MSEIR V	-Trends in CRS incidence -Number of CRS cases averted

	- **scenario 4**: catch-up campaign at 9 months - 14 years (M & F) + 15 - 35 years (F), followed by routine vaccine at 9 months (M & F).							
Wesolowski_2016 [18]	- **Scenario 1**: no vaccination; - **scenario 2**: routine vaccination at 9 months only (M & F); - **scenario 3**: routine vaccination and a start-up campaign for 9 months - 10 years, followed by campaigns at 4 year intervals targeting 1- 5 year-olds (M & F); - **scenario 4**: routine vaccination and a start-up campaign for 9 months - 15 years, followed by campaigns at 4 year intervals targeting aged 1- 5 year-olds (M & F); - **scenario 5**: routine vaccination and a start-up campaign for 9 months - 20 years, followed by campaigns at 4 year intervals targeting 1- 5 year-olds (M & F); - **scenario 6**: routine vaccination and a start-up campaign for 9 months - 25 years, followed by campaigns at 4 year intervals targeting 1- 5 year-olds (M & F);	Madagascar	Africa	Lowe-middle income	No	30 years	MSIRV	-Trends in rubella incidence -Trends in CRS incidence
Winter_2017 [19]	- **scenario 1**: no vaccine; - **scenario 2**: private-sector vaccine at 9-15 months and 4-6 years (M & F); - **scenario 3**: private sector + catch-up for children aged 9 months to 14 years + routine vaccination at 9-12m and 16-24m (M & F).	India	South-East Asia	Lower-middle income	Yes	30 years	MSIRV	-Trends in rubella incidence -Trends in CRS incidence
Wu_2016 [45]	-**Scenario 1**: routine vaccination at 9 months (M & F); -**Scenario 2**: routine vaccination at 6 years (M & F); -**Scenario 3**: routine vaccination at 9 months and 6 years (M & F); -**Scenarios 4**: routine vaccination at 9 months and 6 years (M & F) + catch-up for 9 months - 5 years; -**Scenarios 5**: : routine vaccination at 9 months and 6 years (M & F) + catch-up for 9 months -14 years; -**Scenarios 6**: routine vaccination at 9 months and 6 years (M & F) + catch-up for 9 months - 39 years; -**Scenario 7**: routine vaccination of adolescent girls aged 12 years	Indonesia, East Java province	South-East Asia	Upper-middle income	No	50 years	SEIRV	-Trends in rubella incidence -Trends in CRS incidence -Economic evaluation measure

F: females, M: males, SEIRV: susceptible-exposed-infected-recovered-vaccinated, MSIRV: maternal immunity-susceptible-infected-recovered-vaccinated, MSEIRV: maternal immunity-susceptible-exposed-infected-recovered-vaccinate

Winter et al. performed simulations with different RCV coverage for various regions. Compared to no RCV, private sector vaccination of children at 9-15 months and 4-6 years resulted in higher CRS incidence compared to no RCV. CRS incidence was lower with routine vaccination of children aged 9–12 and 16–24 months old (RCV coverage =60%) combined with a mass campaign targeting children aged 9 months through 14 years (RCV coverage =60%) than with private sector vaccination in all regions at R0 = 5. With higher values of R0 (7, 9 and 11), CRS incidence was higher compared to private sector vaccination in several regions. With routine vaccination coverage of 80% targeting children aged 9–12 and 16–24 months old combined with a mass campaign with 80% vaccine coverage targeting children aged 9 months through 14 years, CRS incidence was lower than with private sector vaccination irrespective of R0 values.

Wu et al. reported that incidence of CRS was lower for all vaccine introduction scenarios compared to when RCVs were not included in the public vaccination schedule. CRS elimination was achieved only in scenario 6.

Time to elimination of rubella

None of the included studies reported the time from RCV introduction to rubella elimination.

Trends in rubella incidence

Wesolowski et al. and Vynnycky et al did not report rubella incidence over time following RCV introduction. Gao et al., Jazbec et al., Motaze et al. and Wu et al. reported lower rubella incidence for all vaccine introduction scenarios compared to no RCV introduction. The drop in rubella incidence was abrupt in scenarios including a mass campaign while rubella incidence dropped progressively (over 5 to 10 years) for scenarios that did not include a mass campaign. Winter et al. found that rubella incidence remained below 5/ 100 000 live births for the entire duration of the simulation when routine vaccination coverage was above 95%.

Number of vaccinated individuals per CRS case averted

Gao et al. reported the lowest number of vaccine doses per CRS case averted 46 years after RCV introduction in scenario 2. Vaccine doses per CRS case averted in each scenario were as follows: scenario 1 = 1500, scenario 2 = 1421, scenario 3=1439, scenario 4= 4474, scenario 5 = 6403, scenario 6 = 2622, and scenario 7 = 2329. Motaze et al. reported that at 80% coverage, the lowest number of vaccine doses per CRS case averted 20 years after RCV introduction was achieved with scenario 6.

Economic evaluation measures

Disability-adjusted life years (DALYs) averted

Only one study, Motaze et al., reported this outcome. At 80% RCV coverage, undiscounted DALY's averted 20 years after vaccine introduction was the same for scenarios 3,4 and 5 (178584). DALYs averted were lowest for scenario 2 (138408) followed by scenario 6 = 168562.

Vaccine cost per CRS cases averted

Two studies reported outcomes related to vaccine cost. Motaze et al. reported that at 80% coverage, the lowest cost per CRS case averted 20 years after RCV introduction was achieved with scenario 6. Wu et al. found that at 80% coverage, the lowest discounted incremental Cost

effectiveness ratio (ICER) post vaccine introduction (cost per CRS case averted 20 years after RCV introduction) was obtained with scenario 2 (USD 277.22). This cost was USD 375.22 for scenario 1, USD 440.15 for scenario 3, USD 571.33 for scenario 4, USD 761.65 for scenario 5, USD 1098.29 for scenario 6, and USD 739.93 for scenario 7.

None of the studies reported time to CRS elimination and time to rubella elimination.

5.5. Discussion

All included studies were deterministic age-structured models and the results did not allow for data synthesis. CRS elimination was achieved over the shortest period with scenarios combining routine immunization of infants to mass vaccination of older individuals. Low coverage with rubella vaccines led to higher CRS incidence compared to no vaccination. Interestingly, we found that strategies involving routine vaccination of children at specific ages outside the routine infant dose were more cost effective than strategies involving mass campaigns.

The reported increase in CRS incidence following rubella vaccination at low coverage is a well described phenomenon [47,48]. The low vaccine coverage resulted from low public vaccination coverage in one study and private sector vaccination in another. It is unlikely for private sector vaccination against rubella to be adopted as a national strategy but this highlights the dangers of not having a public rubella vaccination policy. Public sector vaccination, despite being the obligatory strategy to be included for achieving rubella and CRS elimination, can achieve low levels of coverage if not properly implemented. Achieving at least 80% coverage as recommended by WHO [16] avoids this negative effect of rubella vaccines and countries planning RCV introduction should adhere to this recommendation.

None of the studies reported time to rubella elimination or time to CRS elimination, which are critical outcomes that are important to policy-makers. Arriving at a point estimate is standard in classical epidemiology but dynamical epidemiological studies focus more on understanding factors driving the disease transmission process. Elimination of CRS can be achieved using RCV. Given that countries and funders face competing priorities, optimal vaccination strategies have to be chosen when planning RCV introduction. Routine infant vaccination during the first year of life coupled with vaccination of older children and/or adults was found to result in elimination of CRS over a shorter period.

Comparing the costs or vaccination to the benefits is important in order to maximize use of available resources. None of the included studies was an economic evaluation model but vaccinating children at a specific age within the first decade of life was associated with the lowest cost per CRS case averted. Without public vaccination against rubella, infections predominantly affect children 5-14 years old [49], which could explain why strategies targeting children in this age group lead to more rapid elimination. Furthermore, the drop in rubella incidence with vaccination of children at 6 or 9 years is slower compared to the rapid drop with mass campaigns, with similar long-term impact at lower costs. Several countries previously implemented strategies that do not include a mass campaign but targeted vaccination of older

individuals who are not in the age group for routine infant vaccination [50,51]. Subsequently, the insufficient decrease in rubella transmission allowed for persistence of CRS, leading to modifications in vaccination strategy to incorporate additional vaccination of infants.

All studies that reported rubella incidence found a reduction in incidence for all vaccine coverage levels in all scenarios. While rubella incidence reduces following vaccination, the changes in transmission dynamics with corresponding increase in average age of infection when only infants are vaccinated could have an undesirable impact on CRS incidence. Trends in rubella and CRS incidence were extracted from the included studies and approximate periods required to achieve elimination were approximated. This is not an accurate method of obtaining estimates and the fact that individual studies presented their results in such a manner means it is possible to improve reporting of disease incidence.

Several studies did not report on the method of model validation and none of the included studies reported on the method of fitting. Recommendations for validation of mathematical models have been proposed [52], but there is no consensus on a preferred method. It is common for a validated, published model to be used for simulating disease dynamics in different settings. In this case, authors could refer to the original published model but do not provide details on the method of model validation or fitting. Bearing in mind that it could be laborious to repeat previously published information, it is helpful for researchers conducting systematic reviews to have a clear understanding of the model without having to search further.

Differences in the manner in which outcomes were reported by different studies, even for outcomes reported by more than one included study, rendered quantitative data synthesis impossible. Authors of individual studies could have reported different outcomes considered to be relevant for the settings in which RCV were simulated. However, the lack of recommended outcomes does not encourage authors to report results in such a way that allows for meta-analyses. This limits the ability for more precise estimates to be obtained from individual mathematical modelling studies.

The main limitation of this study relates to differences between included studies in terms of reported outcomes and scenarios simulated which did not allow for synthesis of results. The main strength of the study is that the included studies each modelled rubella vaccine introduction in different settings. This implies that the findings are applicable to those settings and could better inform decision-making.

5.6. Conclusion and recommendations

Compared to vaccination of infants, countries introducing rubella vaccination in their EPI schedule should vaccinate older children and/or adults in order to achieve more rapid decreases in rubella and CRS incidence. There is a wide variety of possible scenarios available to policy-makers in countries that do not yet include rubella vaccination in their public vaccination schedules, but irrespective of the vaccine introduction strategy chosen, improved outcomes were obtained for coverage figures of 80% (the minimum WHO-recommended coverage) and above.

Researchers modelling rubella vaccine introduction should attempt to report effect estimates and corresponding uncertainty intervals to enable pooling of results. Guidelines on reporting of individual mathematical modelling studies and systematic reviews of mathematical modelling studies should be developed such that evidence from mathematical modelling studies can be summarized in a consistent and structured manner.

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Conflict of interest
The authors have no conflict of interest to declare

Author contributions
NVM and CSW conceived the study question. All authors contributed in designing the methods and the protocol registration. ES, NVM, OA and ZM carried out study selection and data extraction. All author reviewed and approved the final manuscript.

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CHAPTER SIX

Discussion and conclusion

6.0. About this chapter

In this final chapter, we summarize the main findings of each component in this PhD project and discuss our contribution to the knowledge base regarding rubella epidemiology and vaccines in South Africa. We discuss the limitations of our research and the implications of our findings pertaining to future research.

The candidate performed the literature review, wrote the chapter and revised it following comments from the supervisors and reviewers.

6.1. Introduction

Planning a major public health intervention such as introducing rubella vaccination into the public immunization schedule could be a daunting task for decision makers. Documented increases in CRS incidence in several countries following RCV introduction, although transient, implies that precautions are required in order to ensure the success of vaccine roll-out. A number of gaps relating to the epidemiology of rubella as well as the projected impact of vaccine introduction are addressed in the research projects presented in this dissertation. These include: establishment of a sentinel site surveillance for CRS, estimation of the rubella immunity gap in public health sector users, simulation of RCV introduction scenarios and systematically reviewing available evidence on mathematical modelling of rubella RCV introduction.

