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Evaluating rubella epidemiology, vaccine coverage and efficacy, and cost-effectiveness to identify strategies for rubella and congenital rubella syndrome elimination in the Democratic Republic of Congo

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Evaluating rubella epidemiology, vaccine coverage and efficacy, and cost-effectiveness to identify strategies for rubella and congenital rubella syndrome elimination in the Democratic Republic of Congo

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Epidemiology

by

Alvan Bing Jun Cheng

2020

ABSTRACT OF THE DISSERTATION

Evaluating rubella epidemiology, vaccine coverage and efficacy, and cost-effectiveness to identify strategies for rubella and congenital rubella syndrome elimination in the Democratic Republic of Congo

by

Alvan Bing Jun Cheng

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2020

Professor Anne W. Rimoin, Chair

Rubella is an acute, usually mild infectious disease characterized by a distinctive red rash. One of the major concerns with rubella is when a susceptible pregnant woman contracts the disease, and the rubella virus infects the placenta and fetus, leading to a range of birth defects known as congenital rubella syndrome (CRS). Despite the availability of a safe and effective vaccine, rubella continues to be a leading cause of vaccine-preventable birth defects. In the Democratic Republic of Congo (DRC), rubella vaccines are not yet available, and as documentation on rubella and CRS has been limited, the burden of infection among adults is unknown. The primary concern with introducing rubella vaccination is the potential for an increase in CRS incidence as a result of low vaccine coverage, due to the increase in the average age of infection. This dissertation aims to provide a backbone for introducing rubella vaccination in the DRC by assessing the prevalence and predictors of rubella antibody seropositivity, evaluating the impact of vaccination on rubella and CRS burden, and comparing the cost-effectiveness of different vaccination scenarios. In the first study, we assess rubella

antibody seroprevalence in adults using serology collected through dried blood spots. We found that rubella seroprevalence is high among adults in the DRC, and a significant proportion of individuals remain susceptible to infection at the beginning of adulthood, including women entering reproductive age. The second study investigates the level of disease burden that could be reduced by the introduction of rubella vaccination. Rubella transmission dynamics were simulated using a stochastic agent-based model, and our results indicate that introduction of rubella immunization in the DRC may decrease the burden of rubella and CRS. The third study objective was to assess the health and economic impacts of implementing rubella immunization under different vaccination scenarios compared to the current no-vaccination scenario in the DRC. Cost-effectiveness analyses were conducted on vaccination scenarios by comparing incremental net costs per disability-adjusted life-year averted and we found that the introduction of rubella vaccination would be highly cost-effective. In conclusion, our results support investment in the introduction of rubella vaccination in the DRC.

The dissertation of Alvan Bing Jun Cheng is approved.

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Chapter 1: Introduction and background

1.1 Rubella infection

Rubella is an acute, usually mild disease characterized by a distinctive red rash that typically occurs during childhood or early adult life.[1] Despite the availability of a safe and effective vaccine, rubella continues to be one of the leading causes of vaccine-preventable birth defects.[2,3] Rubella virus transmission occurs through either direct person-to-person contact or through droplet contact from nasopharyngeal secretions; infected individuals are most infectious when rash is present, but can shed the virus up to a week prior and after rash onset.[4,5] The rubella virus is a togavirus of the genus Rubivirus and is an enveloped single-stranded RNA virus with a single serotype.[6] Humans are the only known reservoir of the rubella virus, and once infected, the virus replicates in the nasopharyngeal mucosa and extends to the local lymph nodes. After 5 to 7 days following exposure, viremia occurs and results in viral spread to target organs.[7,8] The rubella virus can then be found in the blood and in respiratory secretions until about a week prior to rash onset. Shortly after rash onset, viremia typically disappears, but viral shedding in the respiratory tract may persist up to 28 days.[7]

The incubation period for rubella is approximately 18 days (range from 12 to 23 days), and while symptoms are more common in adults, children tend to show few or no symptoms, making rubella infection difficult to detect and diagnose.[1] The clinical manifestation of rubella infection primarily presents as a rash, which occurs in 50-80% of infected individuals, along with other symptoms such as low fever, nausea, runny nose, and conjunctivitis. Starting on the face and neck, the rash progresses down the body and lasts between 1 to 3 days.[1,9] As rubella typically presents as a mild illness, one of the major concerns is when a susceptible pregnant woman becomes infected. Infection during pregnancy can result in the rubella virus infecting the placenta and fetus, leading to a range of birth defects.[7,8]

1.2 Offspring outcomes

Among pregnant women who are infected with rubella during their first trimester, up to 90% of liveborn infants may have congenital rubella syndrome (CRS), a condition which commonly consists of deafness, blindness, mental retardation, and congenital heart defects.[1,9,10] Other issues associated with CRS may include microcephaly, meningoencephalitis, hepatosplenomegaly, hepatitis, thrombocytopenia, and radiolucencies in the long bone.[1,10] While some of the defects associated with CRS may be easily diagnosed at birth, many may not be detectable until months or years later which may result in lifelong disabilities including autism, diabetes, and thyroid dysfunction.[9]

Once the fetus is infected, the virus can multiply and damage essentially any organ system.[7] The degree of organ damage depends highly on the stage of organ maturation with earlier infection resulting in more severe damage, thus the rate of CRS declines with gestational age.[10,11] There are two mechanisms through which organ damage may occur: one through mitotic inhibition apoptosis and the other through damage to the vascular endothelium. Damage via mitotic inhibition apoptosis may result in the destruction of the ocular lens, retardation of growth, bone lesions, and disruption of organ development.[12–15] Damage to the vascular endothelium may result in encephalitis, mental retardation, and central and cochlear deafness.[15,16]

Aside from congenital rubella syndrome, rubella infection during pregnancy may also result in miscarriages, stillbirths, therapeutic abortions, and congenital rubella (CRI) without birth defects. All congenitally infected infants can shed the rubella virus through pharyngeal secretions and through urine up to one year of age, but infants with clinically diagnosed CRS have been shown to shed the virus up to 27 months; infants with CRI are still infectious even though they present no symptoms.[1,8]

1.3 Detection and diagnosis

Detection of rubella cases is heavily reliant on an effective and efficient surveillance system and should be conducted in conjunction with measles case-based surveillance due to their similar clinical appearances. A rubella surveillance system should include surveillance for both rubella cases and CRS cases by targeting newborns and infants up to 11-months old; a suspected rubella case is any individual presenting fever, rash, and adenopathy or joint paint/inflammation.[1,5] Because rubella surveillance is tied with measles surveillance, acquired specimens from all suspected cases of measles and rubella should be tested. Typically, specimens are tested first for measles-specific immunoglobulin M (IgM), and only those that are negative for measles IgM are tested for rubella IgM; testing kits for rubella IgM are more expensive, and testing all samples for both measles and rubella is often not a feasible option in resource-limited countries.[1,10] Detection of rubella-specific immunoglobulin G (IgG) can also be used to confirm infection, and in most cases, rubella IgG can be detected 8 days after rash onset.[1,5,10] A lab-confirmed rubella case is then defined as a suspected rubella case with either a positive blood test for rubella IgM, a minimum fourfold increase in rubella IgG, or detection of the rubella virus through either reverse-transcriptase polymerase chain reaction (RT-PCR) or rubella virus isolation.[1,5,10] Regarding CRS, a suspected case would be any infant less than one-year-old presenting with any combination of heart disease, suspicion of hearing impairment, cataract, congenital glaucoma, microphthalmos, or pigmentary retinopathy, as well as any infant whose mother has a history of suspected or confirmed rubella infection during pregnancy.[1] A laboratory confirmed case of CRS is a suspected CRS case who either has a positive blood test for rubella IgM, sustained rubella IgG antibody levels, or detection of rubella virus.[1,5] Surveillance for CRS cases should identify the majority of infants with suspected CRS; however, there is currently no surveillance system for rubella or congenital rubella syndrome established in the Democratic Republic of Congo (DRC).

1.4 Burden of disease

1.4.1 Worldwide

In 2016, there were 22,361 reported cases of rubella from 165 countries, representing a 97% decline from the 670,894 cases reported in 2000 from 102 countries.[2] This decline in the number of cases is largely due to the introduction of the rubella-containing vaccine (RCV) into the national immunization schedules of 53 additional countries (a total of 152 out of 194 countries have introduced RCV).[2] Only the Region of the Americas has achieved rubella and CRS elimination. The European, Western Pacific, and South-East Asia Regions have set control and elimination target dates; however, the African Region has yet to set regional rubella goals or targets.[2,3] As for CRS, it is estimated that more than 100,000 infants are born worldwide with CRS annually.[4] In the Americas, endemic transmission of rubella and congenital rubella syndrome have been eliminated as of 2015 due to the effective use of rubella-containing vaccines; the last cases of endemic rubella and CRS in the Americas were reported in 2009.[17] In the European Union, CRS is a rare disease, and since 2002, the number of reported cases has varied from 7 to 23 cases annually.[18] However, the number of CRS cases remains especially high in countries that have yet to introduce RCV into their national immunization schedule, such as the Democratic Republic of Congo.[19]

1.4.2 Democratic Republic of Congo

In the Democratic Republic of Congo, while documentation on rubella and CRS has been limited, the burden of rubella infection is likely to be high. Previous studies have estimated that the incidence of CRS in the DRC is approximately 69 per 100,000 live births and that about one-third of children and approximately 80% of women of childbearing age are rubella antibody seropositive.[19,20] Additionally, measles surveillance campaigns have identified rubella cases in all provinces within the country.[21] Taken together, these results indicate that only is rubella virus

prevalent throughout the entire country, but also that a significant proportion of women and children remain at risk for rubella infection. In order to effectively reduce the incidence of both rubella infection and CRS, rubella vaccination must be implemented through routine immunization and achieve high levels of coverage.

1.5 Research objectives and significance

As the Democratic Republic of Congo continues and strengthens its efforts towards measles control and elimination, it may present an opportunity and a platform for addressing rubella-associated disease burden. Currently, little is known about the epidemiology of rubella within the DRC and most of the research done has been focused on children and women, primarily women of reproductive age and pregnant women. The first chapter of my dissertation aims to expand on the epidemiology of rubella by evaluating the prevalence of rubella seropositivity among all adults in the DRC.

One of the suggested strategies for reducing CRS burden has been to provide immunization to only adolescent girls, women of childbearing age, or both.[10] However, this strategy may not prove effective as rubella transmission would continue among adolescent and adult males, and cases of CRS would continue to arise unless all women of reproductive age are vaccinated. In several countries where the vaccine campaigns target women of reproductive age but not men, large rubella outbreaks continued to occur among males and were followed by occurrences of CRS cases.[1] Therefore, it is important to understand the epidemiology of rubella among adults in the DRC before considering rubella vaccine introduction. Additionally, there have been conflicting studies addressing the concern of an increase in CRS burden following RCV introduction, as some have found that low RCV coverage may shift the average age of infection and result in a spike in CRS cases,[22,23] while others have found that this increase may not be imminent and that the likelihood of this paradoxical effect is heavily dependent on the R_0 value of rubella.[24,25] While measles vaccine coverage in the DRC has yet to reach the

recommended 80% threshold for RCV introduction, most countries in the African region expected to have an R_0 value of rubella between 4-7.[26] Thus, the second chapter of my dissertation focuses on evaluating the impact of rubella vaccination on rubella and CRS burden at the current reported coverage rates for the DRC. If RCV introduction does appear to positively impact rubella-associated disease burden in the DRC, it would be important to evaluate the related economic consequences by weighing the decrease in disease-associated costs against the costs required for vaccine introduction and improved rubella surveillance and control. The final chapter of my dissertation therefore examines the cost-effectiveness of introducing rubella immunization into the national vaccination schedule of the DRC. Such information would benefit decision-makers in making future health policy decisions to ensure improved health outcomes while optimizing good value for money.

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Chapter 2: Rubella Seropositivity Among Adults in the Democratic Republic of Congo

2.1 Abstract

Background: Typically a mild disease in children, rubella infection in adults and pregnant women can lead to more serious complications as well as miscarriage, fetal death or congenital rubella syndrome. Rubella vaccines are not yet available as a part of routine immunization in the Democratic Republic of the Congo (DRC), and the burden of infection among adults is unknown.

Methods: In collaboration with the 2013–2014 DRC Demographic and Health Survey, a serosurvey was carried out to assess population immunity to vaccine-preventable diseases. Dry blood spot samples collected from men 15-59 years of age and women 15-49 years of age were processed using the DYNEX Multiplier® chemiluminescent automated immunoassay platform (Dynex Technologies, Chantilly, VA). Multivariable logistic regression was then used to determine risk factors for rubella seropositivity.

Results: Among the 15802 adults, 93% were positive for rubella antibody, 6% were negative, and 1% were indeterminate for rubella antibodies in weighted analyses. Seroprevalence was positively associated with age of respondent and province, with seropositivity highest in Haut-Katanga (98.37%) and Lualaba (98.04%). In multivariable analyses, serologic evidence of infection was associated with age, education level and province.

