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Author

Doshi, Reena Hemendra

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**Assessing trends in measles epidemiology, immunization coverage,
vaccine efficacy, and cost-effectiveness to identify practical strategies for
measles 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

Reena Hemendra Doshi

ABSTRACT OF THE DISSERTATION

Assessing trends in measles epidemiology, immunization coverage, vaccine efficacy, and cost-effectiveness to identify practical strategies for measles elimination in the Democratic Republic of Congo

By

**Reena Hemendra Doshi
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2014
Professor Anne W. Rimoin, Chair**

Immunization has proven to be one of the most cost-effective public health interventions to date. Not only has immunization saved millions of lives, but it has also protected children from severe illness and life-changing disability. Measles, which had once been a significant childhood killer, is now targeted for elimination. Worldwide measles vaccination has led to a 71% decrease in measles-related deaths and an 88% reduction in the World Health Organization African Region (WHO-AFRO) alone. In the Democratic Republic of Congo (DRC), measles immunization has had a profound effect on reducing childhood mortality; however, beginning in 2010 large-scale measles outbreaks threatened past successes. Suspected case counts increased dramatically. This was mainly attributed to a weak routine immunization system and missed supplementary immunization activities. This dissertation aims to inform the improvement and further development of the immunization program in DRC by assessing measles immunization effects, vaccine effectiveness, and compares the cost-effectiveness of different immunization strategies. Chapter 1 is a brief introduction to measles immunization worldwide and in DRC. Chapter 2 is based on measles surveillance data from the Integrated Disease Surveillance and Response (IDSR) and demonstrated that

measles immunization, in particular mass campaigns are extremely effective in DRC. Chapter 3 utilized case-based surveillance data with laboratory confirmation to estimate measles vaccine effectiveness. Finally, chapter 4 further solidifies the importance of mass campaigns in DRC until routine immunization is further strengthened through a cost-effectiveness analysis of three different vaccination strategies.

The dissertation of Reena Hemendra Doshi is approved.

Pamina M. Gorbach

Gerald Kominski

Robert Kim-Farley

Anne W. Rimoin, Committee Chair

University of California, Los Angeles

2014

To my amazing mother and father. Thank you for your constant love and support even from afar.

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VITA

April 2006	B.S., Physiological Psychology Pepperdine University Malibu, CA
Nov. 2006-May 2008	Program Coordinator Division of Endocrinology, Diabetes, Hypertension Brigham and Women's Hospital Boston, MA
May 2008	M.P.H., International Health Boston University School of Public Health Boston, MA
May 2008-Aug. 2008	James A. Ferguson Fellow Global AIDS Program Centers for Disease Control and Prevention Atlanta, GA
Aug. 2008-Sept. 2010	Microbiologist Global AIDS Program Centers for Disease Control and Prevention Atlanta, GA
Jan. 2011-Aug. 2012	Research Supplement to Promote Diversity in Health Related Research National Institute for Drug Abuse
Jan. 2011-Aug. 2012	Graduate Student Researcher Behavioral Epidemiology Research Group University of California, Los Angeles Los Angeles, CA
Jan. 2012- Mar. 2012	Teaching Assistant Principles of Epidemiology University of California, Los Angeles Los Angeles, CA

Aug. 2012-Dec. 2013	Faucett Family Fellowship UCLA-DRC Research Program University of California, Los Angeles Kinshasa, DRC
Jan. 2014-Mar. 2014	Teaching Assistant Principles of Epidemiology University of California, Los Angeles Los Angeles, CA
Jan 2014-Dec. 2014	Graduate Student Researcher UCLA-DRC Research Program University of California, Los Angeles Kinshasa, DRC

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Chapter 1. Introduction and Background

1.1 Introduction

It is estimated that 1.5 million deaths occur among children less than five years of age worldwide, which are attributed to vaccine preventable diseases. Measles accounts for 8% of such deaths despite the fact that a safe and cost-effective vaccine is available[1-3]. In 2012, there were 266,722 measles cases and 122,000 measles related deaths, with over 95% of measles-related mortality occurring in resource-limited settings[4, 5].