Operational factors influence the choice of vaccination strategy and subsequent implementation. Cold chain capacity is recognized as one of the limitations to the introduction of new vaccines into national EPI schedules [1]. The availability of formulations that combine measles and rubella vaccines makes introduction of RCVs unlikely to be limited by cold chain issues. A recent study conducted in South Africa found that vaccine stock-outs do occur [2] and this represents a barrier to the success of the immunization program. Incorporating technological tools with adequate training of health care workers [3] could address such challenges. These and other operational aspects which influence introduction of RCVs are not explored in this research project.

The results presented in this dissertation can serve as the basis for guidelines that align with national public health priorities and resources. A holistic understanding of these results will appropriately position this PhD project and clarify its role in the decision-making process.

6.2. Key findings

Congenital Rubella Syndrome Surveillance in South Africa

This descriptive study aimed to report on laboratory-confirmed CRS in South Africa prior to introduction of RCVs in the EPI schedule. A sentinel site surveillance approach with prospective and retrospective components was adopted. The prospective component covered two years while the retrospective component covered five years. A total of 95 confirmed CRS cases were identified at 28 study sites. The median age of mothers of infants with CRS was 21 years in the retrospective phase and 22 years in the prospective phase. This could imply increased susceptibility in young females of reproductive age. The majority of CRS cases were diagnosed within the first three months of delivery. This study highlights that CRS does occur in South Africa and documents the severe clinical sequelae faced by children born with CRS.

Rubella seroprevalence in South Africa

In this study, residual samples from the measles surveillance program were tested for rubella IgG. Samples from patients with acute measles or rubella infection were excluded. Rubella IgG results were considered as a proxy for rubella immunity and 43% of samples tested were positive. The highest proportion of individuals susceptible to rubella was in the group of participants below one year and this proportion decreased with increasing age. Overall, most susceptible participants were 0-15 years old and women in the reproductive age group represent 5% of females susceptible to rubella. This susceptibility profile highlights the target population for potential catch up immunization campaigns which could be beneficial during vaccine introduction. The absence of RCVs in the public vaccination schedule of South Africa implies that the bulk of individuals who were immune to rubella had previous rubella infection. All samples tested for rubella IgG were sent to the NICD from public health facilities but it is possible that some individuals currently making use of the public health sector might have previously received RCVs from private health care institutions. However, we think this represents a negligible proportion of the sample and does not influence the results.

Simulating rubella vaccine introduction in South Africa

A previously published rubella transmission model was used to simulate introduction of RCVs into the EPI schedule of South Africa. Five vaccine introduction strategies were compared to not RCV introduction. Scenarios including a mass campaign in addition to routine childhood vaccination resulted in faster elimination of rubella and CRS. Vaccinating 1-year-old and 9-year-old children was associated with the lowest number of vaccine doses per CRS case averted. This finding can be explained by the fact that the bulk of susceptible individuals are immunized after eight years of vaccinating cohorts of 1-year-olds. This explanation is supported by findings from the serosurvey which reported that 19.9% of individuals 16 to 49 years old were susceptible to rubella whereas susceptibility among individuals aged 0-11 months, 1-5 years and 6-10 years and 11-15 years was 81.0%, 71.5%, 40.9% and 31.3% respectively. With vaccination attaining the age groups having the bulk of susceptible individuals over seven years (time required for all children 1-15 years old), rubella and CRS elimination is achieved at coverage values as low as

60%. Although the scenarios including a mass campaign targeting all individuals 1-14 years leads to more rapid elimination of rubella and CRS the magnitude of the costs and feasibility of organizing mass vaccination activities are important challenges. There has been no nation-wide mass campaign in South Africa in recent years and a strategy that entails a mass campaign it is unlikely to be chosen by the National Department of Health. Vaccinating 1-year-old and 9-year-old children is an attractive option since the school human papilloma virus vaccination program targets 9-year-old children.

The impact of rubella vaccine introduction on rubella infection and congenital rubella syndrome: a systematic review of mathematical modelling studies

We carried out a systematic review to summarize evidence from mathematical modelling studies that simulated introduction of RCVs in the EPI schedules of countries that did not include rubella vaccines in their public vaccination programs. Seven studies were included following a comprehensive search that applied no language restrictions. All included studies had high to very high methodological quality, designed as deterministic age-structured models from four WHO regions representing low-middle income, high-middle income and high-income settings. Data synthesis (meta-analysis) was not feasible because of differences in the outcomes reported by individual studies. Vaccination of infants and older children was found to result in faster elimination of CRS.

6.3. Contribution to knowledge

The components of this research project enhance the knowledge on several aspects of rubella epidemiology and transmission dynamics in South Africa.

- The establishment of a national sentinel site surveillance program for CRS, linked to the notifiable medical conditions system, demonstrated that CRS cases are spread all over the national territory and that surveillance should be strengthened such that burden of disease can be quantified pre- and post-vaccine introduction. There have not been regular vaccination coverage surveys conducted in South Africa so monitoring of CRS incidence can provide an early signal if the RCV coverage is low and resulting in increased rubella incidence.
- The immunity profile of the population making use of public health sector facilities revealed rubella susceptibility by age group, sex and spatial distribution. It is possible that the immunity profile is different for individuals make use of private sector health care facilities since they offer rubella vaccination. However, the majority of the South African population uses public health facilities and this is the target population for RCV introduction.
- Mathematical modelling of rubella infection dynamics using a robust model that has previously been used in other countries offers insights into the possible outcomes of introducing RCVs. The variety of scenarios, levels of vaccine coverage and parameter

ranges explored gives a unique understanding of rubella transmission in South Africa with and without public sector rubella vaccination. It is possible that varying sub-national disease dynamics result in different outcomes following RCV introduction. Heterogeneous population densities, contact patterns, movement patterns and climate patterns could result in disease incidence trends that were not demonstrated using the model. However, the model could be further adapted and the simulations could be repeated with improved inputs to inform public health strategies.

- Despite the absence of data synthesis, the systematic review found a number of mathematical modelling studies that simulated RCV introduction into public vaccination schedules in different settings. There are not many systematic reviews of mathematical modelling studies and no widely accepted guidelines for reporting of such systematic reviews. With the increasing move towards deriving health care interventions from high quality evidence, the findings from this systematic review could change after incorporating more recent studies in a subsequent update.

6.4. Implications for policy

A strategy for rubella vaccine introduction including routine immunization of infants and older children can achieve rapid elimination of rubella and CRS. A decision will have to be made between either routinely vaccinating older children at a given age or vaccinating all children below a given age during supplementary immunization activities. The former, less costly scenario, is associated with a period of slow decline in rubella incidence as opposed to the latter, more costly scenario that achieves rapid decrease in incidence or even elimination of rubella and CRS. The findings of this research project should be considered along with information on rubella incidence from surveillance data when identifying the target ages for immunization when RCV are introduced in South African EPI schedule.

Measles vaccine is currently administered at 6 and 12 months according to the South African EPI schedule. This measles vaccine is not administered concomitantly with other vaccines. Although rubella vaccines are usually administered to infants at least 9 months old, they can be administered at 12 months. If the dose of measles vaccine administered at 6 months is maintained and RCV replaces the 9 months dose, this might create challenges with implementation of RCV introduction since the route of administration is different for both vaccines. Health care workers would need to be adequately trained to correctly administer both vaccines. Having both monovalent measles vaccine and a RCV will avoid a change in vaccination schedule but requires additional cold chain capacity, which might be difficult to achieve. On the contrary, implementing only a combination vaccine almost certainly requires a change in vaccination schedule since rubella vaccination is not administered 6-months-old infants.

6.5. Limitations

The serological survey done to identify rubella immunity gaps included convenience samples from a large number of public health facilities and all samples were collected from suspected measles cases. Since we did not use a random population sample, our results may not be applicable to the entire South African population.

The estimated cost of introducing RCVs from our model lacks the rigor of well-designed economic evaluation studies. The estimates were based solely on the difference in cost between the current measles vaccine and two types of vaccines combining measles are rubella. Other programmatic costs were not accounted for since the design of our study was not appropriate for that.

6.6. Conclusion

The results from CRS surveillance and serological testing for rubella immunity align with the improved outcomes obtained from simulations of rubella vaccine introduction and justify the implementation of a strategy involving infant vaccination during the first year of life and vaccination of older individuals.

6.7. Future research

Sentinel site surveillance for CRS is likely to miss cases diagnosed in health facilities that are not included. CRS is notifiable in South Africa since 2017 [4] and incidence estimates could be obtained from notification data. This will be an improved means of tracking the impact of rubella vaccination.

Continuous monitoring of rubella and CRS notification data is required to measure the impact of vaccination. It might be worthwhile to also conduct vaccination coverage surveys and overlay coverage and incidence data to identify areas requiring enhanced public health action.

Economic evaluation studies that quantify the cost of treating rubella and CRS from the government's perspective are required. The results can then be compared with the cost of introducing the rubella vaccine to understand the cost-effectiveness of the intervention.

Improving delivery of health care interventions in general has been the target of implementation science. Implementation research projects directed at answering questions regarding best practice for RCV introduction are required to improve on the public health impact of rubella vacination.

CRS occurs following rubella infection in pregnancy so it is important to obtain data on the immunity profile of pregnant women in all provinces of South Africa. Estimates of rubella immunity among pregnant women in localized geographical areas have been obtained [5]. However, the national antenatal HIV survey provides a platform for more generalizable results [6].

Infants with CRS have a wide variety of clinical symptoms that can become apparent later in life. These ocular, immunological, endocrine and neurological abnormalities [7]. Studies that attempt to identify CRS infants beyond the first year of life could improve on the quantification of disease burden.

Finally, studies that quantify rubella and CRS incidence and prevalence should be conducted regularly. This would enable disease trends to be documented to better understand rubella epidemiology as elimination targets are monitored. Variations in number incident measles cases as well as the magnitude and frequency of outbreaks have been described for several countries at different stages on the route towards elimination [8]. It is possible that rubella might exhibit a similar pattern.