Conclusions: Rubella seroprevalence is high among adults in the DRC, and although most viremia and antibody seroconversion occur before 15 years of age, over 10% of individuals remain susceptible to rubella infection at the beginning of adulthood, including women entering reproductive age. To reduce the risk of rubella and CRS, rubella vaccination must be introduced into the national immunization schedule and achieve high coverage. Evaluating the economic

impact and costs associated with vaccine introduction will play an important role in identifying effective immunization strategies and informing future policy decisions.

2.2 Introduction

Rubella is a vaccine-preventable disease that is spread through either direct person-to-person contact or through droplet transmission via nasopharyngeal secretions.[1,2] Despite the availability of a safe and effective vaccine, rubella infection continues to be one of the leading causes of vaccine-preventable birth defects.[3] Among those infected, up to 50% may be asymptomatic or subclinical; individuals that are symptomatic commonly present with rash and low-grade fever, along with any combination of nausea, malaise, mild conjunctivitis, upper respiratory infection, and lymphadenopathy.[4–6] Symptoms tend to be mild and resolve within 1-5 days; however, symptoms in older children and adults may be more severe, such as joint pain and encephalitis.[7–9] Additionally, rubella infection in a pregnant woman may result in miscarriage, stillbirth, or congenital defects known as congenital rubella syndrome (CRS).[10,11] The defects associated with CRS commonly include blindness, deafness, mental retardation, and congenital heart disease.[12–14] Up to 90% of pregnant women infected during the first trimester may give birth to an infant with CRS, and the risk declines with gestational age.[15]

Since the introduction of rubella-containing vaccines (RCVs) in 1969, the incidence of rubella and CRS cases has decreased significantly, and the mortality and morbidity associated with rubella infection has become completely preventable.[16,17] From 2000-2016, global RCV coverage increased by 26%, which has resulted in a 97% decrease in the number of reported cases of rubella.[17] Only the Region of the Americas has achieved rubella and CRS elimination, and in order to achieve the 2020 rubella elimination goals set by the *Global Vaccine Action Plan 2011-2020*, RCV introduction must continue and maintain high coverage rates.[18] The African Region has yet to set regional rubella goals or targets for elimination, and in countries where RCV has yet to be introduced into the national immunization schedule, the burden of rubella and

CRS is likely to be high. Estimates from 2010 have suggested that the incidence of CRS in Africa alone was 116 per 100,000 live births, corresponding to approximately 38,000 cases.[19]

In the Democratic Republic of the Congo (DRC), rubella vaccination is currently not part of the routine immunization (RI) schedule, and there is no specific surveillance system for detecting rubella and CRS cases. However, the country does have a measles-case based surveillance (CBS) system which tests for rubella IgM on specimens that are negative or indeterminate for measles IgM. Despite limitations in documentation, recent studies have estimated the incidence of CRS to be 69 per 100,000 live births and that approximately one-third of children 6- to 59-months are rubella antibody seropositive.[20,21] Additionally, a study analyzing data collected between 2004-2013 from the measles CBS system found that about a quarter of the samples tested for rubella IgM were positive and that the percentage of cases positive for rubella IgM through this system had increased from 20% in 2005 to 46% in 2013.[22] Taken together, these results indicate that not only is the number of identified rubella cases increasing, but also that rubella virus is circulating in the DRC and that a significant proportion of the population remains susceptible to rubella infection.

However, since only specimens from individuals presenting measles-like symptoms are collected, and only a subset of these are tested for rubella IgM, the true burden of rubella among adults in the DRC is unknown. Therefore, using the 2013-2014 Demographic and Health Survey (DHS), we assessed the prevalence of rubella antibody seropositivity in individuals 15-59 years of age in order to provide nationally representative estimates of rubella infection among adults in the DRC.

2.3 Methods

The DRC is a developing country split into 26 provinces with an estimated population of 78.7 million inhabitants.[23] The second DHS (EDS-RDC II) conducted in the DRC took place from November 2013 to February 2014 using a 2-staged stratified cluster design.[24] These

surveys are designed to be nationally representative and to collect data on maternal and child health, as well as basic demographic and health information.[25] Information on sampling design and data collection procedures are described in more detail elsewhere.[26] Data were collected from a nationally representative sample of 18,171 households in which only women 15-49 years of age and men 15-59 years of age were eligible to participate in the survey. Data collected include, but are not limited to, demographics, health outcomes, and household composition.

In addition to survey data, dried blood spots (DBS) were collected from all consenting adults in households where men were approached for individual questionnaires (approximately 50% of households) and analyzed for biomarker data to assess population immunity to vaccine-preventable diseases (VPDs). All survey data from the paper questionnaires were converted to an electronic format using the Census and Survey Processing System (US Census Bureau, ICF Macro, Rockville, MD). All questionnaires are double entered and checked for inconsistencies by comparing the two datasets.

DBS samples were collected using a modified extraction protocol and analyzed at the UCLA-DRC laboratory in collaboration with the Kinshasa School of Public Health located at the National Laboratory for Biomedical Research in Kinshasa, DRC.[27] Laboratory testing was completed using a prototype DYNEX Multiplier® chemiluminescent automated immunoassay instrument with a Measles, Mumps, Rubella, Varicella, and Tetanus (MMRVT) multiplex plate. Quarter inch DBS samples were eluted out in phosphate buffered saline containing 0.05% Tween-20 and 5% dried milk, equating to a 1:143-fold dilution assuming 7 µl of serum per DBS sample. Polystyrene beads coated separately with antigen to measles, mumps, rubella, varicella-zoster virus, and tetanus were immobilized within 54-well M² assay strips with 10 beads per well and processed for IgG antibody detection. Based on epidemiologic studies, the positive/negative cutoff for rubella IgG antibody detection used in our analyses was set at an Assay Score (AS) of 0.37.[28,29]

To assess predictors of rubella seropositivity among adults, χ^2 analyses were conducted on the weighted samples to assess sociodemographic differences between positive and negative test results. Independent predictors of seropositivity were identified through univariate logistic regression models. Multivariable logistic regression models were run with all variables and then with only significant predictors based on backwards selection using Akaike information criterion (AIC) and Bayesian information criterion (BIC). Of the 8,206 individuals with serology data, 7,914 were successfully matched to the DHS dataset. Adults with missing (n=48) or indeterminate serologic test results (n=96) were excluded from the analyses, but those with indeterminate values were included in sensitivity analyses to assess the impact of their removal on the results. Maps of rubella seropositivity prevalence by province were created to examine the spatial distribution of serologic response in adults. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC), and maps were created using ArcGIS software version 10.6 (ESRI, Redlands, CA).

Ethical approval for this study was reviewed and approved by the Ethics Committee of the Kinshasa School of Public Health, Kinshasa, DRC, and by the Institutional Review Board of Human Research Ethics at the University of California, Los Angeles. Informed consent was obtained from all enrolled participants as a part of the DHS survey.

2.4 Results

Among the 7,866 adults included in the analyses, 7,234 (92%) were positive for rubella antibody, 536 (7%) were negative, and 96 (<1%) were indeterminate. After applying the DHS sampling weights, the total sample size resulted in 15,802 adults in which 14,610 (93%) were positive, 998 (6%) were negative, and 194 (1%) were indeterminate.

Overall, the prevalence of rubella antibody among adults was high in all provinces (Fig. 1). The provinces with the highest prevalence were Haut-Katanga (98.37%) and Lualaba (98.04%); Bas-Uele had the lowest (87.25%). Adults who were older (>24 years of age), had

higher education, or had higher socioeconomic status were more likely to test positive for rubella IgG antibody relative to their younger, less educated, and lower socioeconomic status counterparts (Table 1). Controlling for age, the positive relationship between education level and seropositivity remained in all age groups (Fig. 2). Analysis of the serologic test results revealed a positive linear relationship between age and seropositivity; rubella seropositivity increased from 89.5% of 15-year-olds to 100% of 59-year-olds (Fig. 3).

Overall, those living in urban areas were more likely to be seropositive than rural residents (Table 1). Within provinces, this association only held for Kinshasa, Kasai-Oriental, and Haut-Katanga; for the remaining provinces, rubella seropositivity was more likely to be found in rural areas than urban ones (Fig. 4). Additionally, those living in areas of higher population density were also more likely to be seropositive compared to those living in lower population density areas (Table 1).

In multivariable analyses, the odds of rubella seropositivity increased with increasing age up to age 45 (the odds of a positive test result for rubella antibodies was 3.52 times higher for adults aged 40-44 compared to 15-19 year olds; adults aged 45+ had 1.99 times the odds of a positive serologic test compared to 15-19 year olds), level of education (no education compared to secondary or higher education), and province (Haut-Katanga and Lualaba had the highest odds of rubella seropositivity, and Sankuru had the lowest compared to Kinshasa; Table 2). Inclusion of those with indeterminate serology did not impact our results (data not shown).

2.5 Discussion

The results of our study reveal that rubella virus may be widely circulating throughout the DRC: among adults 15-59 years of age, the prevalence of rubella-specific IgG antibodies was >87% in all provinces. These results are consistent with other studies that have examined rubella seroprevalence in other countries of the African region in the pre-vaccine era.[30] In a meta-analysis of three studies of rubella seropositivity among women of reproductive age,

rubella seropositivity was found to be 94.1% in women 14-18 years of age in Ethiopia, 90.1% in women 15-45 years of age in Senegal, and 84% in women 15-34 years of age in Côte d'Ivoire.[30] While these studies included only women, they found that rubella virus was circulating widely in Africa and that rubella infection during pregnancy occurred throughout the region prior to RCV introduction.

Rubella seropositivity was found to be associated with both age and province: 91% of adults aged 15-19 and 95% of adults aged 45+ tested positive for rubella antibody, with the highest prevalence in Haut-Katanga and Lualaba provinces. Our finding of a positive relationship between age and rubella seropositivity is consistent with previous findings from studies assessing rubella immunity in other African countries.[31,32] A study conducted in Ethiopia found that, prior to rubella vaccine introduction, 66.7% of pregnant women 16-19 years of age, 79.9% of pregnant women 25-34 years of age, and 82.3% of pregnant women 35-40 years of age tested positive for rubella-specific IgG antibodies.[31] In a study of pregnant women in Namibia, the prevalence of rubella seropositivity increased from 83% of 15-19 year olds to 90% of 40-44 year olds.[32] However, these studies are limited only to pregnant women, and the results are likely not representative of adults, or even women, in these regions.

As DRC currently relies on its measles CBS to identify cases of rubella infection and rubella is not a reportable disease, it is likely that the estimates obtained through this system are an underestimation and not representative of the true burden of infection. Among the rubella cases identified through this system, only 5% were among those 15 years of age or older (60% of which were female).[22] In our study, we found that among 15-year-olds, 89% of both males and females had serologic evidence of rubella infection and that seropositivity increased with age for both genders. These results indicate that, although most viremia and antibody seroconversion occur before 15 years of age, over 10% of individuals remain susceptible to rubella infection at the beginning of adulthood, including women entering reproductive age. This is concerning as rubella infection during pregnancy may lead to a range of adverse outcomes,

including miscarriage, stillbirths, and infants born with either CRS or congenital rubella infection (CRI).[1,15,33,34] An estimated 90% of fetuses are affected by multiple defects when rubella infection occurs just before conception or during the first trimester.[15] The risk of congenital defects decreases with gestational age, and maternal rubella infection after the 16th week of pregnancy are rarely associated with fetal defects.[34] In order to reduce the risk of rubella and CRS, rubella vaccination must be introduced into the national immunization schedule and achieve high coverage.

This study has a number of limitations. We presumed that a positive test result for rubella IgG was the result of natural infection; however, some adults may have had the opportunity to receive vaccination – while unlikely. As DHS does not collect any data on vaccines provided outside of the national government for pregnant women and children under 5 years old, we were unable to verify whether any individuals received immunization against rubella. Additionally, there might be misclassification of serostatus due to the testing method. However, compared to four commercially available kits, the DYNEX Multiplier® assay exhibited high validity for both sensitivity (range: 89.5–100%) and specificity (range: 77.3–100%); therefore, it is unlikely that misclassification would significantly impact our findings.[29] Furthermore, the cost-effectiveness of the multiplex assay outweighed this limitation as we were also able to evaluate the serology of four other vaccine-preventable diseases. Due to the presence of serologically indeterminate results, we initially excluded these adults from our analyses, yet in sensitivity analysis, inclusion of these individuals did not change our results. Our data suggest that although rubella virus is circulating among adults throughout the DRC, a significant proportion of adults remain susceptible to infection at the start of adulthood and throughout reproductive age.

There exists a safe and effective rubella vaccine, yet only a small number of sub-Saharan African countries have introduced it into their national immunization schedule.[35] According to the WHO, countries should have well-established and effective immunization

programs capable of achieving high levels (≥80%) of measles vaccination coverage through RI and supplementary immunization activities (SIAs) before introducing RCV to avoid potentially increasing the risk of CRS.[16,36] In the DRC, national estimates from WHO-UNICEF reveal that measles RI coverage reached 80% in both 2017 and 2018.[37] Provided with adequate funding, resources, and political will, the rubella antigen may be easily integrated into the RI schedule.