In 2010, the World Health Assembly identified key strategies for measles elimination with a target date of 2015: 1) increase routine immunization (RI) coverage with the first dose of measles-containing vaccine (MCV1) to $\geq 90\%$ nationally and $\geq 80\%$ in every district, 2) reduce annual measles incidence to < 5 cases per million, and 3) reduce mortality by 95% from the 2000 estimate[5, 6]. However, at the end of 2010, the African Region was not on track to achieve this goal due to inadequately low vaccination coverage[6].

Throughout sub-Saharan Africa, deficiencies in routine immunization persist. Of the 28 countries reporting measles outbreaks in 2009-2010, 18 reported $< 90\%$ vaccine coverage of MCV1 [7]. Additionally, 13 countries had held supplementary immunization activities (SIAs), with $< 90\%$ coverage at least 24 months before the outbreak[7]. In the Democratic Republic of Congo (DRC), administrative RI coverage reached as high as 87% in 2012. However the resurgence of measles outbreaks across the country and the large number of children missed during national SIAs suggests that vaccination coverage rates are grossly overestimated and that vaccine efficacy may be low.[6]

Repeated occurrences of measles outbreaks in DRC demonstrate the importance of the re-evaluation of measles virus dynamics and prevention and control

strategies[1]. A number of socio-demographic and systemic factors interact to influence the effectiveness of vaccination programs and measles transmission, including the changing epidemiology, vaccination coverage rates, vaccine efficacy, and the cost of implementation strategies. These factors suggest the need to heavily monitor program scale up, financial commitment, and determine the elements necessary to attain global targets for reducing measles transmission, associated morbidities, and mortality.

To address the gaps in knowledge, this dissertation project utilized national surveillance data from DRC's Ministry of Health (MOH) vaccination program. The data was used to assess the effect of vaccination on the incidence of measles, followed by an epidemiologic field evaluation of vaccine effectiveness in children. Finally, the costs and benefits of administering measles containing vaccine 2 (MCV2) in the form of routine vaccination versus the use of SIAs with varying rates of immunization coverage were assessed using country specific data.

1.2 Epidemiology and Burden of Measles Worldwide

Measles, or rubeola, is derived from the Latin word, *misellus*, meaning miserable[8]. It is one of the most contagious pathogens with outbreaks occurring in populations containing less than 10% of susceptibles[9]. Humans are the only known reservoir of the disease with no evidence of sustained animal transmission[9]. While measles can affect any age groups, it is largely a childhood disease causing disease in children who are neither protected by vaccine induced or natural immunity. Outbreaks are often "fueled" by unvaccinated preschool aged children who are the most susceptible to the disease[10].

The dynamics of urban and rural settings lead to diverse epidemics patterns. Low vaccination coverage in urban settings typically affects infants and younger children and is associated with shorter epidemics, while declining population density in rural settings coupled with increasing vaccination coverage shifts the age distribution toward that of

older children[8]. As population immunity increases, the age distribution shifts toward adolescence and adulthood[9]. Endemic measles is characterized by a yearly seasonal temporal pattern[8]. As the number of susceptibles increase over successive birth cohorts, epidemic patterns of 2-4 years lasting 3 to 4 months will follow[9]. Epidemics tend to fluctuate with the seasons, facilitated by social activities (school) and environmental factors[9]. In most tropical climates the majority of cases will be seen in the dry season[9]. In temperate climates, the incidence of measles typically peaks in late winter and early spring[8, 9, 11, 12].

Prior to the development of the measles vaccine, the disease was responsible for an estimated 130 million cases and more than 2.5 million deaths worldwide (mainly children) annually[8, 13]. Measles incidence decreased substantially from 2000 to 2008, remained stable in 2009, and increased to 339,845 cases in 2010. Then it finally reached a historic low in 2012 with 226,722 cases[5, 14]. By the end of 2012, 36% of countries had not met the World Health Assembly's (WHA) incidence target of 5 cases per million, with 90% of cases occurring in the African, European, and South-east Asia regions[5, 14].