6.8. References

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Appendices

Appendix 1: Supplementary material for chapter 2

Supplementary material 1: Study sites and focal persons

Province	Study site	Focal person
Eastern Cape	-Cecilia Makiwane Hospital	-Felicity Goosen
	-Frere Hospital	-Kim Harper
Free State	-Universitas Academic Hospital	-Jeannette Kriel
	-Pelonomi Hospital	-Ute Hallbauer
Gauteng	-Chris Hani Baragwanath Academic Hospital	-David Moore, Firdose
	-Charlotte Maxeke Johannesburg Academic Hospital	Nakwa
	-Rahima Moosa Mother and Child Hospital	-Daynia Ballot
	-Kalafong Hospital	-Gary Reubenson
	-Dr George Mukhari Hospital	-Nicolette duPlessis
	-Steve Biko Academic Hospital	-Kgomotso Sanyane
		-Melantha Coetzee
KwaZulu-Natal	-Prince Mshiyeni Memorial hospital	-Akhtar Hussain
	-Inkosi Albert Luthuli Hospital	-Christopher Kelly
	-Grey's Hospital	- Graham Ducasse
	-King Edward VIII Hospital	- Radhika Singh
Limpopo	-Mankweng Hospital	-Mohlabi Hamese
	-Pietersburg Hospital	-Christopher Sutton
Mpumalanga	-Rob Ferreira Hospital	- Thulisile Maposa
	-Witbank Hospital	- Norman Dungwa
Northern Cape	-Dr Harry Surtie Hospital	- Magdaleina Blauuw
	-Kimberley Hospital	- Michelle Muller
North West	-Klerksdorp/Tshepong Hospital Complex,	- Omphile Mekgoe
	-Job Shimankana Tabane Hospital	- Philemon Rakgole
	-Mafikeng Provincial Hospital	- Tumelo Leeuw
Western Cape	-Groote Schuur Hospital	- Lloyd Tooke
	-Mowbray Maternity Hospital	- Lucy Linley
	-New Somerset Hospital	- Dave Leroux
	-Red Cross War Memorial Children's Hospital	- James Nuttal
	-Tygerberg Hospital	- Helena Rabie

Supplementary material 2: Case Investigation Form

Patient's Name: _____

Reporting site_____

Notified by:_____Telephone:_____

Date notified: ____/_____/_____

Patient Details

Medical record No: Father's Name: Mother's Name:	Sex: Male___ / Female____ Date of birth:__ /____ /_____ Age: months: ___ days: _____ Year(s): _____

Address: _____ District: _____ Province: _____

Contact mobile number: _____ Father/Mother/Guardian

Clinical Signs and Symptoms [Key: Y=Yes, N=No, U=Unknown]

Place of delivery (city/district/province): _____

Health facility_____

Gestation age at birth (Weeks): _____ Unknown: _____ Birth weight (grams):_____

Defects (please complete all)

Glaucoma	Y	N	U
Pigmentary retinopathy	Y	N	U
Hearing impairment or deafness	Y	N	U
Cataracts	Y	N	U
Congenital heart disease	Y	N	U
If yes describe:			

Microcephaly	Y	N	U
Purpura	Y	N	U
Hepatosplenomegaly	Y	N	U
Meningoencephalitis	Y	N	U
Radiolucent bone disease	Y	N	U
Jaundice, within 24 hours of birth	Y	N	U
Mental retardation	Y	N	U

Outcome: Alive Y N U (*if No*) died on _____/_____/_____ unknown

Patient's Name:

Maternal History

Total number children:_____ Mother's age at birth of infant patient: years: _____

Rubella vaccination: Y N U

Illness during pregnancy:

Conjunctivitis	Y N U	If yes, date of onset: ___/___/_____	Month of pregnancy:
Maculopapular rash	Y N U	If yes, date of onset: ___/___/_____	Month of pregnancy:
Lymph nodes swollen	Y N U	If yes, date of onset: ___/___/_____	Month of pregnancy:
Arthralgia/arthritis	Y N U	If yes, date of onset: ___/___/_____	Month of pregnancy:
Other complications	Y N U	If yes, date of onset: ___/___/_____	Month of pregnancy:

Laboratory-confirmed rubella in the mother: Y N U If yes, date: ____/____/

Laboratory specimen collection

Specimen(s) collected from case: Y N U

Serology Blood Date taken: ____/____/____ Date sent: ____/____/_____

Virology Urine Date taken: ____/____/____ Date sent: ____/____/_____

Oral Swab Date taken: ____/____/____ Date sent: ____/____/_____

Results and Final Classification

Serology results: [as reported by lab]

Lab number:_____

Date blood received at Lab:____/____/____ Date tested:____/____/____

Rubella IgM: 1. Positive 2. Negative 3. Equivocal 4. Pending 8. Not done 9. Unknown

Rubella PCR: 1. Positive 2. Negative 3. Equivocal 4. Pending 8. Not done 9. Unknown

Supplementary material 3: Letter to reporting health professionals

Dear Colleague,

Thank you for accepting to participate in the National Congenital Rubella Syndrome Surveillance program.

Have you identified any confirmed cases of Congenital Rubella Syndrome in your institution during the past month? YES☐ Number of cases: _____, NO☐

Please return your response to villyenm@nicd.ac.za

Name of reporting Clinician: _____ Health Facility:_____

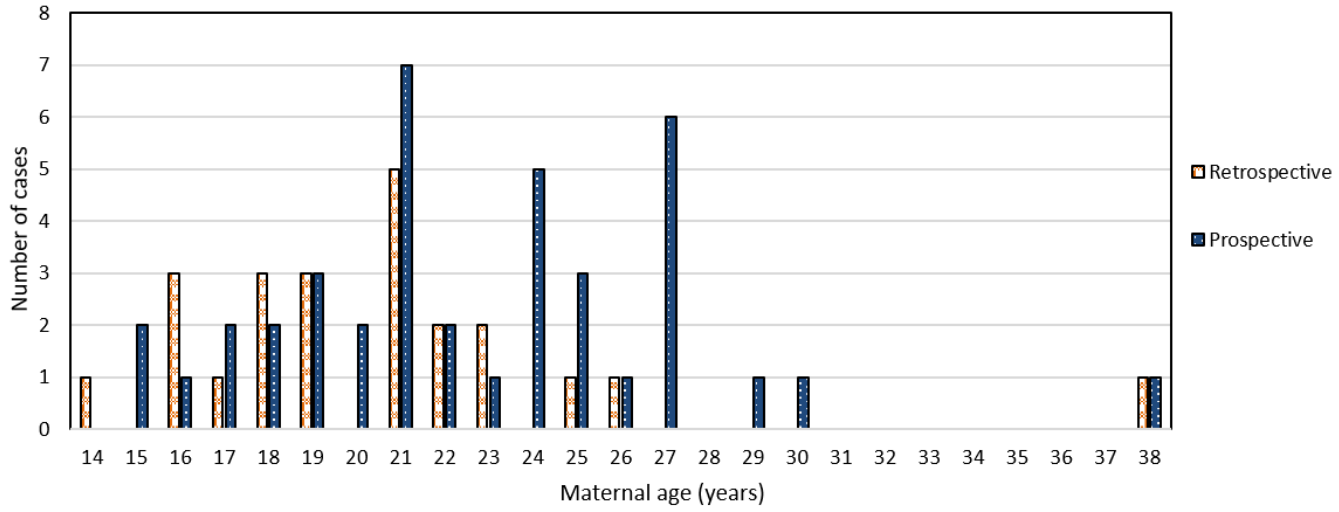
As a reminder, please find below the case definitions for CRS:

<table>
<tr><td colspan="3">Suspected case</td></tr>
<tr><td>An infant who does not meet the criteria for a probable or confirmed case but who has one or more of the following findings:</td><td>-cataracts,
-congenital glaucoma,
-congenital heart disease,
-hearing impairment,
-pigmentary retinopathy,
-purpura,</td><td>-hepatosplenomegaly,
-jaundice,
-microcephaly,
-developmental delay,
-meningoencephalitis,
-radiolucent bone disease.</td></tr>
<tr><td colspan="3">Probable case</td></tr>
<tr><td>Probable case 1</td><td colspan="2">Probable case 2</td></tr>
<tr><td>An infant with no laboratory confirmation of rubella infection but at least two of the following without a more plausible etiology:

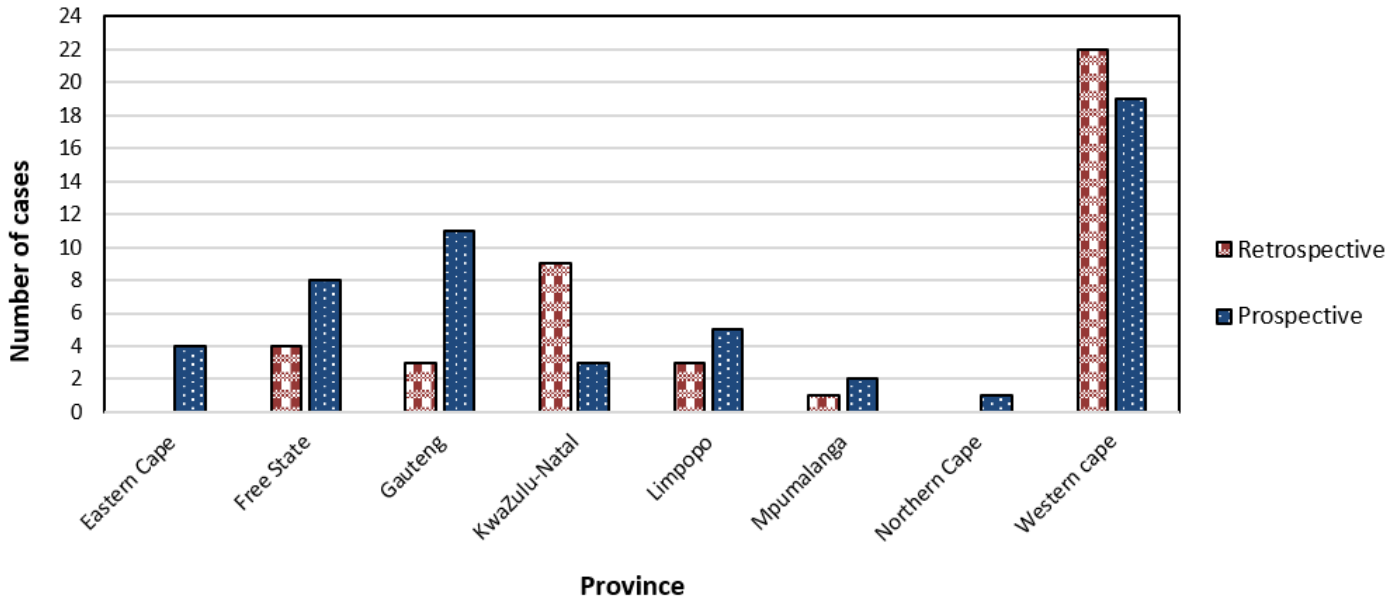
-cataracts or congenital glaucoma,
-congenital heart disease
-hearing impairment,
-pigmentary retinopathy;</td><td colspan="2">An infant with no laboratory confirmation of rubella infection but at least one of the following without a more plausible etiology;
-cataracts or congenital glaucoma,
-congenital heart disease
-hearing impairment,
-pigmentary retinopathy;

AND one or more of the following:
-purpura,
-hepatosplenomegaly,
-jaundice,
-microcephaly,
-developmental delay,
-meningoencephalitis,
-radiolucent bone disease.</td></tr>
<tr><td colspan="3">Confirmed case</td></tr>
<tr><td>An infant with at least one of the symptoms clinically consistent with congenital rubella syndrome listed above and laboratory evidence of congenital rubella infection demonstrated by at least one of the following:</td><td colspan="2">-isolation of rubella virus.
-detection of rubella-specific immunoglobulin M antibody.
-infant rubella antibody level that persists at a higher level and for a longer period of time than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a two-fold decline per month).
-a specimen that is PCR-positive for rubella virus.</td></tr>
</table>