This is one of the few studies to provide nationally representative estimates of rubella infection among adults in the DRC and may help to inform policy decisions and to identify effective vaccination strategies.[10,38] Currently, there are tentative plans for RCV introduction into the national immunization schedule before 2020, with goals of organizing catch-up SIAs for rubella and establishing a system for monitoring CRS.[39] In the interim, it is important to both understand the impact of vaccination at lower than recommended coverage levels, especially on the incidence of CRS, and to evaluate the economic impact and costs associated with vaccine introduction. In the meantime, the country should focus on strengthening surveillance efforts and following the Global Measles and Rubella Strategic Plan, specifically achieving and maintaining high levels of population immunity and conducting research and development in support of cost-effective operations.[3] Monitoring disease progress and improving the capacity to maintain nationally high vaccine coverage levels will be crucial next steps in advancing toward rubella and CRS elimination.

2.6 Tables and figures

Table 2.1. Weighted Demographic Characteristics of 2013-2014 DRC-DHS Respondents 15-59 Years of Age by Rubella Serosurvey Results

	Negative (n = 998)		Positive (n = 14610)		
	n	%	n	%	χ^2 P-Value
Respondent's information					
Age					<.0001
15-19 yrs*	302	30.3	2935	20.1	
20-24 yrs	217	21.8	2619	17.9	
25-29 yrs	162	16.2	2444	16.7	
30-34 yrs	121	12.1	1875	12.8	
35-39 yrs	56	5.6	1599	10.9	
40-44 yrs	39	3.9	1310	9.0	
45+ yrs	99	10.0	1827	12.5	
Sex					0.5746
Male	487	48.8	6828	46.7	
Female	511	51.2	7782	53.3	
Number of household members					0.7277
1-3	159	15.9	2047	14.0	
4-6	372	37.3	5465	37.4	
5-9	287	28.8	4554	31.2	
10+	180	18.0	2544	17.4	
Highest level of education					0.9244
No education	105	10.5	1523	10.4	
Primary	320	32.1	4523	31.0	
Secondary/higher	573	57.4	8543	58.6	
Wealth index†					0.3296
Poorest	211	21.2	2657	18.2	
Poorer	213	21.3	2886	19.8	
Middle	203	20.3	3064	21.0	
Richer	196	19.6	2703	18.5	
Richest	175	17.6	3299	22.6	
Province					0.0032
Kinshasa	78	7.8	1627	11.1	
Kwango	34	3.4	708	4.8	
Kwilu	80	8.1	944	6.5	
Mai-Ndombe	44	4.4	680	4.7	
Kongo Central	54	5.5	558	3.8	
Equateur	33	3.3	446	3.1	
Mongala	34	3.4	385	2.6	

Nord-Ubangi	22	2.2	236	1.6	
Sud-Ubangi	42	4.2	706	4.8	
Tshuapa	19	1.9	351	2.4	
Kasai	38	3.8	410	2.8	
Kasai-Central	51	5.1	590	4.0	
Kasai-Oriental	45	4.5	588	4.0	
Lomami	69	7.0	640	4.4	
Sankuru	36	3.6	231	1.6	
Haut-Katanga	4	0.4	641	4.4	
Haut-Lomami	10	1.0	358	2.4	
Lualaba	2	0.2	298	2.0	
Tanganyka	28	2.8	246	1.7	
Maniema	41	4.1	450	3.1	
Nord-Kivu	78	7.8	1208	8.3	
Bas-Uele	29	2.9	293	2.0	
Haut-Uele	32	3.3	268	1.8	
Ituri	24	2.4	464	3.2	
Tshopo	37	3.7	436	3.0	
Sud-Kivu	32	3.2	849	5.8	
Population density‡					0.7138
Low	513	51.5	7076	48.4	
Medium	229	23.0	3553	24.3	
High	255	25.6	3981	27.2	
Residence					0.0783
Urban	312	31.3	5402	37.0	
Rural	685	68.7	9208	63.0	

*Only women between the ages of 15-49 and men between the ages of 15-59 were invited to participate in the survey.

†Wealth index is an aggregate measure of the household's cumulative living standard taking account of the household's ownership of selected assets, materials used for housing construction, and types of water access and sanitation facilities.

‡Population density was calculated by dividing the population of each province (based on projections from the latest census) by the area of each province (in km2) and then categorizing into tertiles.

Table 2.2. Weighted Logistic Regression of Sociodemographic Factors Associated with Rubella Seropositivity of 15 to 59-Year-Old 2013–2014 DHS Respondents

	OR_{crude} (95% CI)	$OR_{adjusted}$* (95% CI)
Respondent's information		
Age		
15-19†	ref	ref
20-24	1.24 (0.92-1.68)	1.26 (0.92-1.72)
25-29	1.56 (1.06-2.29)	1.63 (1.10-2.42)
30-34	1.60 (1.06-2.41)	1.67 (1.09-2.54)
35-39	2.94 (1.78-4.84)	3.13 (1.89-5.17)
40-44	3.45 (1.63-7.30)	3.52 (1.65-7.49)
45+	1.89 (1.13-3.16)	1.99 (1.17-3.38)
Sex		
Male	ref	-
Female	1.09 (0.81-1.45)	-
Number of household members		
1-3	ref	-
4-6	1.14 (0.82-1.58)	-
5-9	1.23 (0.87-1.73)	-
10+	1.10 (0.73-1.64)	-
Highest level of education		
No education	0.98 (0.68-1.41)	0.79 (0.54-1.15)
Primary	0.95 (0.70-1.28)	0.91 (0.67-1.24)
Secondary/higher	ref	ref
Wealth index‡		
Poorest	ref	-
Poorer	1.20 (0.87-1.66)	-
Middle	1.08 (0.73-1.59)	-
Richer	1.10 (0.74-1.63)	-
Richest	1.50 (1.01-2.21)	-
Province		
Kinshasa	ref	ref
Kwango	0.99 (0.41-2.36)	0.99 (0.42-2.37)
Kwilu	0.56 (0.24-1.29)	0.57 (0.24-1.33)
Mai-Ndombe	0.74 (0.30-1.82)	0.76 (0.30-1.89)
Kongo Central	0.49 (0.23-1.03)	0.51 (0.25-1.06)
Equateur	0.65 (0.35-1.19)	0.65 (0.34-1.26)
Mongala	0.54 (0.29-0.99)	0.56 (0.30-1.04)
Nord-Ubangi	0.50 (0.23-1.10)	0.52 (0.23-1.19)
Sud-Ubangi	0.80 (0.41-1.57)	0.87 (0.45-1.69)
Tshuapa	0.88 (0.38-2.02)	0.91 (0.39-2.12)

Kasai	0.51 (0.24-1.08)	0.56 (0.28-1.12)
Kasai-Central	0.56 (0.27-1.17)	0.58 (0.27-1.25)
Kasai-Oriental	0.62 (0.32-1.22)	0.66 (0.34-1.31)
Lomami	0.44 (0.25-0.78)	0.48 (0.27-0.84)
Sankuru	0.31 (0.17-0.57)	0.32 (0.17-0.60)
Haut-Katanga	7.93 (2.48-25.38)	8.54 (2.66-27.43)
Haut-Lomami	1.70 (0.62-4.65)	1.85 (0.66-5.17)
Lualaba	5.82 (1.33-25.44)	6.26 (1.41-27.84)
Tanganyka	0.42 (0.20-0.86)	0.45 (0.22-0.94)
Maniema	0.52 (0.21-1.31)	0.52 (0.21-1.32)
Nord-Kivu	0.74 (0.36-1.53)	0.813(0.38-1.78)
Bas-Uele	0.48 (0.19-1.23)	0.49 (0.19-1.29)
Haut-Uele	0.39 (0.17-0.90)	0.41 (0.18-0.94)
Ituri	0.93 (0.34-2.53)	1.03 (0.36-2.90)
Tshopo	0.57 (0.29-1.11)	0.58 (0.29-1.17)
Sud-Kivu	1.25 (0.58-2.71)	1.35 (0.61-2.97)
Population density¥		
Low	ref	-
Medium	1.13 (0.77-1.64)	-
High	1.13 (0.82-1.57)	-
Residence		
Urban	1.29 (0.97-1.71)	-
Rural	ref	-

*Using backwards selection, only significant predictors (based on Akaike information criterion and Bayesian information criterion) were retained in the final model; predictors in adjusted model include respondent's age, highest level of education, and province.

†Only women between the ages of 15-49 and men between the ages of 15-59 were invited to participate in the survey.

‡Wealth index is an aggregate measure of the household's cumulative living standard taking account of the household's ownership of selected assets, materials used for housing construction, and types of water access and sanitation facilities.

¥Population density was calculated by dividing the population of each province (based on projections from the latest census) by the area of each province (in km2) and then categorizing into tertiles.

OR indicates odds ratio; CI, confidence interval.

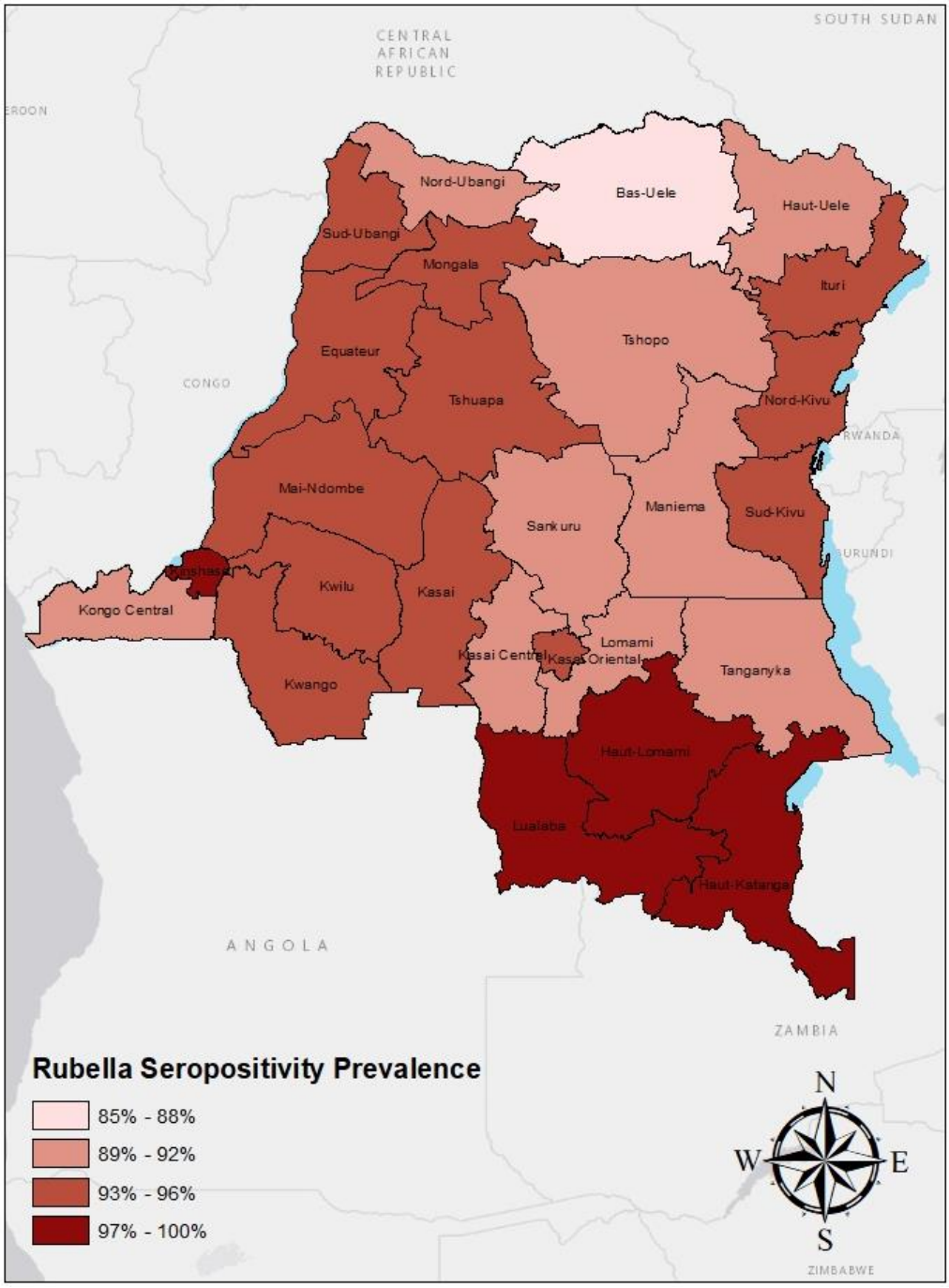

Figure 2.1. Geographic distribution of rubella seropositivity for 2013-2014 DRC-DHS by province among women 15-49 years of age and men 15-59 years of age.