Over the last decade, measles vaccination has led to a dramatic reduction in mortality. The 2003 pledge by the WHA to reduce measles mortality by 50% compared to the 1999 estimates was successfully met in 2005; a reduction from 873,000 to 345,000 deaths[9]. Between 2000 and 2007, 578 million children were vaccinated, preventing more than 11 million deaths[15]. In 2012, mortality was reduced by more than 78% worldwide and 88% in the Afro region alone[5, 9, 15, 16]. Furthermore, increased attention to high quality surveillance and high vaccination coverage rates has led to the interruption of indigenous measles transmission in the WHO region of the Americas[9, 11]. The remaining five WHO regions have set measles elimination goals and four have set target dates.

In sub-Saharan Africa, increased routine vaccination coverage coupled with the administration of a second dose through supplementary immunization campaigns (SIAs) has led to significant reductions in incidence and mortality[9]. The 2010 regional measles incidence was 17.2 per million and in 2011 it increased to 223.6 per million. However, case counts are collected through national passive surveillance systems suggesting that reported numbers are severely underestimated. The true statistics are possibly 10-20 times greater[17]. In 2012, 16 (37%) of member states of the region had met the target measles incidence of <5 cases per 1 million; up from 12 (30%) in 2010[18, 19]. Despite the enormous progress, the failure to deliver at least one dose of MCV remains the primary reason for measles mortality. large-scale outbreaks beginning in 2009 in 28 sub-Saharan African countries threaten the success achieved[18, 20].

In 2010, DRC saw a resurgence of measles cases. In 2011, the number of reported cases increased dramatically 3,364 to 134,041 cases[6]. Without sustained levels of population immunity, large-scale outbreaks in DRC and other African countries demonstrate the virus's ability to easily re-enter communities lacking strong vaccination programs[9].

1.3 Pathogenesis and Clinical Manifestations

Measles virus is a member of paramyxoviridae family; belonging to the genus *Morbillivirus*[9, 11, 12, 21]. There is only one known serotype of the virus, however, genetic variability is seen among wild-type viruses. At present, 23 genotypes have been identified, but the variation does not appear to have any biologic significance with regards to vaccine efficacy[11, 12].

The measles virus invades the respiratory epithelium of the nasopharynx and replicates for 2-3 days developing a primary viremia.[11, 12] Secondary viremia occurs 5-7 days later, lasting 4-7 days[11, 12]. At 11-14 days, viremia peaks, declining rapidly over a few days[11]. The incubation period is generally 8 to 12 days[2]. The prodrome

phase of disease (2-4 days) begins with a stepwise increase in fever reaching 103F-105F[9]. The fever is followed by symptoms similar to other common respiratory infections, including a runny nose, coryza, cough, and conjunctivitis[2, 22]. A sore throat, headache, abdominal pain, and generalized mild lymphadenopathy may also occur[22].

About 14 days after exposure, a maculopapular rash appears, beginning at the hairline, proceeding down to the face and neck[2, 11]. The rash persists for 3-7 days, appearing as discrete lesions (sometimes becoming confluent on the upper body) and will gradually spread, covering the body, eventually reaching the hands and feet[2, 11, 22]. Fine desquamation may occur on certain areas of the body, and the rash will fade in the order it appeared[11]. About 1 day before the onset of the rash, Koplik's spots (a rash on the mucous membrane) will develop in more than 70% of those infected[11, 22]. The spots are small, blue-white in color, appearing as raised lesions in the mouth[2, 11]. Infected individuals begin to improve about 3 days after the onset of rash and will recover almost completely 7-10 days after onset[12].

The severity and range of complications vary extensively depending on a number of individual and environmental factors[12]. However, approximately 30% of cases will develop at least one complication, most commonly among children under five and adults over the age of 20[11]. Complications of measles have been found in every organ system and rates vary according to underlying conditions and age[22]. The mildest forms of the disease often occur in adults with some form of partial immunity; these infections may have mild respiratory systems with a mild rash and may never be diagnosed as measles[22].