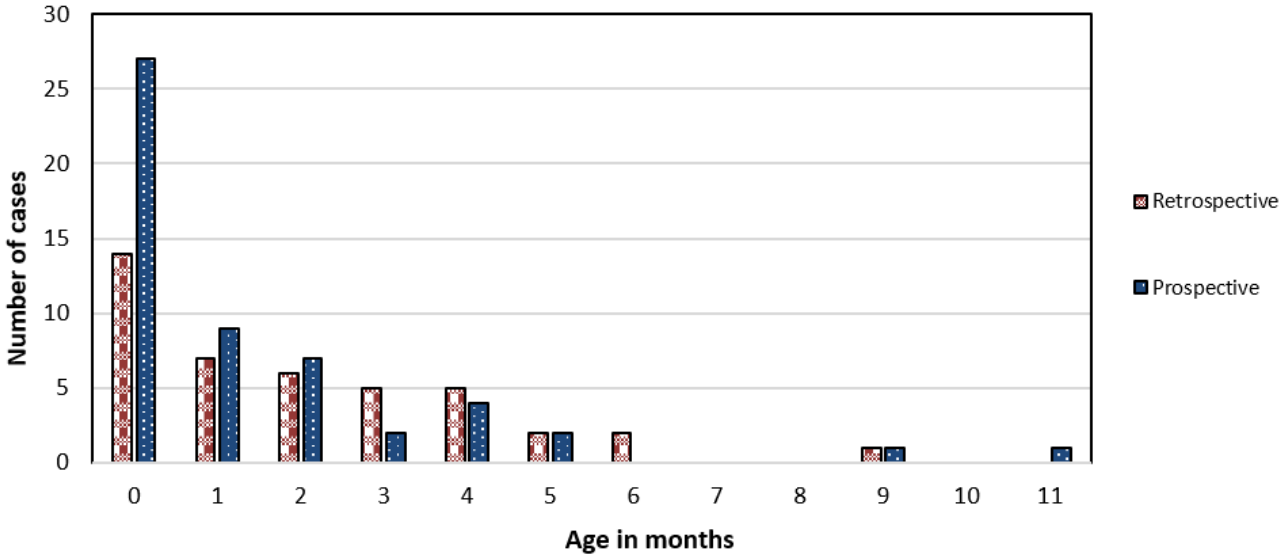
Supplementary material 4: Ages of mothers of infants with laboratory-confirmed congenital rubella syndrome 2010-2017



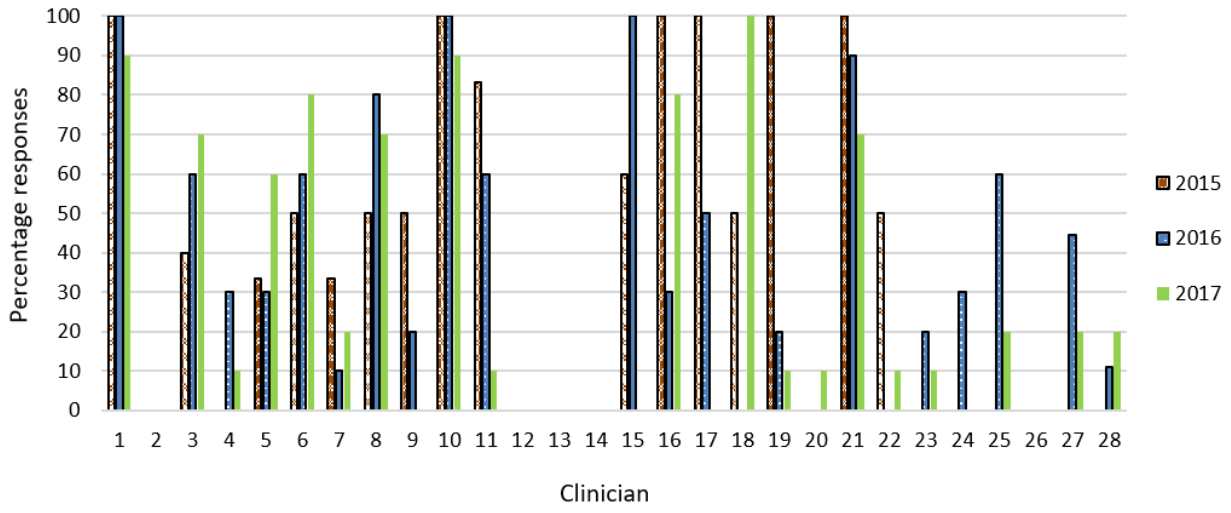
Supplementary material 5: Number of cases of congenital rubella syndrome per province in South Africa from 2010 to 2017.



Supplementary material 6: Age of CRS cases at diagnosis in South Africa from 2010 to 2017



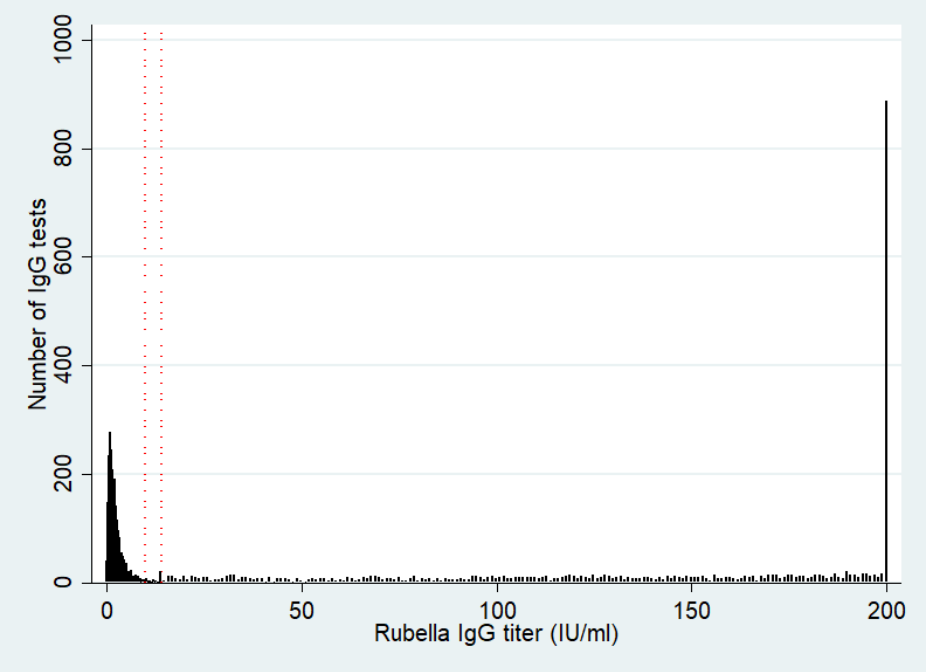
Supplementary material 7: Surveillance adequacy indicator in South Africa from 2015 to 2017.



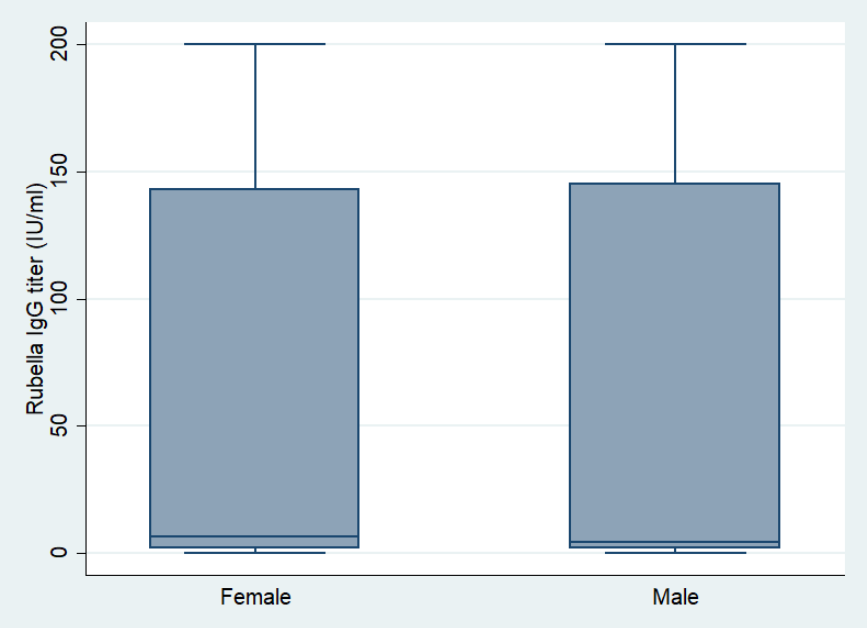
Supplementary material 8: CRS cases reported at sentinel surveillance sites, South Africa, 2010-2017

Province & study site	Retrospective phase (N=42)					Prospective phase (N=53)			
	2010	2011	2012	2013	2014	2015	2016	2017	Site Total
Eastern Cape Province									
Cecilia Makiwane Hospital	0	0	0	0	0	2	0	0	**2**
Frere Hospital	0	0	0	0	0	2	0	0	**2**
Free State Province									
Pelonomi Hospital	0	0	0	0	0	1	0	2	**3**
Universitas Hospital	0	2	0	1	1	5	0	0	**9**
Gauteng Province									
Charlotte Maxeke Johannesburg Hospital	0	0	0	0	0	0	1	0	**1**
Chris Hani Baragwanath Hospital	0	0	0	0	0	0	1	0	**1**
Dr George Mukhari Academic Hospital	0	0	0	0	0	0	1	1	**2**
Kalafong Hospital	0	0	0	0	0	0	1	0	**1**
Rahima Moosa Mother and Child Hospital	0	0	0	0	0	0	1	0	**1**
Steve Biko Academic Hospital	0	0	0	1	2	0	2	3	**8**
KwaZulu-Natal Province									
Inkosi Albert Luthuli Central Hospital	0	1	1	2	1	2	0	0	**7**
King Edward VIII Hospital	0	0	0	0	3	0	0	0	**3**
Prince Mshiyeni Memorial Hospital	0	0	0	0	1	1	0	0	**2**
Greys Hospital	0	0	0	0	0	0	0	0	**0**
Limpopo Province									
Mankweng Hospital	0	0	0	0	1	0	0	1	**2**
Pietersburg Hospital	0	0	0	0	2	3	0	1	**6**
Mpumalanga Province									
Rob Ferreira Hospital	0	0	0	0	0	1	0	0	**1**
Witbank Hospital	0	0	0	0	1	1	0	0	**2**
Northern Cape Province									
Kimberley Hospital	0	0	0	0	0	1	0	0	**1**
Dr Harry Surtie Hospital	0	0	0	0	0	0	0	0	**0**
North West Province									
Job Shimankana Tabane Provincial Hospital	0	0	0	0	0	0	0	0	**0**
Klerksdorp/Tshepong Hospital	0	0	0	0	0	0	0	0	**0**
Mafikeng Provincial Hospital	0	0	0	0	0	0	0	0	**0**
Western Cape Province									
Groote Schuur Hospital	1	2	0	0	1	0	0	0	**4**
Mowbray Maternity Hospital	0	0	0	0	0	1	0	0	**1**
New Somerset Hospital	0	0	0	1	2	1	0	0	**4**
Red Cross War Memorial Children's Hospital	3	3	2	1	3	9	1	0	**22**
Tygerberg Hospital	1	1	1	0	0	7	0	0	**10**
Total per year	**5**	**9**	**4**	**6**	**18**	**37**	**8**	**8**	**95**

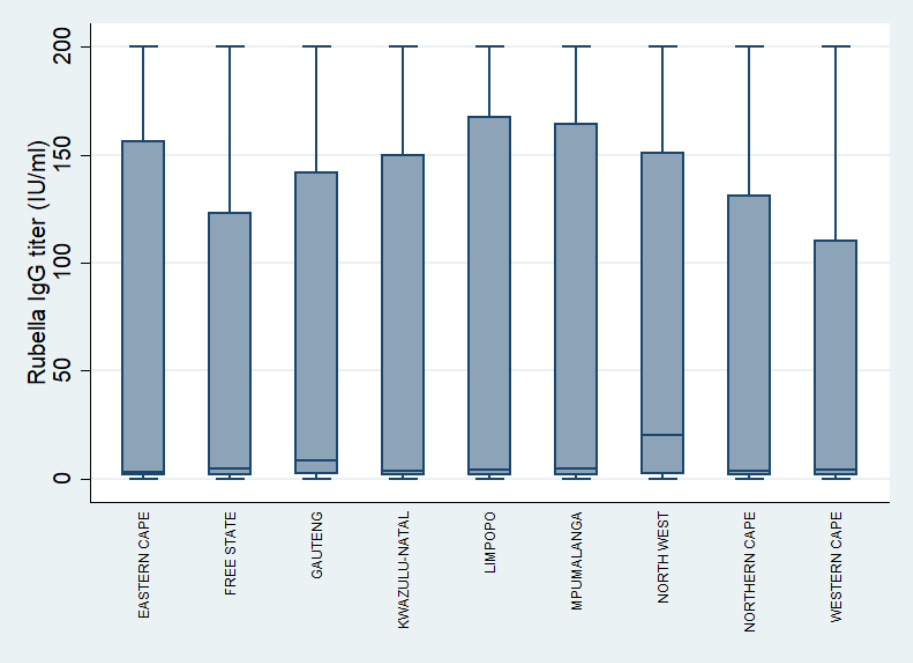
Appendix 2: Supplementary material for chapter 3