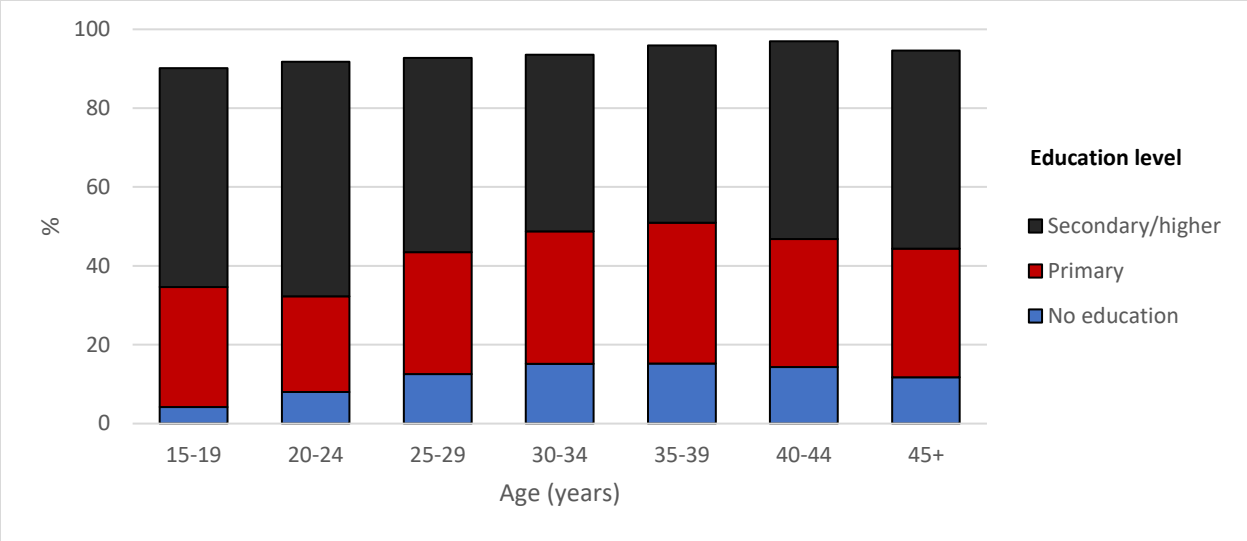

Figure 2.2. Percent of positive rubella antibody test results according to education level within age groups among 15- to 49-year-old female and 15- to 59-year-old male 2013-2014 DRC-DHS respondents.

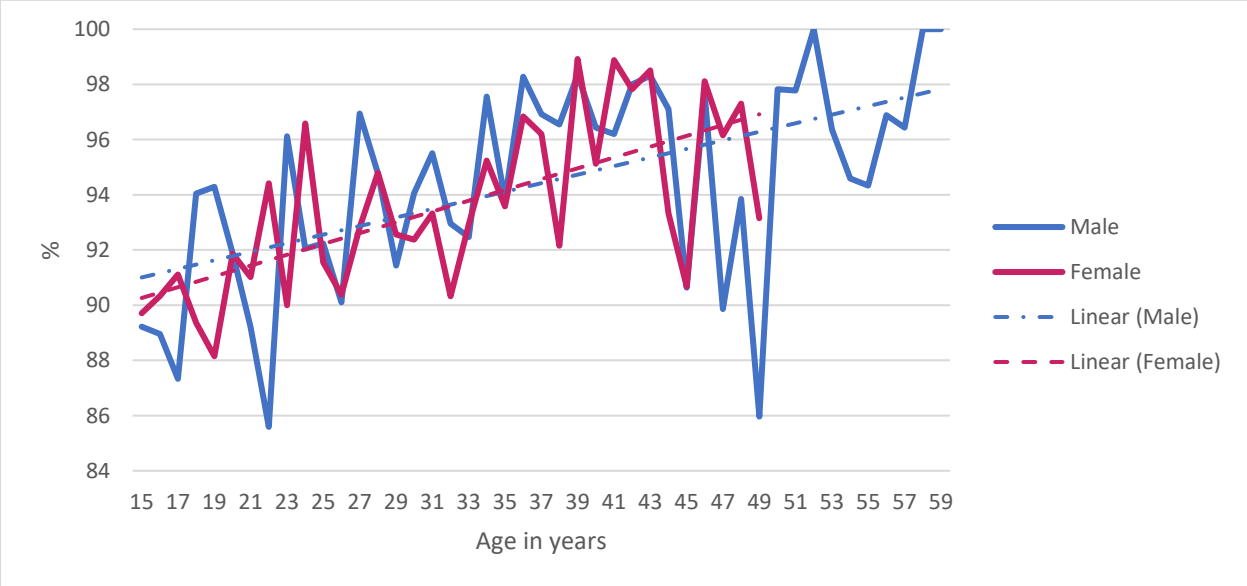

Figure 2.3. Percent of rubella seropositivity by age and sex among 15- to 49-year-old female and 15- to 59-year-old male 2013-2014 DRC-DHS respondents (with linear trend lines).

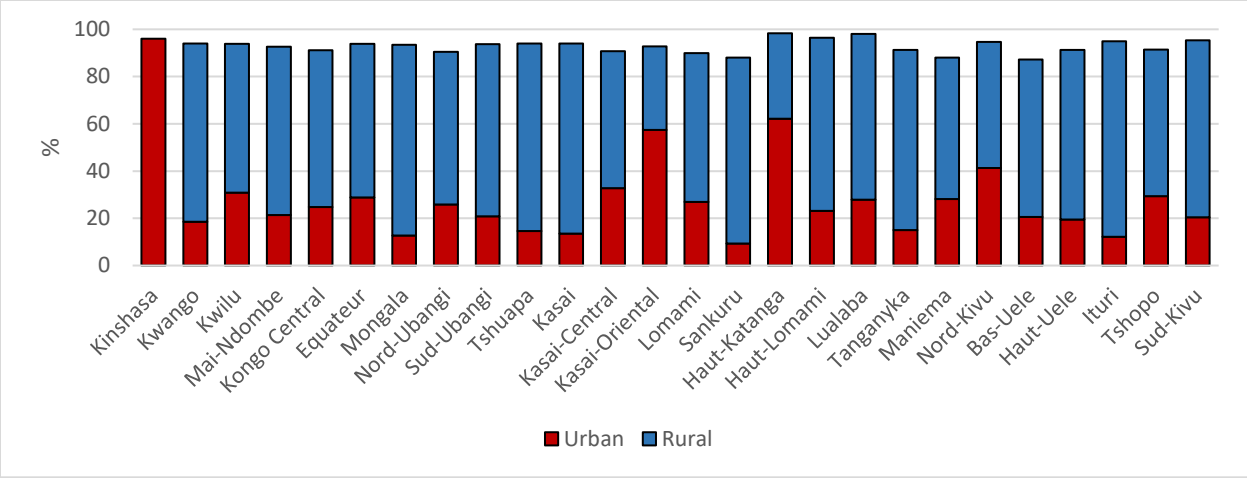

Figure 2.4. Rubella seroprevalence according to place of residence for 2013-2014 DRC-DHS by province among women 15-49 years of age and men 15-59 years of age.

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Chapter 3: Modeling the Impact of Rubella Immunization in the Democratic Republic of Congo

3.1 Abstract

Background: Rubella infection among adults can result in severe complications, especially among pregnant women which may lead to infant mortality or infants born with congenital defects. In the Democratic Republic of Congo, rubella and congenital rubella incidence is high, but measles eradication efforts may provide an opportunity for potential interventions. This paper investigates the level of disease burden that could be reduced by incorporating rubella vaccination into the national immunization schedule as a combined measles-rubella-containing vaccine.

Methods: We modeled two vaccination scenarios using an agent-based disease transmission model to simulate natural rubella dynamics along with the effect of immunization. We compared estimates of rubella infection and congenital rubella syndrome burden over a 30-year period against modeled estimates resulting from the current scenario of no vaccination. Levels of routine immunization were assigned at the province level.

Results: With no rubella immunization, our model estimated there to be 151,021,183 rubella cases and 147,543 congenital rubella syndrome cases. After introducing rubella vaccine, the number of rubella cases decreased to 1.5-8.1 million cases and congenital rubella syndrome cases decreased to 2.9-27.1 thousand cases depending on the vaccination scenario.

Conclusions: The likelihood of an increase in congenital rubella syndrome burden as a result of low vaccine coverage heavily depends on the basic reproduction number of rubella. Modeling results indicate that introduction of rubella immunization in the Democratic Republic of Congo at the current reported vaccination rates may decrease the burden of rubella and congenital rubella syndrome.

3.2 Introduction

The rubella virus (RV), a togavirus and sole member of the *Rubivirus* genus, is an enveloped single-stranded RNA virus with a single serotype.[1,2] In an infected individual, the virus multiplies within the epithelial cells of the respiratory tract and then extends to the local lymph nodes through the blood stream. Secondary replication occurs and the virus then spreads to target organs.[3] Generally a mild disease in children, rubella may be more severe in adults and can result in severe complications when pregnant women are infected. While more than 50% of cases are asymptomatic, common symptoms include rash and low-grade fever plus any combination of nausea, malaise, mild conjunctivitis, upper respiratory infection, and lymphadenopathy.[4–6] Infection during pregnancy may result in miscarriage, stillbirth, or a range of congenital abnormalities known as congenital rubella syndrome (CRS).[7,8] Symptoms associated with CRS typically include cataracts, cardiac abnormalities, and sensorineural deafness, though many other defects may be observed as the RV can affect any organ.[9,10] Transmission of RV occurs through droplets from the respiratory tract, and infected individuals may be contagious from 7 days before to 7-12 days after rash onset.[1] Humans are the only host for RV, and there are no known animal reservoirs.

Worldwide, the number of reported rubella cases has decreased by 97% from 2000-2016 as global coverage with rubella-containing vaccine (RCV) increased by 26% within this time period.[11] The most commonly used licensed rubella vaccines are based on the live, attenuated RA 27/3 strain cultured in human diploid cells and can be administered as either a monovalent formulation or as a combination with other vaccine viruses, such as measles, mumps, and varicella.[9,12] A single dose of the rubella vaccine induces high seroconversion rates (≥95%) and provides long-term immunity, similar to that produced by natural infection.[12,13] In most countries, RCV is administered along with measles vaccine and thus follows the two-dose schedule for measles: the first dose at 9 months or 12-15 months and the second dose at 15-18

months or 4-6 years.[14,15] By the end of 2016, 152 (78%) countries had introduced RCV into their national immunization schedules; however, due to differences in population sizes between countries, more than half of infants (53%) worldwide remain unvaccinated against rubella.[11] In the Democratic Republic of Congo (DRC), rubella vaccine has yet to be introduced into the national immunization schedule, and the burden of rubella and CRS is likely to be high.

Before introducing RCV into a country's national immunization schedule, the World Health Organization (WHO) recommends that the country first achieve ≥80% coverage of the first dose of measles-containing vaccine (MCV1) through either routine immunization (RI) or vaccination campaigns. Previous mathematical models have suggested that an increase in CRS incidence may result from low coverage of RCV, due to the increase in the average age of infection.[16,17] The occurrence of clusters of CRS cases in Costa Rica and Greece following a period of inadequate vaccine coverage has magnified this caution of RCV introduction.[18,19] However, this caution may result in a missed opportunity as rubella vaccine can be easily combined and administered with measles vaccine (MRCV). In South Africa, simulations of rubella vaccine introduction at the current estimates for measles vaccine coverage revealed that, due to a low basic reproduction number (R_0) for rubella, the burden of CRS would be reduced despite vaccine coverage being below the recommended 80% threshold.[20] Evidence from several countries has suggested that rubella may frequently have a low R_0, indicating that disease incidence could be reduced at lower coverage.[20–23] Based on these results, introduction of rubella vaccination in the DRC may reduce the burden of rubella and CRS even though the most recent Multiple Indicator Cluster Survey conducted revealed measles RI coverage to be much lower than the 80% threshold.[24]

Despite the availability of an effective and affordable vaccine, rubella remains a leading cause of vaccine-preventable birth defects.[11] Recently, the Global Alliance for Vaccines Initiative (GAVI) has opened a funding window for rubella vaccination.[25] As the DRC already provides

two doses of measles vaccine through a combination of routine immunization and supplementary immunization activities (SIAs), introducing RCV as a combined measles-rubella vaccine may provide an opportunity for progressing towards rubella and CRS elimination. The DRC's Expanded Program on Immunization (EPI) has committed to measles elimination by 2020, and these efforts should be taken advantage of to progress towards the rubella elimination goals set by the *Global Vaccine Action Plan 2011-2020* (GVAP).[26,27] However, it is imperative to evaluate the impact of rubella vaccination prior to vaccine introduction due to the inverse relationship between RCV coverage rates and CRS incidence. Therefore, in collaboration with the Institute of Disease Modeling (IDM) and the 2013–2014 Demographic and Health Survey (DHS), we used an agent-based model to assess different vaccination scenarios in order to assess the impact of incorporating rubella vaccination into the national immunization schedule in the DRC.

3.3 Methods

Rubella transmission dynamics in the DRC were simulated using the Generic branch of Epidemiological MODeling software (EMOD), a stochastic agent-based model of disease transmission.[28] A representative diagram of the health states and transitions included in the model can be seen in Figure 1. Using data from the most recent DHS conducted in the DRC in 2013-2014 (EDS-RDC II),[29] the model was calibrated to best match the reported age-of-infection data specific to each province. Fixed input parameter values included known disease properties (e.g., infectious period), demographic variables (e.g., birth rate), and interventions (e.g., calendar of past SIAs). All simulations maintained a non-zero level of total infectiousness at all times, and persistent importation pressure ensured that re-introduction of disease was possible if local elimination were to occur.