Respiratory complications, including otitis media, occur in about 5-15% of cases. It most frequently occurs among younger children with some developing permanent hearing loss[22]. Pneumonia is common, occurring in about 5-10% of cases, and is the

leading cause of death for young children infected with measles[22]. An estimated 8% of infected individuals will develop gastrointestinal complications, specifically diarrhea, which can lead to severe dehydration and if not treated appropriately, death[11]. Other severe complications may ensue such as encephalitis, an inflammation of the brain, and sub-acute sclerosing panencephalitis (SSPE), a slow progressing infection of the central nervous system

While severe disease is rare in developed countries, case fatality rates among children may reach as high as 10% in resource-limited areas and as high as 30% in refugee settings[23, 24]. Incidence and mortality are often higher among infants too young to be vaccinated. However, seroconversion rates post-immunization are significantly lower in infants under 9 month of age due to competing maternal antibodies[25]. Exposure in the first few months of life leads to higher rates of mortality [26]. The risk of developing a severe form of the disease increases 1) among children under 5 living in overcrowded conditions, 2) among malnourished children especially with vitamin A deficiencies, and 3) among immuno-compromised patients such as those with HIV/AIDS[2, 22]. Nevertheless, those who recover will be immune for the remainder of their lives[2].

1.4 Transmission and Diagnosis

Measles is highly infectious with an estimated secondary attack rate of 75-90% of susceptible household contacts [27]. The basic reproductive rate (R_0) is estimated to be between 12-18 compared to 4-7 for mumps, polio, and rubella[28]. Transmission occurs by respiratory droplets or particle aerosols with infectivity greatest at 3 days before rash onset[9, 12, 22]. It is most often contracted by an infected person coughing or sneezing or being in direct contact with virus infected nasal or throat secretions[2]. The pre-rash symptoms mirror those of other common respiratory infections. Thus infected individuals often unknowingly participate in social activities facilitating transmission. Those infected

with the virus become infectious about four days prior to the onset of rash and will remain infectious for four days after the rash begins[2].

While the non-specificity of measles symptoms make accurate diagnosis difficult, WHO has created a standard case definition. The clinical case definition is any person presenting with fever, maculopapular rash, and one of the following: cough, coryza, or conjunctivitis[9, 26, 29]. A laboratory confirmed case should meet the clinical case definition and is serologically positive for measles IgM[29]. An epidemiological linked case is defined as having contact with a laboratory confirmed case and presenting with rash within the past 30 days. Suspected cases should be discarded if neither clinical nor laboratory definitions are met[29]. In countries currently working toward measles mortality reduction and elimination goals, WHO recommends the use of IgM enzyme-linked immuno-assay (ELISA) for confirmation of acute measles infection for specimens collected during the first 30 days after rash onset (Fig. 1)[30].

1.5 Treatment and Prevention

Vitamin A deficiency has been associated with an increased rate of measles complications, specifically eye infections that could lead to blindness. Supplementation with vitamin A has been shown to reduce complications and measles mortality by 50%[9]. In developing countries, WHO's current policy recommends children aged 12 months or older, diagnosed with measles, to receive two doses of vitamin A supplements.[2, 9]

While no specific antiviral therapy exists, drugs such as ribavirin and interferon α are sometimes used to treat severe forms of the disease[9]. Avoidance of complications includes supportive care focusing on nutrition and ensuring that infected children receive adequate amounts of fluids. In addition, antibiotics can be used to treat bacterial infections such as pneumonia and eye or ear infections[9].

The most important preventative tool is routine vaccination. Since development in 1963, measles vaccination has seen tremendous success worldwide[9]. While relatively inexpensive at about \$0.21-0.26 per dose (excluding wastage, personnel, and transportation), it costs just under \$1 in total to vaccinate a single child[2]. Nevertheless, there remains a number of limitations in vaccine distribution in regards to thermostability, the use of injection equipment, and required age for administration[25, 31]. The vaccine requires the use of a cold chain at 4–8°C until use[7]. Trained staff must then reconstitute the vaccine with diluent using a needle and syringe[7]. After reconstitution, the vaccine faces the risk of bacterial contamination and loss of potency with exposure to high temperatures and light after only 6 hours[7].