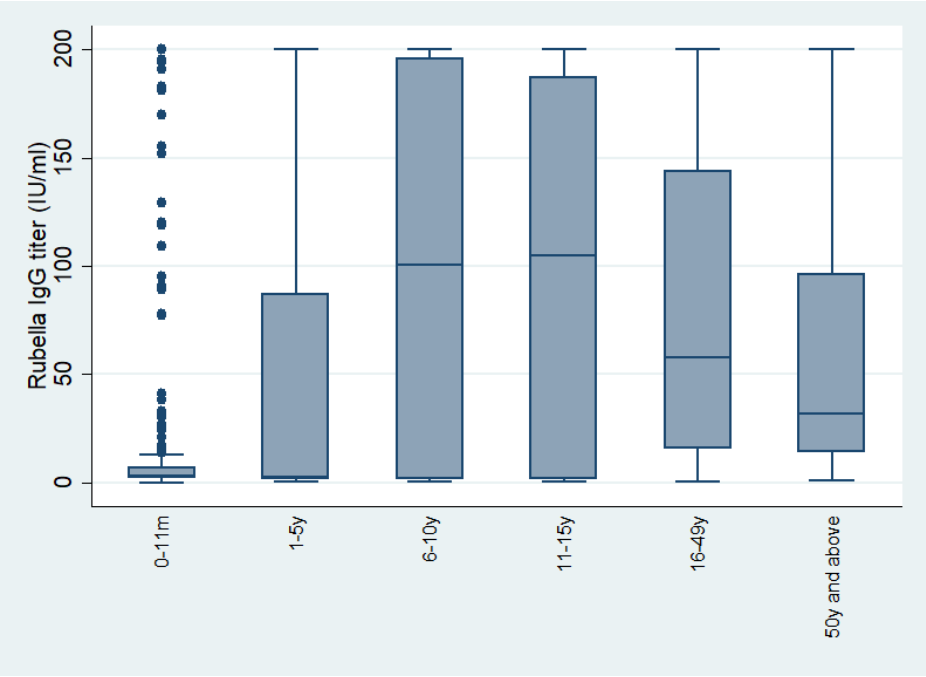
S1: Histogram of rubella IgG titers (IU/ml) in the sample. The two vertical dotted lines represent the limits of rubella IgG corresponding to equivocal results (10-14).



S2: Box and whisker plot of rubella IgG titers (IU/ml) by sex.



S3: Box and whisker plot of rubella IgG titers (IU/ml) by province.



S4: Box and whisker plot of rubella IgG titers (IU/ml) by age group with individuals below 12 months split into two groups (0-6 months and 7-11 months)

Appendix 3: Supplementary material for chapter 4

Supplement 1: Model Description

We developed a discrete-time stochastic age-structured compartmental rubella transmission model for South Africa, building from previous work describing rubella dynamics [16,20]. The key feature of the model is a matrix that at every time-step defines transitions from every combination of epidemiological stage (maternally immune 'M', susceptible 'S', infected 'I', recovered 'R', and vaccinated 'V', taken to indicate the effectively vaccinated) and age group (1 month age groups up to 20 years old, then 1 year age groups up to 100 years old; 321 total age groups) to every other possible combination of epidemiological stage and age group. The discrete time-step was set to about 16 days (i.e., 24 time steps in a year), the approximate generation time of rubella. We simulated a deterministic run for each of the vaccination scenarios from year 1995 to 2050.

Epidemiological Parameters
Figure S1 displays the epidemiological transitions of the transmission model. The model is age-structured so that each epidemiological transition is age-specific, and depending on the parameter also time-specific. Here, d_a is the probability of losing maternal immunity by age class a, φ_a is the probability an individual in age class a becomes infected, r is the recovery rate, and $v_{a,t}$ is the probability an individual in age class a and time-step t is successfully vaccinated.

The duration of protection by rubella maternal antibodies ranges between 3 and 9 months; accordingly, we modelled the probability of remaining in the maternally immune epidemiological stage over age (1-d_a) as an exponential decay function with a constant rate of 0.95 per month [28].

The probability of infection by age, φ_a (also called the age-specific force of infection, FOI) is a function of $\mathbf{n}(t)$, a vector describing the population at time t, defined as,

$$\mathbf{n}(t) = (\mathrm{M}_{1,t}, \mathrm{S}_{1,t}, \mathrm{I}_{1,t}, \mathrm{R}_{1,t}, \mathrm{V}_{1,t}, \mathrm{M}_{2,t}, \ldots \mathrm{V}_{z,t})^{\mathrm{T}}$$

according to

$$\varphi_a(\mathbf{n}(t)) = 1 - exp\left(\frac{-\sum_j \beta_{a,j,t}\, I_{j,t}^{\gamma}}{\sum \mathbf{n}(t)}\right)$$

where z is the total number of age classes (here z = 321), $\beta_{a,j,t}$ is the rate of transmission between individuals in age class a and j at time-step t, also known as the Who-Acquires-Infection-From-Whom (WAIFW) matrix, and $I_{j,t}^{\gamma}$ is the number of infected individuals in age class j and time-step t, while γ captures the non-modeled heterogeneities in age mixing and the effects of discretization of the underlying continuous process. We fix γ at 0.97 reflecting values obtained for measles in England and Wales [27] , because discrete-time models that do not incorporate this exponent result in unrealistically unstable dynamics prone to frequent extinction. Given that rubella transmission is frequency dependent, we divide the number of infected individuals in each age class by the total population size at time-step t ($\sum \mathbf{n}(t)$).

Transmission to individuals in age group a from individuals in age group j for each time-step t is defined by $\beta_{a,j,t} = \overline{\beta_{a,J,}}(1 + \alpha\, cos(2\pi t))$, where $\overline{\beta_{a,J}}$ is mean transmission from individuals in age group j to age group a, and α is a parameter controlling the magnitude of seasonal fluctuations. Previous validation of this model has shown that model results for the burden of CRS were robust to the magnitude of seasonal fluctuations [16]; we set α to 0.35 and held it constant over time [16]. Mean transmission from individuals in age class j to age class a, $\overline{\beta_{a,J}}$, was estimated by rescaling population-adjusted age-contact rates (per POLYMOD study based on diary entries [26]) to reflect the assumed basic reproductive number (R_0) of

rubella. The value of R_0 used in this analysis of 7.9 and was obtained from a previously published modelling study estimating R_0 for 40 African countries [21]. We proceeded to run simulations with different estimates for R_0 in a sensitivity analysis. The highest estimate used was an R_0 of 12 which was estimated in Ethiopia [22] and the lowest estimate estimated in Burkina Faso was 3.3 [21].

The recovery rate, *r*, is equal to 1, such that by the next time-step (or rubella generation) all infected individual will immediately move into the recovered class.

The probability an individual in age class *a* and time-step *t* is successfully vaccinated, $v_{a,t}$, depends on the assumed vaccination coverage rate assumed over time and vaccine effectiveness over age. The vaccination coverage rate ranges from 0 to 1 and is vaccination scenario specific (Table 1 in the main text). Vaccination effectiveness rate over the first 11 months of life was empirically estimated from data extracted from Boulianne et al. 1995 [29] forcing saturating at 97% and staying constant at 97% for all ages 12 months and older.

Demographic Parameters
Demographic parameters (population size, crude birth rates, and age-specific death rates) were country-specific and extracted from the United Nations World Population Prospects 2015 (cran package *wpp2015*).

The number of births per time-step *t* were estimated by multiplying the crude birth rate per time-step *t* (i.e., annual crude birth rate divided by 24 generations in a year) by the total population at time-step *t* ($\sum \mathbf{n}(t)$). Age-specific death rates as of 1995, extracted at five year age intervals, were estimated for all 321 age classes using smoothing splines and held constant over time. We assumed a constant rate of aging into the next age class (i.e., 1 divided by the length of age class *a* in years multiplied by 24).

To simulate rubella dynamics, we first needed country-specific rubella endemic populations ($\mathbf{n}(1)$). We began with fully susceptible populations based on country-specific population and age structure estimated for 1995. The one year age interval population estimates were stratified into 321 age classes using smoothing splines. In order to move beyond the transient non-seasonal outbreaks to populations representing endemic rubella, we seeded infected individuals into the population and iteratively simulated rubella dynamics for four 20-year increments assuming constant births and deaths. At the end of each 20 year cycle, we rescaled the mean transmission ($\overline{\beta_{a,J}}$) by the assumed R_0 and the population by the 1995 population and age structure, and then simulated again, four times total. The result was a country-specific population representing endemic rubella in 1995 ($\mathbf{n}(1)$). In 2015, we rescaled the population size ($\mathbf{n}(t)$) based on population total estimates for the respective year to correct for small population size differences that accumulate over time in our model.

Model Outcomes of Interest
Our model outputs the number of individuals in each age class and epidemiological stage at every time-step, allowing us to directly extract the number of rubella cases (i.e., the number of individuals in the 'I' infected epidemiological class) per age and time-step.

Age- and time-specific CRS cases were estimated by multiplying the age-specific number of susceptible individuals and probability of becoming infected over 16 week period (based on model output from each vaccination scenario), the sex ratio of the population and age-specific fertility rate (extracted from the United Nations World Population Prospects 2015), and finally the probability of CRS following rubella infection during the first 16 weeks of pregnancy (estimated 0.65 [14]).

The effective reproduction number (R_E) was estimated from the model output using the next generation method [39].

Model diagram of age-structured model.

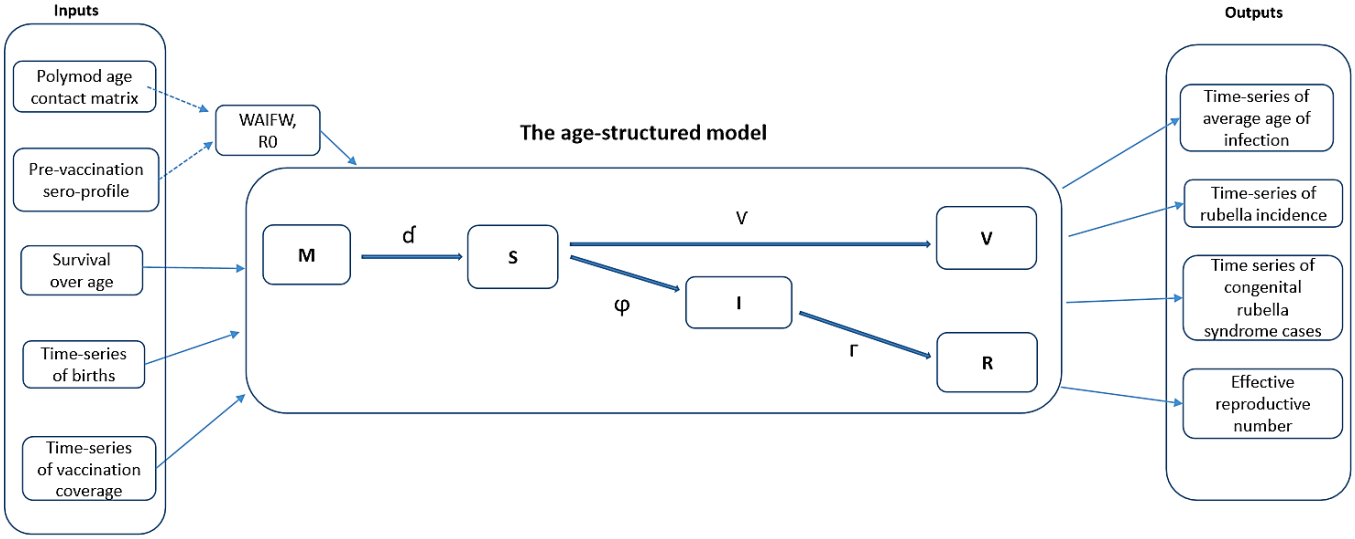


Figure S1. Relationship between data and the age-structured model. Solid lines ending in arrows indicate either data or elements inferred from data (i.e., R0, the appropriate structure of the WAIFW) that directly enter the model. Individuals in the maternal immunity (M), susceptible (S), infected (I), recovered (R) and vaccinated (V) compartments are represented with arrows representing movement between compartments: ɗ is the probability of losing maternal immunity, ϕ is the probability of becoming infected, r is the recovery rate and *v* is the probability of being vaccinated.