Simulations of the DRC population reflected age- and gender-based demography of each of the provinces and included all ages. All simulations had a time horizon of 30 years

representing the period from 2021-2050, and each year consisted of 365 discrete time steps. Birth, aging, and mortality occurred during each time step in the simulations. Birth rates and mortality probabilities for children under 5 years old were both age- and province-specific and were estimated from the EDS-RDC-II data[29]; mortality probabilities for individuals ≥ 5 years of age were adjusted to provide a national population structure similar to the DHS estimated population in 2013. These model parameters are summarized in Table 1. Simulations provided province-level resolution, and our primary outcomes for this analysis were the number of rubella and CRS cases.

In order to estimate the infectivity of rubella within each province of the DRC, simulations were used to generate estimated age-stratified seronegativity profiles for each province. These profiles were then compared to the observed profiles obtained from serosurvey data collected as part the EDS-RDC-II in order to identify the R_0 value with the highest likelihood. Rubella infections were characterized by incubation and infectious period distributions with mean 17 days and 6 days respectively. All estimated R_0 values by province are depicted in Figure 2. Individuals could only receive one infection and would receive life-long immunity following infection. Each infectious individual was randomly assigned an infectivity from a distribution with a mean equal to the base infectivity for their province. Rubella infections for each province were independent of each other, and the total infectivity of each province determined the total number of infections occurring during each subsequent time step. The total number of CRS cases was calculated post hoc using fixed probabilities for each age group.

We modeled different vaccination scenarios for RCV introduction in the DRC as a combined measles-rubella vaccine. Immunity to rubella was assumed to be binary, and both naturally-derived immunity and vaccine-conferred immunity were assumed to provide life-long protection. Individuals could also receive maternal immunity, which provided an average of 3 months protection; if an individual had maternal protection and received immunization, life-long

immunity was not conferred. All vaccination simulations began with an SIA catch-up campaign (targeting individuals between 9 months to 15 years of age) in 2020 and follow-up SIAs (targeting children between 9 months to 5 years of age) occurred every 4 years subsequently. To assess the impact of vaccination on rubella and CRS burden, we modeled two scenarios of nationwide RCV introduction with the first dose administered through RI at the current reported province-level MCV1 coverage rates and the second dose administered through SIAs with varying coverage rates of 70% and 50%. For baseline comparison, we modeled the incidence of rubella and CRS under the current situation of no RCV implementation.

3.4 Results

Without the introduction of rubella vaccination, our model estimated the total number of rubella and CRS cases in the DRC over 30 years to be 151,021,183 and 147,543 respectively (Fig. 3). The provinces with the greatest burden of rubella were Nord-Kivu, Sud-Kivu, Haut-Katanga, and Kinshasa, with each province modeled to have over 10 million cases of rubella infection. The provinces with the lowest estimated rubella burden were Bas-Uele and Haut-Uele. For CRS, Kasai and Tanganyika had the highest overall burden, each estimated to observe over 10,000 cases, while Mai-Ndombe had the lowest overall burden with under 1,000 cases. The predicted incidence of rubella per 100,000 was highest in Haut-Katanga and Lualaba and lowest in Haut-Uele and Maniema. The estimated incidence of CRS per million population was highest in Tanganyika and Haut-Uele and lowest in Haut Katanga and Mai-Ndombe for the baseline scenario.

With nationwide RCV introduction at province-specific RI rates and 50% SIA coverage, the model estimated disease burden to reduce to 8,126,323 rubella cases and 27,070 CRS cases (Fig. 3). The provinces with the highest predicted rubella burden, as well as the highest incidence of rubella infection, were Tshuapa and Mai-Ndombe, each with over 800,000 cases. The provinces with the lowest estimated burden and incidence of rubella were Sud-Kivu and

Nord-Kivu with 4,861 and 5,505 cases respectively. CRS cases were estimated to be highest in Haut-Katanga with approximately 3,000 cases, while six provinces (Sud-Kivu, Nord-Kivu, Kinshasa, Haut-Uele, Kasai-Central, and Ituri) were modeled to observe less than 100 cases over the 30-year time period. The incidence of CRS for the 50% SIA coverage scenario was estimated to be highest in Maniema and Lualaba and lowest in Nord-Kivu and Sud-Kivu.

When SIA coverage was increased to 70%, the number of rubella and CRS cases decreased to 1,477,302 and 2,859 respectively (Fig. 3). Similar to the 50% SIA coverage vaccination scenario, the provinces with the highest estimated burden and incidence of rubella infection were Mai-Ndombe and Tshuapa with over 300,000 cases in each province. Correspondingly, Mai-Ndombe and Tshuapa were also predicted to have the highest burden and incidence of CRS with 586 and 538 cases respectively. Meanwhile, Kasai-Central observed the lowest estimated burden and incidence of both rubella infection and CRS with 856 cases of rubella and 3 cases of CRS over the 30-year time period. A comparison of rubella and CRS burden by province and vaccination scenario is portrayed in Figure 4.

3.5 Discussion

With GAVI providing increased support and funding, countries may be considering introducing rubella vaccination into their national immunization schedules. Previously, countries have withheld RCV introduction due to the potential for a paradoxical increase in CRS incidence[17]; however, this endeavor may provide an opportunity to reduce rubella and CRS burden and may also strengthen existing measles immunization efforts.[30] Prior to the vaccine introduction, countries must have an understanding of the current epidemiology of rubella and CRS and should potential areas of increased disease burden due to lower than recommended levels of vaccination coverage in order to evaluate the effectiveness of RCV introduction and the potential for rubella elimination.

Consistent with previous studies on RCV introduction, our data suggests that the addition of rubella vaccination can result in important public health benefits in reducing rubella-related diseases. Additionally, our results indicate that even with RI coverage rates lower than the recommended 80%, introducing rubella vaccination into the national immunization schedule of the DRC has the potential to significantly reduce rubella and CRS burden within the country when it is supplemented with SIAs at coverage rates as low as 50%. As routine immunization remains sub-optimal and estimated coverage rates are low,[24,31] these results are likely due to the low R_0 values of rubella across provinces in the DRC.

One of the primary concerns of introducing rubella vaccination is the potential increase in CRS burden. A review of the literature suggests that an increase in CRS burden due to low vaccine coverage may not be imminent and that the likelihood of this paradoxical effect is heavily dependent on the R_0 value of rubella.[32,33] In areas where the R_0 of rubella is assumed to be 5-7, while short-term increases in CRS may occur, introduction of rubella immunization has been estimated to result in long-term decreases in CRS burden.[33] The median R_0 value of rubella across the African region has been estimated to be 5.2, with most African countries expected to have an R_0 between 4-7.[34] In the DRC, we estimated the R_0 of rubella to be <7 in all provinces except for Mai-Ndombe (R_0=8). Both of the vaccination scenarios modeled here are estimated to result in significant decreases in rubella and CRS burden. Introducing RCV at the reported province-level RI coverage rates supplemented by 50% coverage SIAs would prevent 142,885,860 rubella cases and 120,473 CRS cases. Increasing SIA coverage to 70% would prevent an additional 6,649,021 rubella cases and 24,211 CRS cases.

Our assumption of 70% SIA coverage may be an overestimation. However, notable decreases in rubella and CRS burden were still observed when SIA coverage was dropped to 50%. Additionally, we assumed follow-up SIAs to occur every 4 years, which represents a conservative estimation as the WHO recommends SIAs to be implemented every 3 years in

countries with weak routine immunization systems in order to ensure high coverage and to control measles transmission.[35] This strategy is recommended to continue until ≥80% RI coverage is achieved.[36,37] Our agent-based simulation analyses broadly support introduction of rubella vaccination into the national immunization schedule of the DRC, particularly when bolstered by adequate SIA efforts.

Our analyses are subject to a number of limitations. First, the SIA coverage we included in our model may not represent true coverage rates. However, our assumptions of 50% and 70% are likely conservative estimates as SIA coverage data has been reported to achieve ≥90% and even exceed 100%. Second, disease transmission and vaccination within provinces were modeled to be independent of each other. We were unable to model migration between provinces, which could lead to increased rubella transmission among susceptible populations. Instead, we included a non-zero infectivity to all provinces to represent the risk of imported infections. This ensured that the probability of infection would remain non-zero in the event that local elimination would occur (i.e. zero infectivity from infected individuals). Finally, we could not model the probability of an individual receiving a second vaccine dose given that they received the first as this dependence of MRCV1 and MRCV2 is unknown.

Our analysis provides broad optimism that introduction of rubella vaccination into the DRC's national immunization schedule will result in decreases in rubella and CRS burden, provided SIA coverage rates are adequately high. As our results highlight the importance of vaccination campaigns to prevent short- and long-term increases in CRS incidence, evaluation of the costs associated with vaccine introduction must be considered. Moving forward, strengthening of routine immunization programs to reduce the dependence on supplementary vaccination campaigns would be beneficial. If RI coverage can achieve and maintain high rates, there is high potential for the elimination of rubella in the DRC.

3.6 Tables and figures

Table 3.1. Parameters included in disease model

Province	Estimated 2019 population*	Birth rate (per 100,000)†	Mortality†					RI coverage‡	Vaccine efficacy¥
			0-29 days	30-359 days	360-1829 days	1830-34679 days	≥34680 days		
Bas-Uele	1,177,029	39.7	1.12E-03	1.11E-04	3.20E-05			0.437	
Equateur	2,247,840	45.8	9.79E-04	1.14E-04	5.08E-05			0.519	
Haut-Katanga	5,440,816	49.0	1.23E-03	1.17E-04	3.70E-05			0.655	
Haut-Lomami	3,632,535	49.0	1.23E-03	1.17E-04	3.70E-05			0.542	
Haut-Uele	1,701,503	39.7	1.12E-03	1.11E-04	3.20E-05			0.600	
Ituri	5,226,511	39.7	1.12E-03	1.11E-04	3.20E-05			0.689	
Kasai	4,099,745	53.0	8.02E-04	1.52E-04	4.79E-05			0.298	
Kasai-Central	4,369,364	53.0	8.02E-04	1.52E-04	4.79E-05			0.753	
Kasai-Oriental	4,882,512	46.5	1.05E-03	1.02E-04	4.43E-05			0.420	
Kinshasa	8,647,308	36.1	5.56E-04	1.05E-04	2.49E-05			0.759	
Kongo Central	3,635,569	43.6	1.62E-03	1.08E-04	3.27E-05			0.686	
Kwango	2,294,566	42.4	9.08E-04	9.54E-05	2.35E-05			0.478	
Kwilu	4,592,343	42.4	9.08E-04	9.54E-05	2.35E-05	2.35E-05	1.0	0.544	97%
Lomami	3,600,553	46.5	1.05E-03	1.02E-04	4.43E-05			0.422	
Lualaba	2,090,404	49.0	1.23E-03	1.17E-04	3.70E-05			0.422	
Mai-Ndombe	1,762,664	42.4	9.08E-04	9.54E-05	2.35E-05			0.377	
Maniema	2,391,851	39.1	1.12E-03	9.23E-05	3.20E-05			0.221	
Mongala	2,314,755	45.8	9.79E-04	1.14E-04	5.08E-05			0.319	
Nord Kivu	8,783,179	40.9	8.73E-04	4.89E-05	1.72E-05			0.801	
Nord-Ubangi	1,452,136	45.8	9.79E-04	1.14E-04	5.08E-05			0.389	
Sankuru	1,846,756	46.5	1.05E-03	1.02E-04	4.43E-05			0.389	
South Kivu	6,445,549	48.8	1.66E-03	1.43E-04	3.56E-05			0.733	
Sud-Ubangi	2,636,370	45.8	9.79E-04	1.14E-04	5.08E-05			0.431	
Tanganyika	2,815,857	49.0	1.23E-03	1.17E-04	3.70E-05			0.358	
Tshopo	2,965,751	39.7	1.12E-03	1.11E-04	3.20E-05			0.298	
Tshuapa	1,945,663	45.8	9.79E-04	1.14E-04	5.08E-05			0.349	

*UN OCHA Country Office in Democratic Republic of Congo. DR Congo - Health Zones

†Demographic and Health Surveys (DHS). Deuxième Enquête Démographique et de Santé (EDS-RDC II 2013-2014). Rockville, MD

‡National Institute of Statistics and United Nations Children's Fund. Multiple Indicator Cluster Survey in the DRC, 2018.; 2018.