There are a number of attenuated measles vaccines that are available alone or in combination with other vaccines (generally mumps and rubella), with every country offering some formulation of a MCV in their national immunization program[27]. While WHO recommends vaccination at 9 months of age, choosing the correct age requires a balance between the probability of infection and the optimal age for seroconversion. Therefore it can be given between 6 to 12 months of age[9]. While a number of factors determine whether children develop protective antibody levels, including inhibitory maternal antibodies, immunological maturity of the child, and dosage and strain of vaccine virus, 85% of children typically become immune with one dose of vaccine[9]. A second dose is necessary to achieve sufficiently high vaccine coverage levels and most children will respond to a second dose[9]. Additionally, tradeoffs in timing of dosage must be made in choosing the optimal strategy. Protecting infants as early as 9 months of age is important because maternal antibodies are waning; however, MCV1 is only 85% effective at this age and will increase to 95% if delayed to 12 months of age[32].

1.6 Global Measles Immunization

In 1974, after the successful eradication of smallpox, the Expanded Programme

on Immunization (EPI) was established through a WHA Resolution, with goals to ensure that all children in every country had access to life-saving vaccines[33]. Worldwide, vaccination has had an enormous impact on global public health. A strong commitment to vaccination led to the successful eradication of one disease (i.e. smallpox) and the elimination of poliomyelitis in almost all countries. Vaccination against measles, pertussis, and diphtheria among children has led to the avoidance of 2 to 3 million childhood deaths annually[15].

In 2005, at the 58th WHA, WHO and UNICEF announced their joint framework Global Immunization Vision and Strategy (GIVS) for 2006-2015[34]. For the first time, GIVS allowed immunization goals to be a part of every health agenda; with the goal to strengthen and expand immunization to every person[34]. The framework proposed to increase and sustain high vaccine coverage rates, ensure access to high quality vaccines, strengthen systems, and increase capacity for surveillance and monitoring by 2015[34].

In 2006, Measles Rubella (MR) Initiative supported a five-year strategic plan with the goal to reduce measles mortality by 2010 to 90% of the 2000 levels[16].

Approximately 12.7 million measles deaths were averted as a result of immunization activities in 2000-2008; with 8.4 million deaths averted by increasing routine coverage and the remaining 4.3 million deaths averted through the implementation of SIAs[17].

While these activities resulted in a 78% reduction in mortality, the goal was not met mainly due to slow implementation of the immunization activities in India and large outbreaks in Africa[16, 17] . Nevertheless, global routine coverage of MCV1 rose from 72% in 2000 to 85% in 2010[16]. In the WHO AFR region, reported MCV1 coverage increased from 55% to 87% in 2001-2012, while WHO/UNICEF regional estimates were 73%; a long way from the 95% population immunity needed for interruption[18]. Both mathematical models and country experience have repeatedly demonstrated that

interrupting endemic measles transmission requires $\geq 95\%$ levels of population immunity[7]. By 2011, all 194 member states of WHO had officially adopted a two-dose measles vaccine delivery strategy[16].

Routine Immunization

The importance of vaccinating infants immediately following loss of maternal antibodies is critical. While all countries offer MCV1 as part of their routine immunization services, not all offer MCV2 in their routine services. Those who receive a second dose via routine services typically constitute a group that is already protected[25]. Maintaining high levels of routine coverage is the first step toward measles elimination. Without high RI coverage levels, the number of susceptibles build up while those unvaccinated wait for SIAs or natural immunity through infection[35].

Mass Vaccination Campaigns

Mass immunization campaigns are commonly known as National Immunization Days (NIDs) or SIAs[36]. In DRC, these activities can occur at the national level (NIDs) or the local level (LIDs). While the goal of these campaigns are to vaccinate all children in a targeted age group (typically 9 months to 59 months), in a short amount of time (usually 3 days), regardless of immunization history; these are not intended to replace routine vaccination services[34, 36]. An effective campaign should result in a rapid increase in population level immunity (herd immunity) because outbreaks are determined by the number of susceptible individuals in the population[12] [34].