Supplement 2: CRS incidence over time for scenarios 2 to 6 compared to scenario 1 with extreme values of R_0

Prior to RCV introduction, the incidence of CRS when R_0 =3.3 was about three-fold that of R_0=12. A lower value of R_0 implies the rate of infection is lower. As a result, individuals are becoming exposed to the pathogen later in life. The risk of infection is therefore higher in adulthood compared to the case when R_0 is higher and this leads to an older age distribution of infected individuals and therefore a higher CRS incidence.

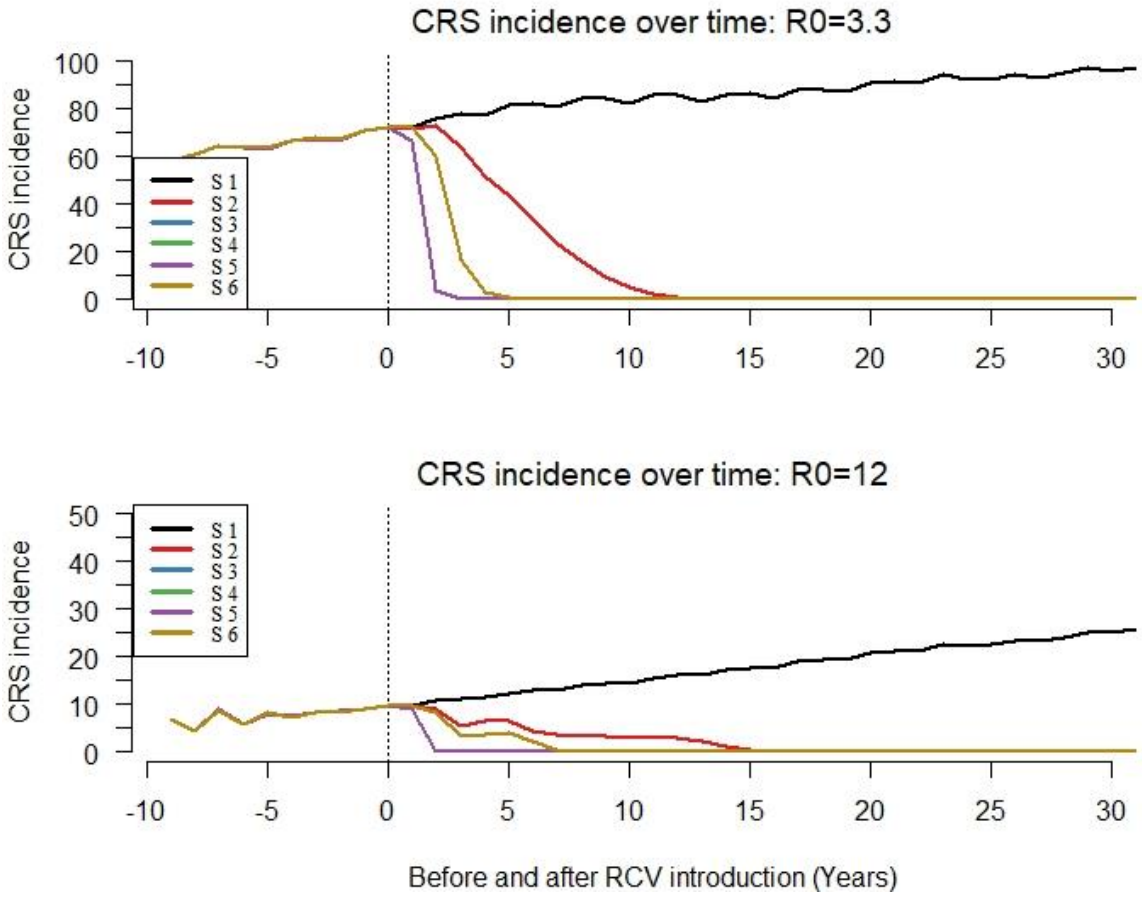


Figure S2: CRS incidence over time at 80% RCV coverage for scenarios 2 to 6 compared to scenario 1 with R0 values of 3.3 and 12. The lines for scenarios 3 and 4 overlap with that of scenario 5 so only this line is visible. The vertical dotted line represents the year of RCV introduction.

Supplement 3: CRS cases averted and DALYs averted over time for scenarios with RCV compared to no RCV

Table S3. Number of CRS cases averted and corresponding number of undiscounted DALYs averted for each scenario involving RCV introduction (2 to 6) compared to scenario 1. Estimates are shown for a range of routine vaccine coverage levels (60% through 95%) and for three time horizons: 10, 20 and 30 years.

Scenario/RCV coverage	10 years post RCV introduction		20 years post RCV introduction		30 years post RCV introduction	
	CRS averted	DALYs averted	CRS averted	DALYs averted	CRS averted	DALYs averted
Two 60%	1288	29484	2173	49759	2565	58738
Two 65%	1511	34594	3124	71543	4321	98955
Two 70%	1715	39271	4508	103240	6912	158280
Two 75%	1893	43344	5682	130122	9911	226957
Two 80%	2042	46759	6044	138408	10716	245392
Two 85%	2164	49562	6230	142658	10903	249684
Two 90%	2264	51853	6358	145601	11032	252627
Two 95%	2346	53731	6455	147814	11128	254840
Three 60%	3664	83911	7629	174711	11950	273659
Three 65%	3664	83911	7798	178574	12471	285579
Three 70%	3664	83911	7798	178584	12472	285610
Three 75%	3664	83911	7798	178584	12472	285610
Three 80%	3664	83911	7798	178584	12472	285610
Three 85%	3664	83911	7798	178584	12472	285610
Three 90%	3664	83912	7798	178585	12472	285611
Three 95%	3664	83912	7798	178585	12472	285611
Four 60%	3664	83911	7797	178560	12277	281152
Four 65%	3664	83911	7798	178584	12472	285603
Four 70%	3664	83911	7798	178584	12472	285610
Four 75%	3664	83911	7798	178584	12472	285610
Four 80%	3664	83911	7798	178584	12472	285610
Four 85%	3664	83911	7798	178584	12472	285610
Four 90%	3664	83912	7798	178585	12472	285611
Four 95%	3664	83912	7798	178585	12472	285611
Five 60%	3664	83911	7798	178584	12472	285610
Five 65%	3664	83911	7798	178584	12472	285610
Five 70%	3664	83911	7798	178584	12472	285610
Five 75%	3664	83911	7798	178584	12472	285610
Five 80%	3664	83911	7798	178584	12472	285610
Five 85%	3664	83911	7798	178584	12472	285610
Five 90%	3664	83912	7798	178585	12472	285611
Five 95%	3664	83912	7798	178585	12472	285611
Six 60%	3084	70615	7218	165288	11891	272314
Six 65%	3130	71680	7264	166353	11938	273379
Six 70%	3168	72550	7302	167223	11976	274249
Six 70%	3200	73274	7334	167947	12008	274973
Six 80%	3227	73889	7361	168562	12034	275588
Six 85%	3250	74428	7384	169101	12058	276127
Six 90%	3272	74927	7406	169600	12080	276626
Six 95%	3295	75445	7429	170118	12102	277144

Supplement 4: Change in effective reproductive number over time for all RCV coverage values.

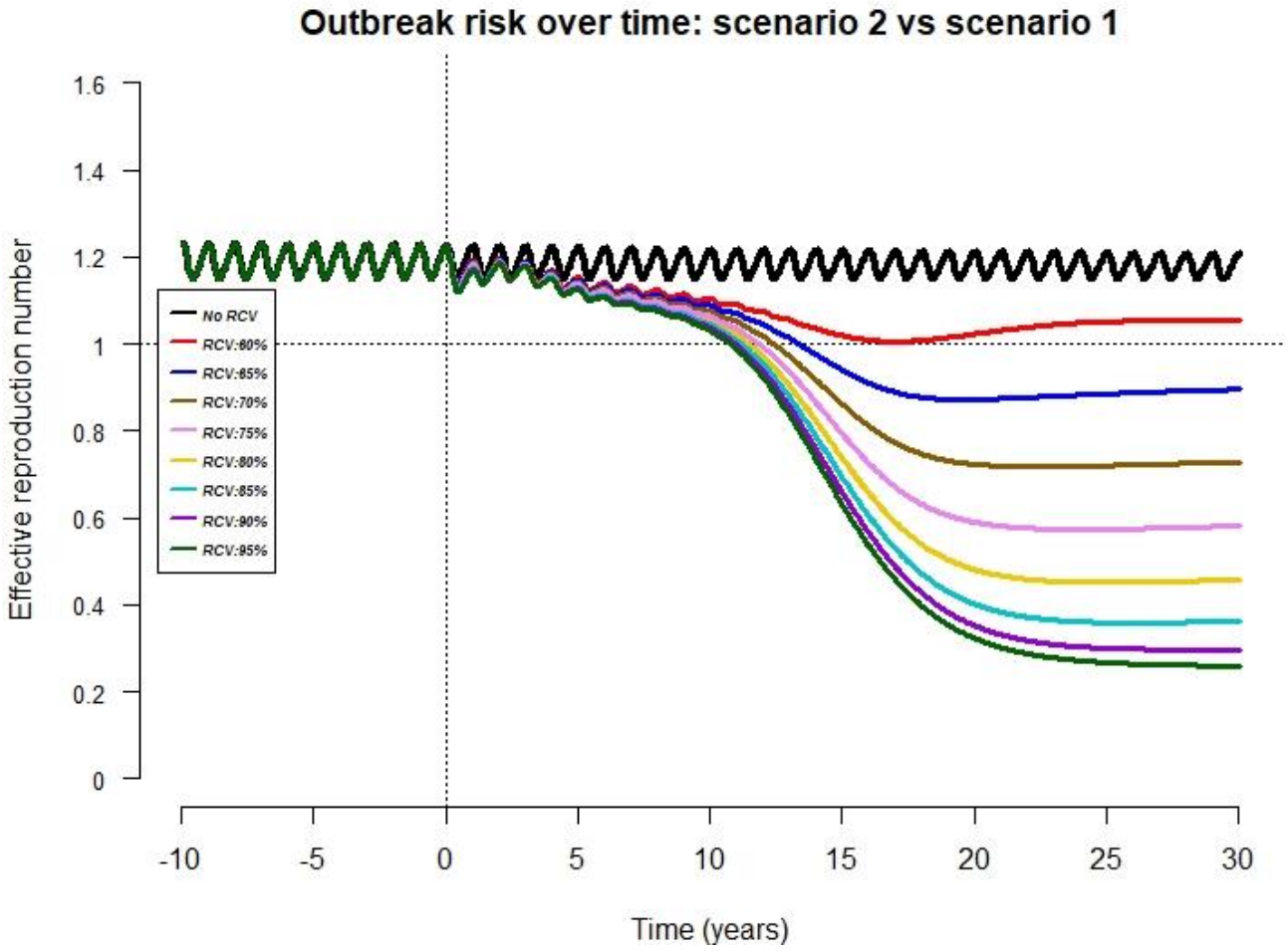


Figure S4a. Change in R_E over time for scenario 2 compared to scenario 1. While R_E never drops to values below one for 60% vaccine coverage, it takes between 11 and 14 years for R_E to drop below one with vaccine coverage levels of 65% to 95%. The slow drop in RE can be explained by the time it takes for successive vaccinated cohorts to age and achieve sufficient reduction in rubella incidence. .