¥Center for Disease Control and Prevention: Measles, Mumps, and Rubella (MMR) Vaccination: What Everyone Should Know [https://www.cdc.gov/vaccines/vpd/mmr/public/index.html]

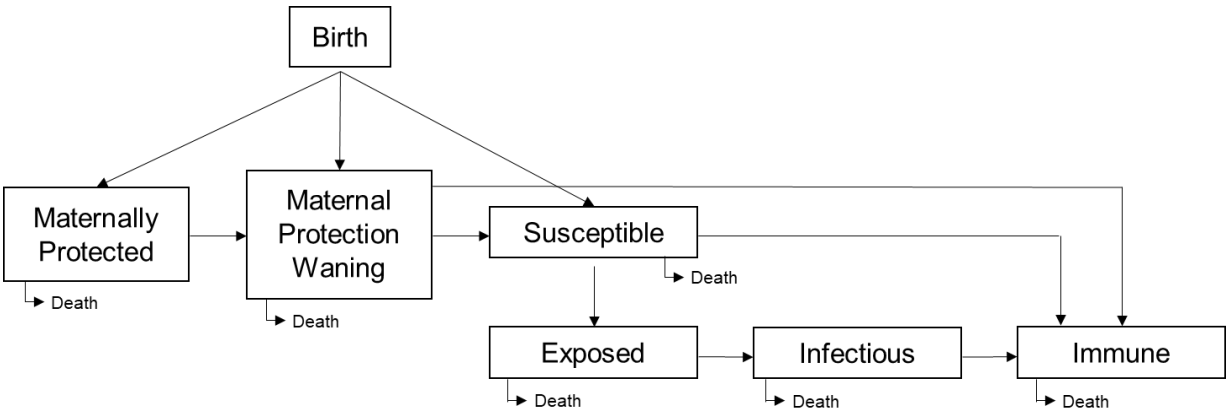


Figure 3.1. Compartmental model of health conditions and transitions included in the disease model. There is no direct transition from maternally protected or exposed to immune (vaccination under these states is assumed to not confer immunity). Mortality is possible for all conditions and is unrelated to disease.

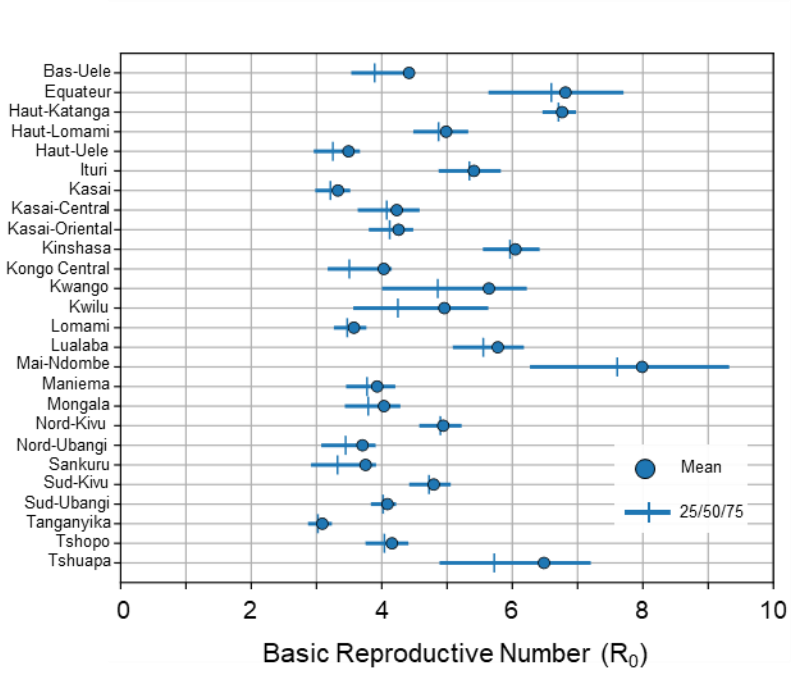
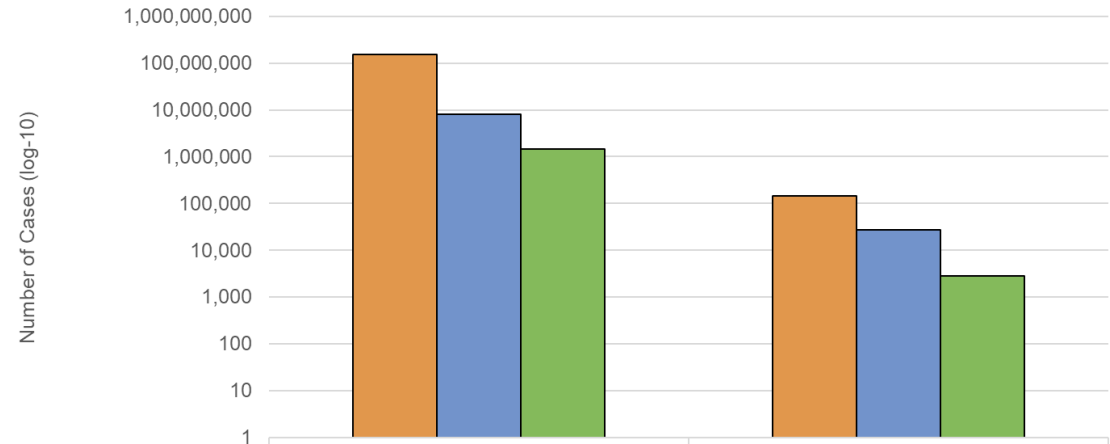


Figure 3.2. Scatter plot of R_0 values by province with mean and interquartile range.



	Rubella	Congenital Rubella Syndrome
Baseline (no RCV)	151,021,183	147,543
Nationwide RCV (50% SIA)	8,126,323	27,070
Nationwide RCV (70% SIA)	1,477,302	2,859

Figure 3.3. Estimated total number of rubella and congenital rubella cases from 2021-2050 stratified by vaccination scenario.

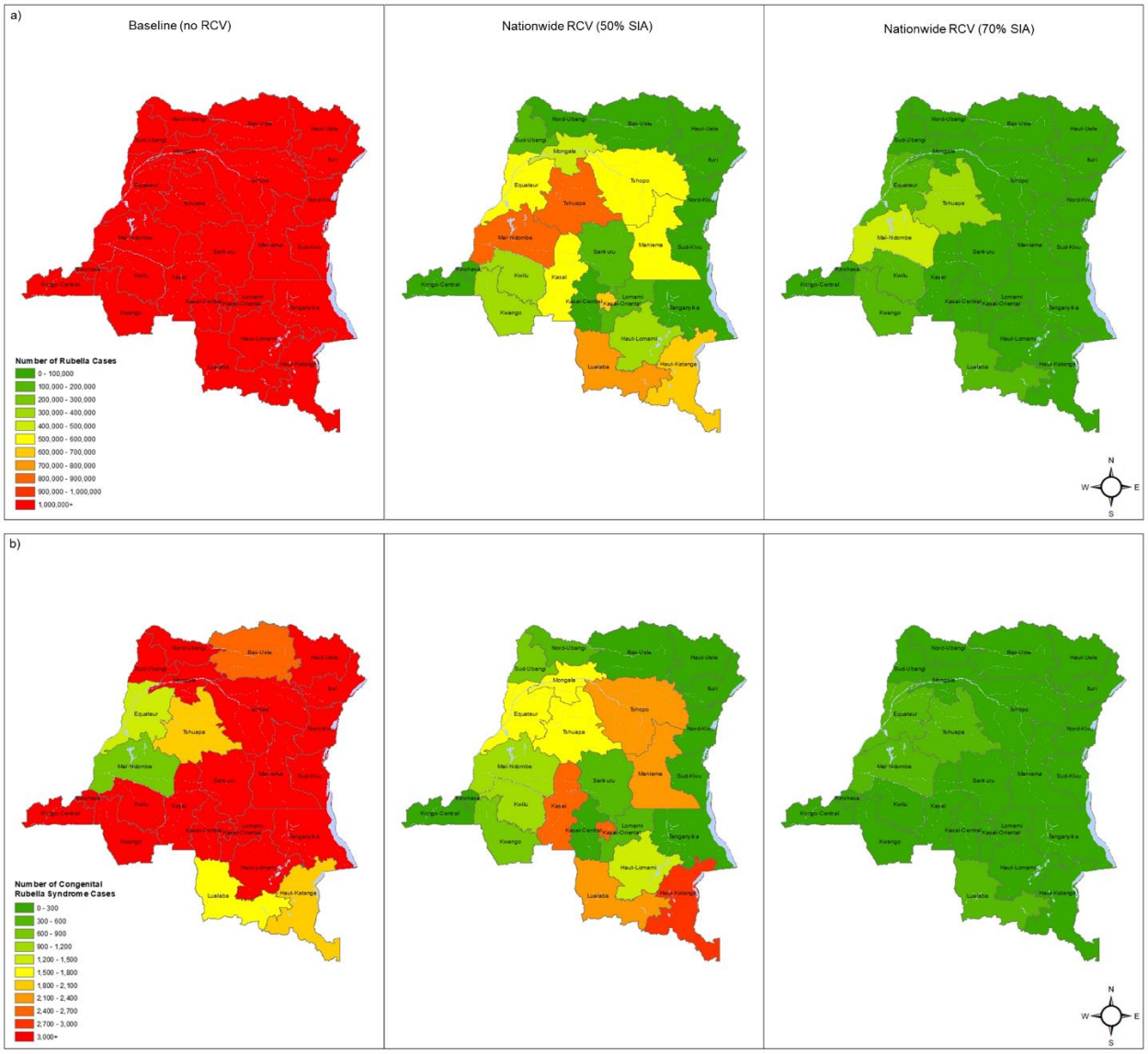


Figure 3.4. Maps of a) rubella and b) CRS incidence in the Democratic Republic of Congo by province and vaccination scenario.

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Chapter 4: A Cost-Effectiveness Analysis of Rubella Vaccination Strategies for Children in the Democratic Republic of Congo

4.1 Abstract

Background: One of the goals of both the Global Measles and Rubella Strategic Plan and the Global Vaccine Action Plan is to achieve rubella elimination worldwide, with high rubella vaccination coverage as one of its main milestones. Only one dose of rubella vaccine is required to achieve high levels of immunity, and countries may combine measles and rubella vaccination to achieve more robust immunity. In the Democratic Republic of Congo, while poor health infrastructure has limited routine immunization (RI) efficiency, the use of supplementary immunization activities (SIAs) may provide an opportunity to reduce the burden of rubella and congenital rubella syndrome by incorporating rubella vaccination into the national immunization schedule.

Methods: We estimated the cost-effectiveness of three vaccination scenarios by comparing incremental net costs per disability-adjusted life-year averted. Data specific to the Democratic Republic of Congo was used, and rubella vaccination coverage was assumed to equal province-level measles vaccination coverage. When not available, values extracted from other low-income countries were used. Inputs included the probabilities and costs of health outcomes caused by rubella infection or vaccination, treatment costs, vaccination costs, surveillance costs, and programmatic costs.

Results: Compared to scenario 1 (no rubella immunization), scenario 2 (RCV1 by RI, RCV2 by 50% SIA) would cost an additional $524 million and reduce total disability-adjusted life-years (DALYs) by 2.95 million. Compared to scenario 1, scenario 3 (RCV1 by RI, RCV2 by 70% SIA) would reduce total DALYs by 3.52 million and cost an additional $313 million.

Conclusions: Including rubella vaccination into the national immunization schedule of the Democratic Republic of Congo substantially reduced disease burden and was highly cost-effective for both vaccine scenarios. While our results support investment in the introduction of rubella vaccination, decision-makers must consider all relevant data in a country-specific context to ensure optimal benefits.

4.2 Introduction

Since the availability of rubella-containing vaccines (RCV) in 1969, global incidence of rubella has decreased significantly.[1,2] From 2000 to 2016, the number of countries administering RCV as part of their national immunization schedule increased by 54% (from 99 to 152 countries), and during this time period, the number of reported rubella cases decreased by 97% from 670,894 cases in 102 countries to 22,361 cases in 165 countries.[2] Typically, rubella is a mild disease in children and manifests with a rash and low-grade fever along with any combination of nausea, malaise, mild conjunctivitis, upper respiratory infection, and lymphadenopathy.[3–5] In adults, rubella infection may be more severe and include symptoms such as joint pain and encephalitis; however, the primary concern of rubella is when a pregnant woman becomes infected.[6–8] When this occurs, the rubella virus can cross the placental barrier and infect fetal tissue, potentially resulting in either fetal death or a constellation of abnormalities, commonly including congenital heart defects, deafness, cataracts, and mental retardation, known as congenital rubella syndrome (CRS).[9,10] Among pregnant women infected with rubella during the first trimester, up to 90% of liveborn infants may present with CRS, and the risk decreases with gestational age.[11]

In most countries where RCV is available, it is administered in conjunction with either measles (MR) or measles and mumps (MMR), and typically follows the two-dose schedule for measles: the first dose at 9 months or 12-15 months and the second dose at 15-18 months or 4-6 years.[12,13] While a single dose of RCV is sufficient enough to provide long-term immunity with

a high seroconversion rate of ≥95%, a second dose could be beneficial in capturing those who were either not vaccinated or who received the first dose, but did not seroconvert.[1,14] Although less than a quarter of countries have yet to introduce RCVs, due to differences in population sizes between countries, more than half of infants (53%) worldwide remain unvaccinated against rubella.[2] In the Democratic Republic of Congo (DRC), rubella vaccine has yet to be introduced into the national immunization schedule, and the burden of rubella and CRS is likely to be high. Despite limitations in documentation, recent studies have estimated that ~3,000 infants are born with CRS annually in the DRC and that approximately one-third of children 6- to 59-months are rubella antibody seropositive.[15,16]

The primary goal of rubella immunization is to prevent congenital rubella, and there are two general approaches of using RCVs: focus solely on reducing CRS by immunizing only adolescent girls and women of childbearing age or focus on interrupting transmission of rubella virus by immunizing all children through routine immunization (RI). Research in the US, Israel, Japan, Iceland, and Norway has evaluated the economic impact of rubella-associated morbidities and the cost-effectiveness of rubella vaccination in these populations.[17–22] It has been documented by Gudnadóttir and by Golden and colleagues that vaccination targeting specifically susceptible adolescent girls and women may be a more cost-effective strategy compared to vaccination of all children[19,21]; however, with this approach, the epidemiology and circulation of rubella would likely remain unaffected as most infections occur before the age of immunization.[1] Additionally, elimination of CRS would not likely be achieved through this strategy as it would require every susceptible woman to be vaccinated.[1]

Another consideration prior to introducing RCV is the suggested inverse relationship between RCV coverage and CRS incidence. Previous mathematical models have suggested that an increase in CRS incidence may result from low coverage of RCV, due to the increase in the average age of infection.[23,24] The World Health Organization (WHO) recommends that a

country first achieve ≥80% coverage of the first dose of measles-containing vaccine (MCV1), through either RI or vaccination campaigns, before incorporating RCV into the national immunization schedule. This caution has been amplified following instances where a rise in CRS cases have occurred following a period of low vaccination coverage, such as in Costa Rica and Greece.[25,26] However, simulations in South Africa have suggested that in areas where the basic reproduction number (R_0) for rubella is low, CRS incidence could be reduced even when vaccine coverage falls below the recommended level.[27] Based on these findings, incorporating rubella vaccination into the national immunization schedule of the DRC may provide an opportunity to reduce the burden of rubella and CRS.