Generally, those countries with weakened health systems supplement routine services with mass campaigns[34]. Evidence suggests that the use of mass campaigns are highly effective in accessing hard-to-reach populations unable to utilize routine health services[12]. Nevertheless, to be successful SIAs should target all age groups and all geographic areas, achieving high coverage among the entire susceptible

population[10, 30]. Furthermore, follow-up campaigns are needed every 2-4 years until routine coverage rates reach at least 90% in order to prevent outbreaks in new birth cohorts[32]. Without improved routine immunizations rates, the frequency of SIAs must be increased[37].

Immunization in DRC

DRC is the second largest country in Africa by land mass and has population of 77.9 million[38]. DRC struggles to recover from a devastating multi-year conflict, resulting in mass population displacement, extreme violence, and collapse of the public health infrastructure[38]. The country continues to suffer from inadequate roads and limited electricity and water coupled with a lack of human resources. These challenges have led to limited development and improvement of health infrastructure.

At the direction of the Ministry of Health (MOH), the 4th Direction is the office of Disease Control (Fig. 2). Situated under the arm of the 4th direction is the DRC's EPI office, which is responsible for the coordination of routine vaccination programs for all 11 provinces, 44 antennes (where vaccine distribution occurs), and 513 of the 515 health zones (two of which are non-functional). On average, an antenne constitutes 10 health zones. Each health zone is composed of roughly 15 health sects, which constitutes the level at which public health interventions occur.

Since 2004, the country's effort to reduce measles mortality has consisted of a 3-pronged approach: 1) increasing routine vaccination coverage, 2) implementing SIAs, and 3) scale up of epidemiologic surveillance[6]. While the country has seen an increase in routine vaccination coverage rates, up from 63% in 2006 to 73% in 2012 (WHO reported rates), rates are still incredibly low for sufficient measles control[6, 39]. Beginning in August 2010, the country saw a resurgence of measles epidemics throughout the country[6]. In March 2011, large scale outbreaks occurred in five provinces (Katanga, Maniema, South Kivu, Kasai Oriental et Kasai Occidental)[6]. The

outbreaks were largely caused by insufficient vaccination coverage by routine services and SIAs coupled with reduced awareness due to decreased circulation in past years[17].

The country continues to suffer from a lack of financial commitment to vaccination activities, which has led to shortages in trained health personnel and ruptures in vaccine stock[6]. Furthermore, the quality of the vaccine is unknown due to the inability to effectively maintain and monitor an adequate cold chain for transport to the local level[6]. In addition, the failure in communicating the importance of vaccination calendar adherence to parents has contributed to poor coverage rates[6]. While the number of children vaccinated increased from 2007 to 2008, the numbers decreased in 2009 and 2010. This demonstrates problems maintaining adequate vaccine stockpile and having mothers adhere to the proscribed vaccination calendar[6].

The first major catch-up campaigns were conducted in several provinces in 2002 (Kasaï Oriental, Nord Kivu) and 2004 (Kasaï Occidental, Maniema, Katanga, Maniema, Sud-Kivu)[40]. Case-based (CB) surveillance for measles was implemented in 2002 to coincide with SIAs, with information collected on onset of rash, age, and vaccination status[41]. It was not until 2006, that the country began implementation of a national catch-up SIA[42]. A passive surveillance system is in place and suspected measles cases should be reported directly to the MOH weekly. For suspected outbreaks, WHO recommends laboratory confirmation of only 5 cases, with the classification of the other cases on an epidemiological basis[29].

In order to meet the 2020 measles elimination target, DRC has set a number of interim goals for 2015 detailed in the 2012 strategic plan for measles elimination: 1) increase national MCV1 coverage to 95% with no health zone less than 80%, 2) incorporate MCV2 into routine health services, 3) reinforce measles surveillance with a

thorough investigation of each suspected case, 4) improve data quality, and 5) mobilize all local and international partners[6].