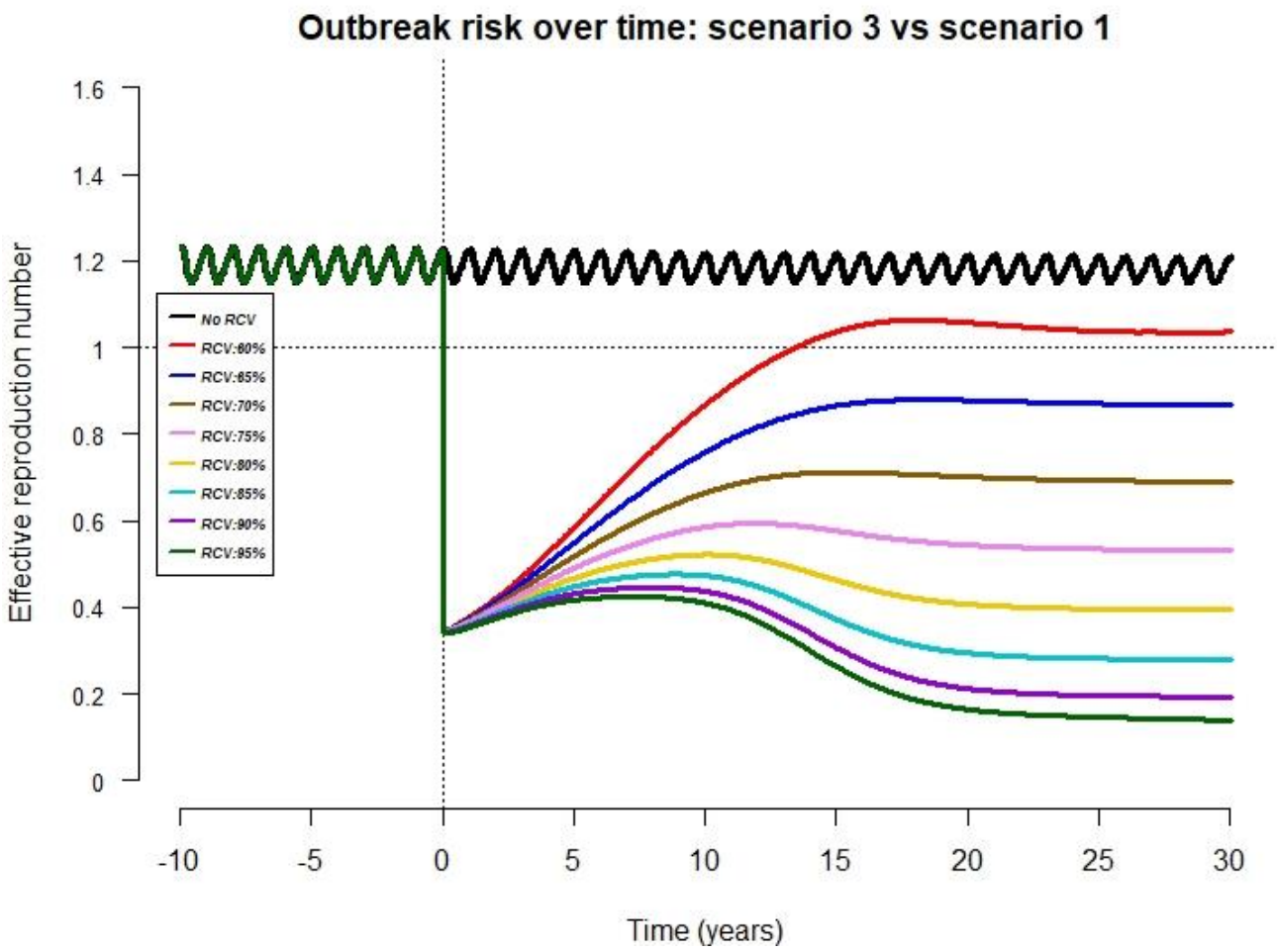


Figure S4b. Change in R_E over time for scenario 3 compared to scenario 1. Following RCV introduction, R_E immediately drops to values way below one due to the wide age range of vaccinated individuals during the initial mass campaign. There is then a progressive rise in R_E corresponding to accumulation of susceptible individuals missed during routine vaccination and the initial SIA, with this rebound being less prominent with increasing routine vaccine coverage. R_E eventually goes above one only for 60% RCV coverage**.**

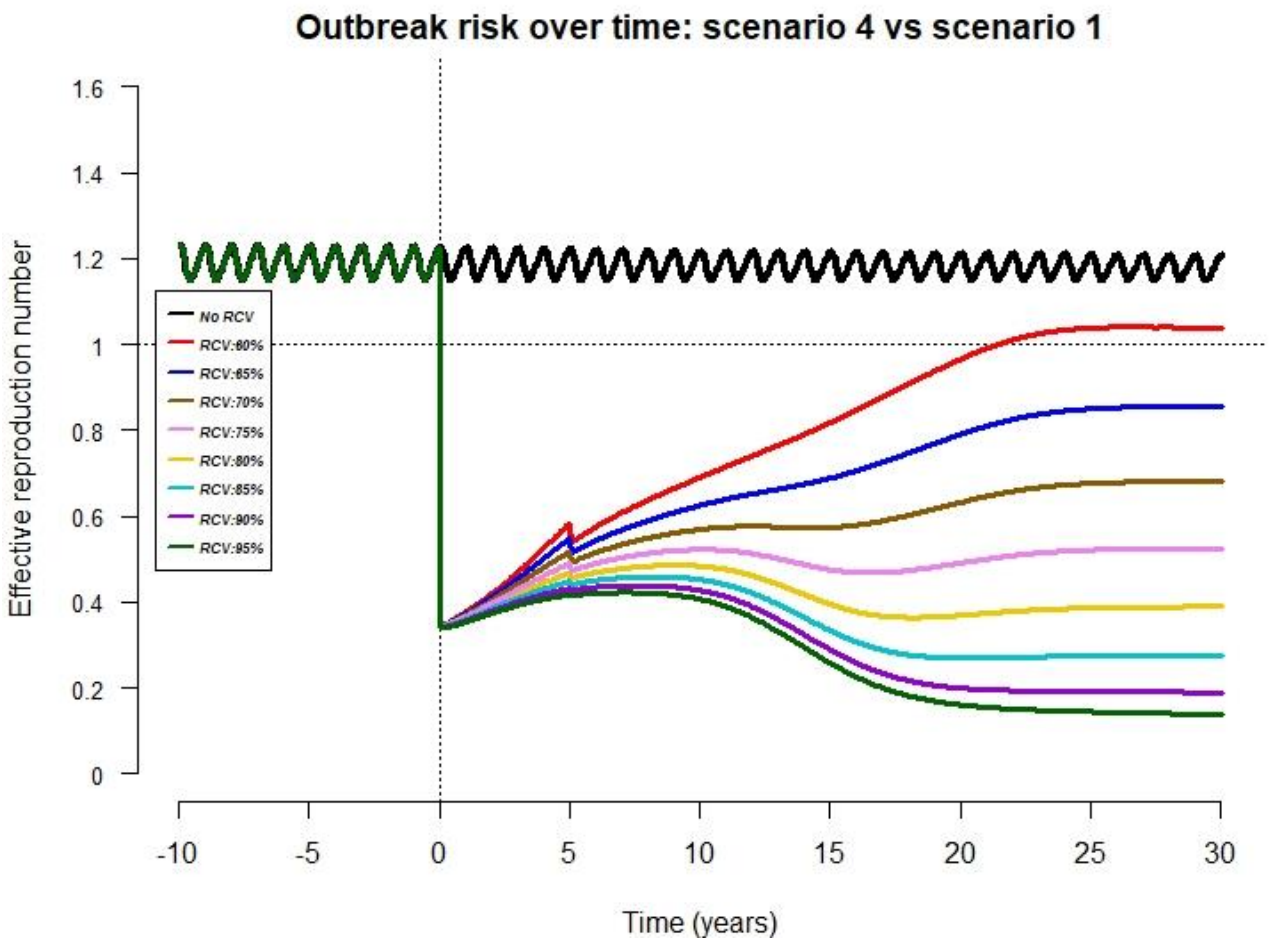


Figure S4c. Change in R_E over time for scenario 4 compared to scenario 1. Following RCV introduction, R_E immediately drops to values way below one due to the wide age range of vaccinated individuals during the initial mass campaign. There is then a progressive rise in R_E corresponding to accumulation of susceptible individuals missed during routine vaccination and the initial SIA, with this rebound being less prominent with increasing routine vaccine coverage. Following the second mass campaign 5 years after RCV introduction, R_E drops again but resumes an upward trend, eventually going above one only for 60% RCV coverage.