While the DRC does not currently provide RCV, it does provide two doses of measles vaccination through a combination of RI and supplementary immunization activities (SIAs). Although the health infrastructure in the DRC has struggled with limited roads and access to electricity and water, slight improvements in vaccine coverage have been realized. Based on WHO/UNICEF estimates, national MCV1 coverage in the DRC have been steadily increasing from 72% in 2009 to 80% in 2017[28]; however, based on estimates from the most recent Multiple Indicator Cluster Survey conducted in the DRC, measles RI coverage was much lower than the recommended 80% threshold.[29] As rubella and measles immunization can be easily combined, there may be opportunity to leverage ongoing measles elimination activities to support rubella elimination. Comparing the costs and benefits of introducing rubella vaccination as a combined MR vaccine may provide insight in selecting the most optimal strategy for rubella immunization in the DRC.

Data on the public health and economic consequences of RCV introduction in the DRC will play an important role in guiding future policy decisions, vaccine delivery strategies, and other prevention and control efforts for rubella-related disease. While several studies have evaluated the cost-effectiveness of rubella and CRS elimination, few have considered varying

vaccination strategies. Differences in public health infrastructure and rubella epidemiology between regions requires analyses to be country-specific. Therefore, the aim of this analysis was to assess the health and economic impacts in DRC of implementing rubella immunization under different vaccination scenarios compared to the current no-vaccination scenario.

4.3 Methods

We developed a cost-effectiveness model to compare varying scenarios for rubella vaccine introduction in the DRC. The primary outcome measure is the incremental net cost per disability-adjusted life-year (DALY) averted. DALYs combine years of life lost due to premature death (YLLs), calculated from the average life expectancy at the age and year of rubella/CRS mortality, and life-years lost due to disease morbidity (YLDs), calculated using the duration of rubella/CRS by standard DALY weights. DALY weights indicate the proportion of healthy time lost due to living with rubella infection/CRS. Health outcomes include vaccine-related complications, rubella infection, and CRS.

We used an ingredients-based approach to estimate vaccination-related costs by assigning a value to each dose of MR vaccine administered through either routine services or an SIA. Costs associated with RI included personnel, injection equipment (auto-disable syringes and safety boxes), cold chain costs (vaccine carriers, cold boxes, ice packs, refrigerator parts, and fuel), and transportation. Additional costs were incorporated into the model for vaccines administered through SIAs, including social mobilization, supervision, and planning/training, as well as higher costs for cold chain, transportation, and personnel in order to account for difficult-to-reach populations. The wastage factor indicates the fraction of vaccines not used, and wastage factors for SIAs are generally smaller than for RI. In the DRC, the wastage factor was estimated at 3.42 for RI and 1.15 for SIAs.[30–33] The Centers for Disease Control and Prevention (CDC) estimates one dose of RCV to be 97% effective, thus a small proportion of individuals will always remain susceptible even after vaccination.[34] We also included global level costs

associated with vaccine stockpile and recommended surveillance for rubella and CRS. All immunization-associated costs and inputs are summarized in Table 1.

Health outcome probabilities and costs associated with rubella and CRS, as well as vaccine-related complications, were obtained through literature review. Costs associated with rubella infection and vaccine-related adverse events varied by gender and age and were calculated with costs associated with home care. Health outcomes were measured in DALYs and were gender- and age-specific. On average, adult women were more likely to experience adverse events, related to both rubella infection and vaccination, and thus had greater DALYs. Health outcome costs and DALYs can be seen in Table 2. Specific health outcomes include anaphylaxis, febrile seizures/convulsions, thrombocytopenia, arthropathy, cardiac defects, eye abnormalities, auditory defects, and intellectual disability. Probabilities for these outcomes varied by gender and age and are summarized in Table 3.

The vaccination scenarios we assessed included: 1) No RCV introduction (baseline comparison), 2) RCV introduction nationwide with the first dose through RI at the current reported province-level MCV1 coverage rates and the second dose through SIAs at 50% coverage, 3) RCV introduction nationwide with the first dose through RI at the current reported province-level MCV1 coverage rates and the second dose through SIAs at 70% coverage. All costs and health outcomes were modeled over a time horizon of 30 years and were discounted at a rate of 3%.

4.4 Results

Compared to scenario 1, scenarios 2 and 3 were more effective regarding health outcomes, with scenario 3 being the most effective, however, scenario 1 was the least expensive option (Fig. 1). Over 30 years, without the introduction of rubella immunization, there would be 151,021,183 cases of rubella and 147,543 cases of CRS, and the costs associated

with rubella infection were estimated to total $1.8 billion. Regarding specific health outcomes, this scenario would lead to 3,243 cases of encephalitis, 8,330 cases of thrombocytopenia, and 2,979,048 cases of transient arthropathy, resulting in 3,595,394 DALYs (Table 4).

Introducing two doses of rubella vaccination at province-specific RI coverage rates and 50% SIA coverage (scenario 2) would cost an additional $524.5 million, but would prevent 142,894,860 cases of rubella and 120,473 cases of CRS (Table 4b). While vaccination costs would total $2 billion, disease costs would be reduced by $1.5 billion. Health outcomes associated with vaccination would result in 2,305 cases of anaphylaxis, 230,452 febrile seizures/convulsions, and 230 cases of thrombocytopenia. Health outcomes associated with rubella infection would total 163 encephalitis cases, 425 thrombocytopenia cases, and 228,592 transient arthropathy cases (Table 4a). Compared to scenario 1, scenario 2 would reduce DALYs to 643,004 (a reduction of 2,952,390 DALYs) and the incremental cost-effectiveness ratio (ICER), defined as the cost per DALY averted, for scenario 2 compared to scenario 1 would be 177.64 (Table 4b).

When SIA coverage was increased to 70% (scenario 3), the increase in total costs was reduced to $312.9 million when compared to no rubella vaccination. Vaccination and disease costs would total $2.1 billion and $29.6 million respectively, a decrease of $1.7 billion relative to scenario 1 (Table 4b). Vaccine-related adverse events would include 2,773 anaphylaxis cases, 277,288 febrile seizures/convulsions, and 277 thrombocytopenia cases, while adverse events associated with rubella infection would include 30 cases of encephalitis, 76 cases of thrombocytopenia, and 26,717 cases of transient arthropathy (Table 4a). Compared to scenario 1, scenario 3 would reduce the total number of DALYs by 3.5 million, resulting in 71,901 DALYs, and the ICER comparing scenario 3 to 1 would equal 88.82 (Table 4b). Therefore, none of the scenarios dominated over the rest as scenario 1 required the lowest total costs, but scenario 3 yielded the fewest number of rubella and CRS cases.

4.5 Discussion

Introducing RCV in the DRC through routine immunization and supplementary immunization activities is projected to reduce rubella-associated morbidity, compared to no vaccination, with increased expenditures. Our results demonstrate that administering rubella vaccination as a combined MR vaccine would be highly cost-effective, even at the current province-level RI rates with SIA coverage rates as low as 50%.

The WHO recommends rubella vaccination as a safe and effective measure to reduce the burden of congenital rubella infections, including CRS. Additionally, WHO recommends that countries already providing 2 doses of measles vaccine, through either RI, SIAs, or both, should consider including RCVs in their immunization programs and suggests that countries should take advantage of accelerated measles control and elimination activities in order to do so.[1] Past studies have proven rubella vaccination to be cost-effective and economically justified, however, these studies have focused on high- and middle-income countries where coverage is >80%.[35–37] Few studies have examined the cost-effectiveness of rubella vaccination at sub-optimal levels of coverage in low-income countries in Africa. Our simulations indicate that administering RCVs at the current reported province-level coverage rates would result in a decrease in the number of DALYs associated with rubella infection when complemented with SIA services.

In terms of projected advantages, scenario 2 would cost an additional $524.5 million, but would prevent 2,952,390 DALYs when compared to scenario 1. Scenario 3 would prevent an additional 571,103 DALYs and would cost $211.5 million less than scenario 2. Compared to scenario 1, both scenarios 2 and 3 would save over $1 billion in disease-related costs and the majority of costs resulted from programmatic costs related to vaccine stockpile and management and to establishing and maintaining rubella and CRS surveillance systems.

The WHO's Choosing Interventions that are Cost-Effective (WHO-CHOICE) project defines a highly cost-effective intervention as one that costs less than the national annual gross domestic product (GDP) per capita per DALY averted; a cost-effective intervention would cost less than three times the national annual GDP per capita per DALY averted.[38–41] The nominal GDP per capita for the DRC is estimated to be ~$500.[42–44] The ICERs resulting from our analyses suggest that introducing rubella vaccination in the DRC would be highly cost-effective for both scenario 2 ($177.64/DALY averted) and scenario 3 ($88.82/DALY averted). As there have been documented limitations on the use of cost-effectiveness thresholds,[45,46] decision-makers should consider these results alongside all relevant country-specific data, such as affordability, budget impact, feasibility, and any other criteria deemed important in the local context, in order to ensure optimal health outcomes and the best use of expenditures.

While our analyses conclude that RCV introduction would be highly cost-effective, some limitations to our study exist. We included costs estimated based on available evidence from other low-income countries as accurate data on non-vaccine and programmatic costs specific to the DRC were not available. However, some of the global level costs may be overestimated as these costs were estimated for all countries regardless of income classification. Our analyses did not account for all of the possible factors that may impact the costs and health outcomes of vaccination efforts. For example, while we incorporated transportation costs as part of non-vaccine costs, there may be increased costs associated with traveling across different terrains or traveling to more remote areas. Additionally, variables that would be difficult to quantify and that could not be included in our model may exist. For example, the efforts of introducing a new vaccine and conducting additional vaccination campaigns may divert time and resources from other health initiatives which could lead to inaccurate costs. Disease costs and probabilities were also obtained from proxy countries, but there is likely heterogeneity across provinces in the DRC that could not be accounted for in our model. While these costs may not represent all

of the costs associated with rubella complications, they do attempt to account for costs associated with loss of productivity and receiving home care. Lastly, the ICERs calculated here are point estimates and are likely to have uncertainty in both the measure of cost and the measure of effectiveness. Future studies may consider conducting bootstrap analyses in order to approximate confidence intervals to address these uncertainties.

In general, introducing rubella vaccine as a combined MR vaccine appears to be a cost-effective scenario in the DRC, provided that SIA rates reach at least 50% coverage. While our results suggest that disease burden may be reduced by administering RCV at the current province-level RI coverage rates, targeted efforts to achieve and maintain high RI rates should be prioritized. Decision-makers need to consider practical limitations and all relevant data and estimates in a context-specific process in order to ensure improved health outcomes while optimizing good value for money.

4.6 Tables and figures

Table 4.1. Variables associated with immunization activities with sources.