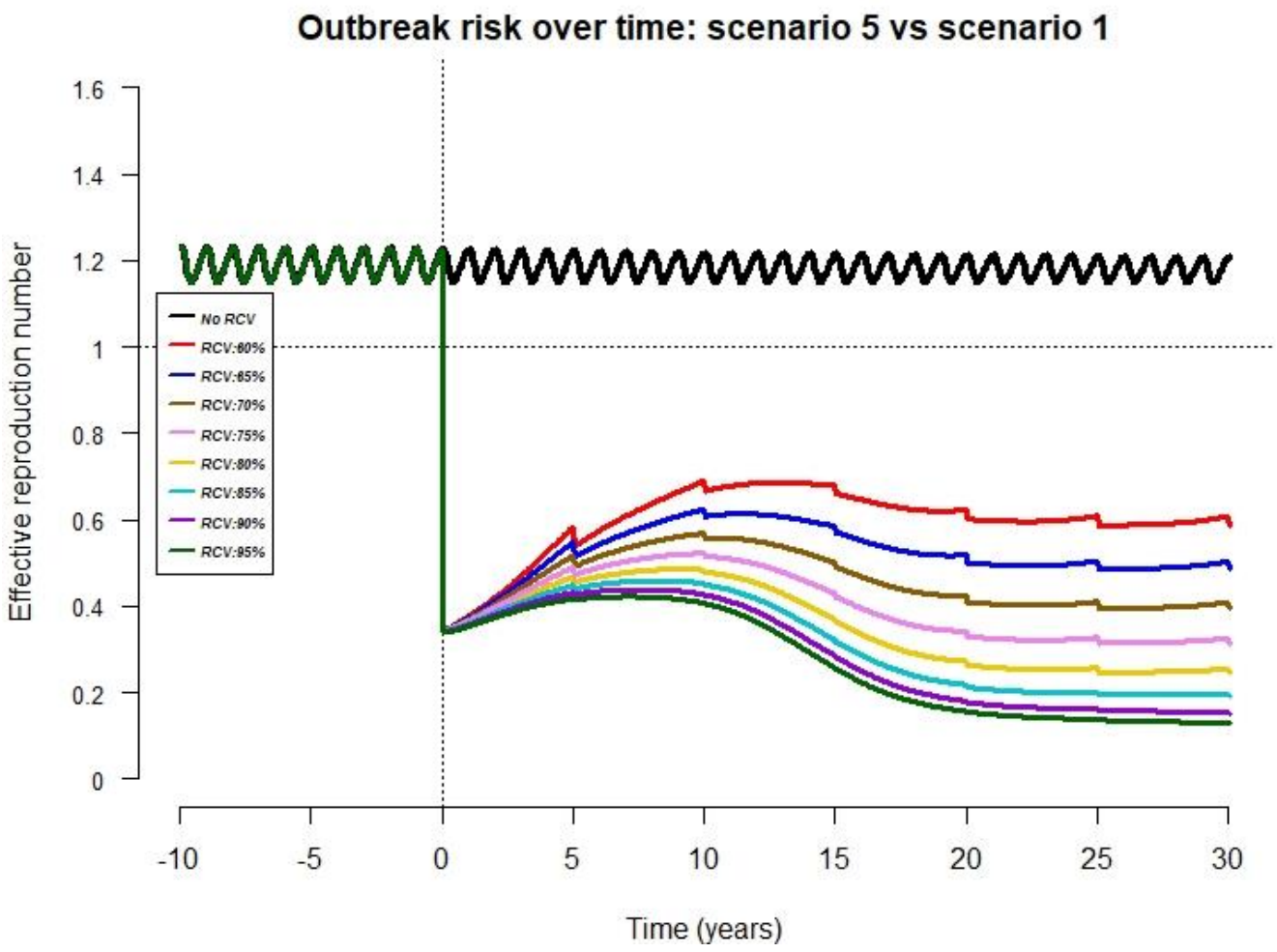


Figure S4d. Change in R_E over time for scenario 5 compared to scenario 1. Following RCV introduction, R_E immediately drops to values way below one due to the wide age range of vaccinated individuals during the initial mass campaign. There is then a progressive rise in R_E corresponding to accumulation of susceptible individuals missed during routine vaccination and the initial SIA, with this rebound being less prominent with increasing routine vaccine coverage. Following subsequent mass campaigns every 5 years, R_E drops again but resumes an upward trend. In this scenario, R_E never goes above one irrespective of RCV coverage.

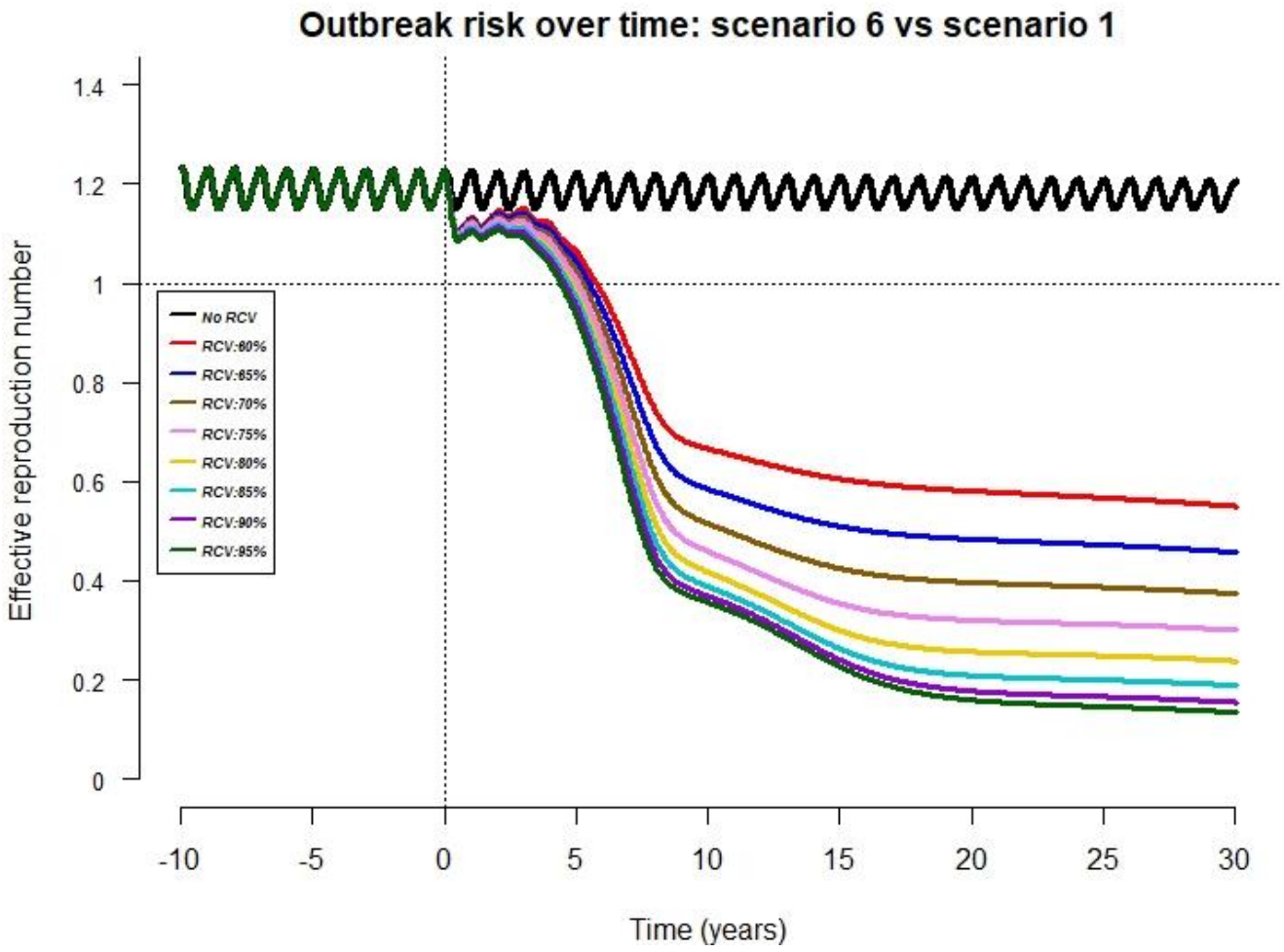


Figure S4e. Change in R_E over time for scenario 6 compared to scenario 1. It takes between 4 and 6 years for R_E to drop below one for all vaccine coverage levels with higher vaccine coverages associated with quicker decrease in R_E. The slow drop in RE can be explained by the time it takes for successive vaccinated cohorts to age and achieve sufficient reduction in rubella incidence.

Supplement 5: Change in R_E over time for scenarios 2 to 6 compared to scenario 1 with extreme values of R_0

For both values of R_0, scenarios that entail a mass campaign have an immediate drop in R_E but contrary to the lower value of R_0 (3.3), there is a rebound effect for scenarios 3 to 5 with the higher value of R_0 (12) and a slower drop in R_0 to values below one for scenarios 2 and 6. This is due to higher rubella transmission with higher R_0 values.

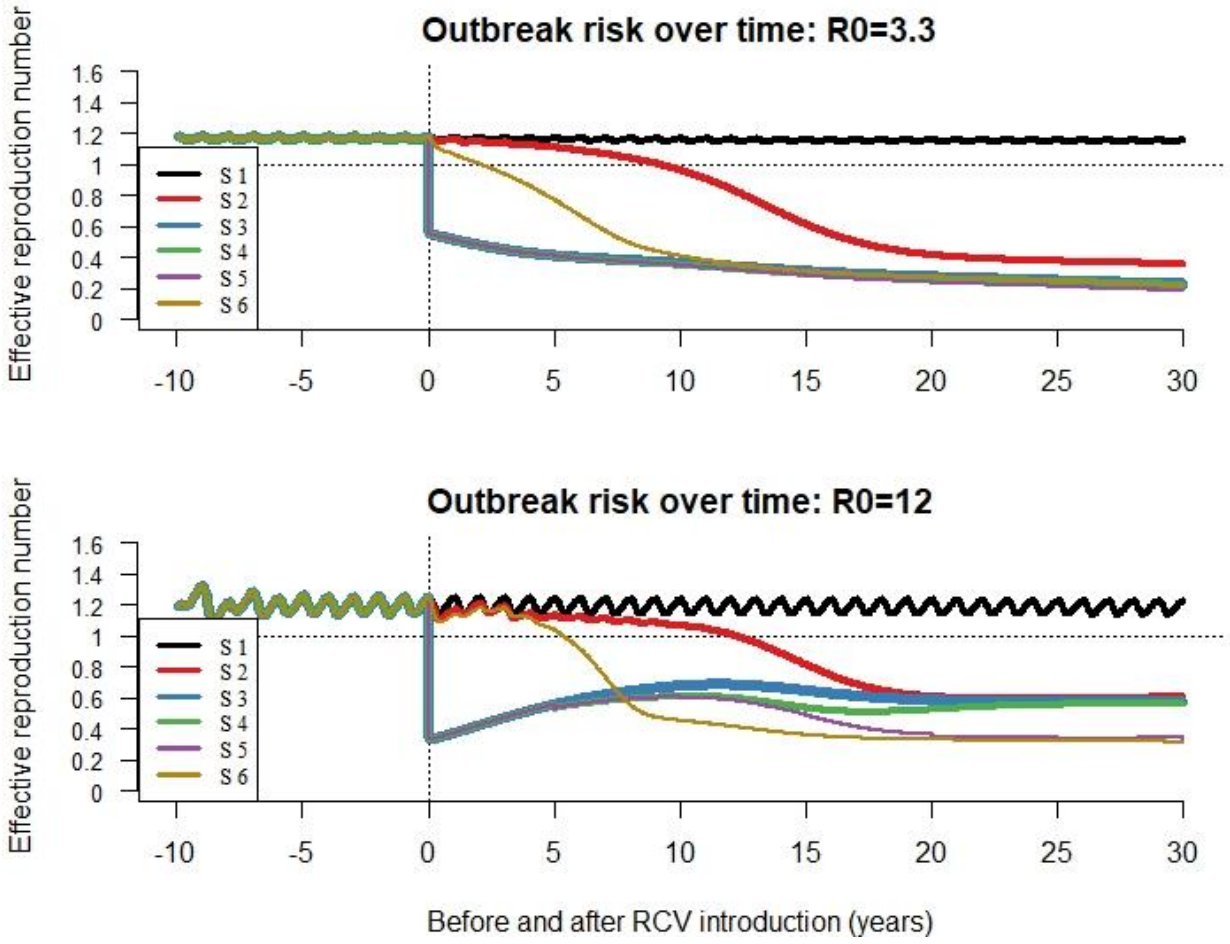


Figure S5. Change in R_E over time at 85% RCV coverage for scenarios 2 to 6 compared to scenario 1 with R0 = 12. The vertical dotted line represents the year of RCV introduction.

Appendix 4: Stellenbosch University Human Research Ethics Committee Approval

UNIVERSITEIT STELLENBOSCH UNIVERSITY

Approval

New Application

27/03/2019

Project ID :7900

HREC Reference # S18/08/177(PhD)

Title: Burden of congenital rubella syndrome and potential impact of rubella vaccine introduction in South Africa

Dear Dr Nkengafac Motaze,

Your response to modifications requested on your **New Application** received on 28/01/2019 11:15 was reviewed by members of **Health Research Ethics Committee** and found to be satisfactory, therefore your study has been **approved**.

Please note the following information about your approved research protocol:

Protocol Approval Period: 27 March 2019 to 26 March 2020

Please remember to use your project ID (7900) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/7900

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Melody Shana,

Coordinator,

HREC1

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)●REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1) ●IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services