Variable	Value	Source
Routine Immunization (per dose)		
Vaccine w/freight		
MCV	$0.318	[1]
MRCV	$0.656	[2]
Non-vaccine Cost (injection equipment use and disposal, cold chain, personnel, training, and other misc. costs)	$0.350	[3,4,5]
Total RI costs per dose (MCV)	$0.668	
Total RI costs per dose (MRCV)	$1.006	
Supplementary Immunization Activities (per dose)		
Vaccine w/freight		
MCV	$0.318	[1]
MRCV	$0.656	[2]
Non-vaccine Cost (addition of social mobilization, supervision, planning/training, administrative costs, and transportation costs)	$0.810	[5,6]
Total SIA costs per dose (MCV)	$1.128	
Total SIA costs per dose (MRCV)	$1.466	
Global Level Costs		
Cost to create a global rotating MR vaccine stockpile (one-time cost)	$50,000,000	[5]
Annual surveillance costs, including expanded rubella and CRS surveillance, pre-eradication	$60,000,000	[5]
Annual technical support, operational research, stockpile management, communication, and coordination costs, pre-eradication	$35,000,000	[5]
Wastage factor		
RI	3.42	[3,4]
SIAs	1.15	[4,7,8]
Discount rate	0.03	Assumption

1. Vaccine Price Data - Measles [https://www.unicef.org/supply/files/2018_04_04_Measles.pdf].

2. Vaccine Price Data - Measles-Rubella [https://www.unicef.org/supply/files/2018_04_17_MR.pdf].

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7. Programme Enlargi de Vaccination: Measles Vaccination Budget: 2013. In.; 2013.

8. Vaccination PEd: RDC Synthese du Budget Campagne de Suivi 2013: Bandundu, Equateur, Kinshasa, Orientale. In.; 2013.

Table 4.2. Health outcome costs and DALY estimates by gender associated with vaccination and rubella infection.

Vaccine or Virus	Costs*		Source
Vaccine adverse events (per dose)			
0 to 14 years	$0.003		
Females, ≥15 years	$0.100		
Males, ≥15 years	$0.003		
Rubella infection			
Females, 0 to 14 years	$5		
Females, ≥15 years	$46		
Males, 0 to 14 years	$5.49		
Males, ≥15 years	$9.54		
CRS (per case)	$11,266		
	DALYs		[1]
	Male	Female	
MRCV			
<5 years	0.00002	0.00002	
5 to 14 years	0.00002	0.00002	
15 to 44 years	0.00001	0.0035	
45+ years	0.00001	0.000115	
Rubella infection			
<5 years	0.0003	0.0003	
5 to 14 years	0.0003	0.0003	
15 to 44 years	0.0195	0.195	
45+ years	0.006	0.055	
CRS	29	29	

1. Thompson KM, Odahowski CL. The Costs and Valuation of Health Impacts of Measles and Rubella Risk Management Policies. Risk Anal. 2016;36(7):1357-1382. doi:10.1111/risa.12459

*Cost inputs account for treatment costs, productivity losses, and costs associated with home care.

Table 4.3. Health outcome probabilities by gender and age group.

	Male				Female				
Health Outcome	<5 yr	5–14 yr	15–44 yr	45+ yr	<5 yr	5–14 yr	15–44 yr	45+ yr	Source
Vaccine Adverse Events (per dose)									
Anaphylaxis	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	
Febrile seizures/convulsions	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
Minor reactions	10	10	10	10	10	10	10	10	
Thrombocytopenia	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	
Thrombocytopenia mortality	0.000003	0.000003	0.000003	0.000003	0.000003	0.000003	0.000003	0.000003	
Arthropathy, transient (excluding adult men)	--	--	--	--	0.01	0.01	0.1	0.1	
Arthropathy, chronic (≥15-year-old women)	--	--	--	--	0	0	0.01	0.01	
									[1]
Rubella Adverse Events (per infection)									
Asymptomatic infection	49.9	49.9	49.0	49.0	49.9	49.9	39.6	39.6	
Encephalitis	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	
Encephalitis mortality	0.00009	0.00009	0.00011	0.00011	0.00009	0.00009	0.00011	0.00011	
Thrombocytopenia	0.005	0.005	0.006	0.006	0.005	0.005	0.006	0.006	
Thrombocytopenia mortality	0.00014	0.00014	0.00018	0.00018	0.00014	0.00014	0.00018	0.00018	
Transient arthropathy	0.3	0.3	2	2	0.3	0.3	21	21	
Chronic arthropathy	0	0	0.4	0.4	0	0	4	4	
Uncomplicated illness	49.9	49.9	49.0	49.0	49.9	49.9	39.6	39.6	

1. Thompson KM, Odahowski CL. The Costs and Valuation of Health Impacts of Measles and Rubella Risk Management Policies. Risk Anal. 2016;36(7):1357-1382. doi:10.1111/risa.12459

Table 4.4. Results of cost-effectiveness analysis comparing rubella vaccination scenarios 1-3 over 30 years, Democratic Republic of Congo.

a. Summary of health outcomes by vaccination scenario.

Health Outcome	Baseline (no vaccine)	Nationwide RCV (50% SIA)	Nationwide RCV (70% SIA)
Anaphylaxis	0	2,305	2,773
Febrile seizures/convulsions	0	230,452	277,288
Minor reactions	0	23,045,232	27,728,752
Thrombocytopenia	8,330	655	353
Thrombocytopenia mortality	236	19	10
Asymptomatic infection	79,665,984	3,952,929	726,031
Encephalitis	3,243	163	30
Encephalitis mortality	150	8	1
Transient arthropathy	2,979,048	240,114	40,582
Chronic arthropathy	489,618	40,113	4,377
Uncomplicated illness	79,665,984	3,952,929	726,031

b. Summary of the cost-effectiveness analysis comparing scenarios 2 and 3 to scenario 1.

Vaccination Scenario	Total Costs Over 30 Years (US$)				Effectiveness				ICER ($ per DALY averted)
	Disease Costs	Vaccination Costs*	Total Costs	Δ Cost	Rubella Cases	CRS Cases	Total DALYs	Δ DALYs (averted)	
1	$1,767,291,729	$0	$1,767,291,729	--	151,021,183	147,543	3,595,394	--	--
2	$254,383,617	$2,037,364,310	$2,291,747,927	$524,456,198	8,126,323	27,070	643,004	2,952,390	177.64
3	$29,574,806	$2,050,659,847	$2,080,234,654	$312,942,924	1,477,302	2,859	71,901	3,523,493	88.82

[1]Scenario 1: No RCV introduction, Scenario 2: Nationwide RCV1 through RI, RCV2 through 50% SIA coverage, Scenario 3: Nationwide RCV1 through RI, RCV2 through 70% SIA coverage

[2]All costs and DALYs were discounted at a rate of 3%. Costs were rounded to the nearest dollar.

*Vaccination costs account for the difference in costs between MCV and MRCV.

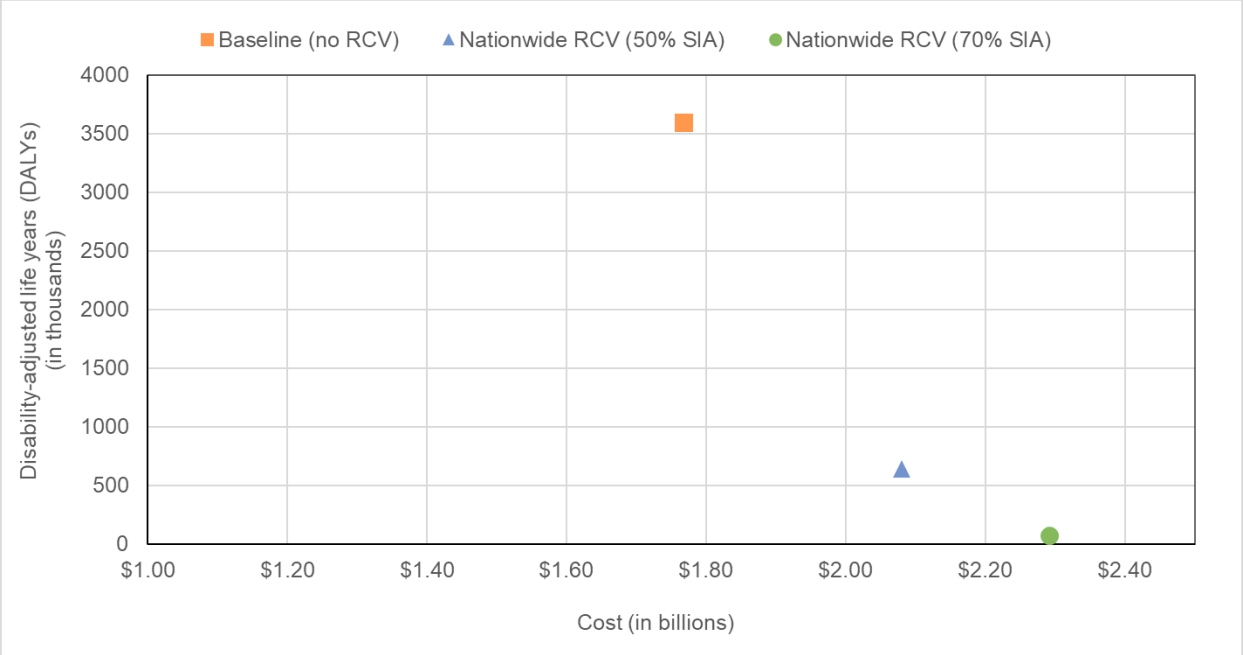

Figure 4.1. Cost-effectiveness analysis for three scenarios of rubella immunization.

4.7 References

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Chapter 5: Public health significance

While rubella no longer constitutes as serious a threat as it once did in several countries, it remains a danger for millions of mothers and children in low-income countries. Despite the progress that has been made towards rubella elimination and control, approximately 100,000 babies are born with congenital rubella syndrome (CRS) annually worldwide,[1] and the number of CRS cases remains especially high in countries without rubella immunization.[2] In the Democratic Republic of Congo (DRC), rubella immunization has not been introduced into the country's national vaccination program, although there were tentative plans to do so by 2020,[3] and the incidence of CRS has been estimated to be 69 per 100,000 live births, equating to approximately 3,000 infants.[2] As rubella-containing vaccines (RCVs) are typically administered in conjunction with measles vaccination, it is highly recommended that countries take advantage of efforts towards measles control and elimination to introduce rubella immunization, and while RCVs have proven highly effective in reducing rubella-related disease burden, there has been concern around introducing the vaccine at low coverage rates. Estimates from the most recent Multiple Indicator Cluster Survey (MICS) indicate that measles vaccination coverage among provinces in the DRC are mostly below the 80% recommended level, with only one province surpassing this threshold at 80.1%.[4] As the country may still be considering RCV introduction in the near future, this dissertation aims to fill in gaps in the current understanding of rubella epidemiology in the DRC and to evaluate the health and economic impact of introducing rubella vaccination at the current province-level coverage rates.

In the first study of rubella seropositivity, rubella seroprevalence was found to be high among adults in the DRC and was associated with increasing age and province. Our findings highlight that there may be widespread circulation of the rubella virus throughout all provinces in the DRC and that although most viremia and antibody seroconversion occur before 15 years of age, over 10% of individuals remain susceptible to rubella infection at the beginning of

adulthood, including women entering reproductive age. This is concerning as up to 90% of fetuses can be affected by multiple defects among pregnant women infected with rubella.[5] In order to reduce the risk of rubella-associated diseases, rubella vaccination must be introduced into the national immunization schedule and achieve high coverage, and any consideration to introduce rubella vaccination must account for the impact of vaccination at lower than recommended coverage levels, especially on the incidence of CRS, as well as the economic impact and costs associated with vaccine introduction.

The last two studies focused on evaluating the change in rubella and CRS burden that would follow RCV introduction and on comparing the cost-effectiveness of various vaccination scenarios. Our results show that vaccine introduction in the DRC would result in significantly decreased rubella and CRS burden over a 30-year period, despite low rates of vaccine coverage. The probability of an increase in CRS cases following periods of low RCV coverage is likely to be heavily dependent on the reproductive number (R_0) of rubella,[6,7] and we estimated the R_0 of rubella to be low enough (<7) throughout provinces in the DRC that this paradoxical effect would be avoided. In terms of costs and benefits, introducing rubella vaccine as a combined vaccine with measles immunization appears to be a cost-effective scenario in the DRC. Using the guidelines defined by the World Health Organization's Choosing Interventions that are Cost-Effective project, RCV introduction would be considered highly cost-effective, compared to no vaccination, when current routine immunization levels are strengthened by supplementary immunization activities (SIAs) with at least 50% coverage. However, these results should be considered along with practical limitations and all relevant data in a context-specific process to guarantee health benefits at optimal costs. While measles vaccine coverage has been lower than the recommended 80% in the DRC, our results broadly support investment in addition of rubella immunization.

As the Global Alliance for Vaccines Initiative has opened a funding window for rubella vaccination, there may be an opportunity to take advantage of measles eradication efforts in the DRC to progress towards rubella control and elimination. As the DRC has planned for RCV introduction in recent years, these findings may prove useful in future decisions in health policy. In the interim, the country should focus on establishing and strengthening rubella and CRS surveillance, to provide better estimates on disease burden, as well as on achieving and maintaining high levels of population immunity. More accurate estimates on vaccine coverage, especially SIA coverage, and on treatment costs would also help to inform future research. Once RCVs are successfully incorporated into the DRC's national immunization schedule, further analyses on the impact of vaccination will be needed so that other countries that have yet to introduce RCVs may be better informed. Monitoring disease progress and improving the capacity to maintain nationally high vaccine coverage levels will be crucial next steps in advancing toward rubella and CRS elimination.

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