Choosing an Immunization Strategy in DRC

Choosing an appropriate vaccination strategy heavily influences the rate of accumulation of susceptible individuals in a population. The decision has significant cost implications that should be evaluated thoroughly at an individual country level basis. An economic analysis can offer invaluable insight into disease dynamics, risk, benefits, and costs of varying scenarios. The resurgence of measles outbreaks in DRC suggest that health spending decisions may not be based on evidence and analysis of costs and benefits[32]. Interpretable data on what strategies are needed to effectively and efficiently control measles is critical.

While a number of studies have assessed the cost-effectiveness of measles elimination or eradication, few studies have focused on the cost-effectiveness of altering vaccination strategies. The diversity of measles epidemiology and health system infrastructure across countries makes analysis context specific; however, similarities can be drawn. In Uganda, with a routine MCV1 vaccination coverage rate of 68%, the value of SIAs was found to be highly cost-effective[43]. While the cost of a mass campaign varies from country to country due to varying transportation costs, the average cost often falls within the range US\$0.72-US\$1.10 per child vaccinated[30, 44]. Model sensitivity analysis demonstrated that the value of SIAs decreased with increasing routine coverage rates[43]. These results are expected based on the fact that SIAs are used to increase population level immunity in those not reached by routine services[43]. However, SIAs in remote areas often requires more resources for transport and social mobilization[45].

A 2003 study of vaccination strategies in Zambia suggested that offering MCV2 through mass immunization campaigns was the most cost-effective method of delivering

the vaccine. This was mainly due to the campaigns being better able to access hard-to-reach populations[46]. The study found that the administration of both doses of MCV through routine services needed 99.5% vaccination coverage to result in the same reduction of disease as would be achieved using SIAs with 80% coverage[46].

In order to achieve high vaccination coverage rates, community demand for vaccination services with strong advocacy and regular communication with stakeholders is critical. A secure vaccination supply with strong logistics and program management coupled with skilled medical staff is necessary[7]. Detailed vaccination coverage data will be needed to determine if population immunity levels are adequate for elimination targets[7]. For resource limited country lacking adequate infrastructure, suffering from civil unrest, or hard-to-reach populations (like DRC) specialized immunization strategies need to be developed[7].

Analysis of other eradication programs suggests that strong management at the global, regional, and national levels is critical[47]. Clear objectives, with appropriate strategies should be developed and thoroughly outlined with dedicated well-trained staff appointed and held accountable for actions[47]. Strong management is necessary to develop valid incidence, mortality, and coverage rates to monitor measles elimination progress and meet stated targets[13].

1.7 Ministry of Health (MOH) Disease Surveillance Program Structure

National Level: Disease surveillance activities are the responsibilities of the 4th Direction (one of thirteen offices under the MOH): the office for Disease Surveillance and Epidemiology. The office coordinates disease surveillance, outbreak investigations, and epidemiological research. The reporting structure is based on WHO guidelines for

disease reporting and weekly epidemiologic reports on 13 diseases (including measles) are reported upward to the national level.

Provincial Level: There are 11 provinces in DRC. Each province has a Provincial Medical Coordinator (PMC) who leads the coordination of public health activities. The PMC is responsible for collecting morbidity and mortality data for each disease from all districts and health zones, which is transmitted to the national level. Each province also has a WHO appointed Provincial Medical Epidemiologist (PME) who provides technical assistance for surveillance activities.

District Level: Each province is composed of two to five health districts, which in turn coordinate the health zones within the district. Each district has a District Health Officer (DHO) who is responsible for coordination all health activities and supervision of the health zone staff.

Health Zone: Currently, there are 516 health zones; two (located in North Kivu) are non-functional. Each zone has a Health Zone Doctor (HZD) who is responsible for the supervision of all medical staff at the local health facilities. Communication and transportation difficulties frequently delay or postpone reporting. The HZD collects weekly surveillance data for submission to the district and provincial levels. Nurses in each health zone coordinate a number of activities including disease prevention (expanded program for immunization (EPI)), antenatal clinics, nutrition programs, primary health care, and disease surveillance. The nurses also have the responsibility of creating surveillance reports for submission to the HZD.

Figure 1.1: WHO classification of measles cases, Democratic Republic of Congo [48]

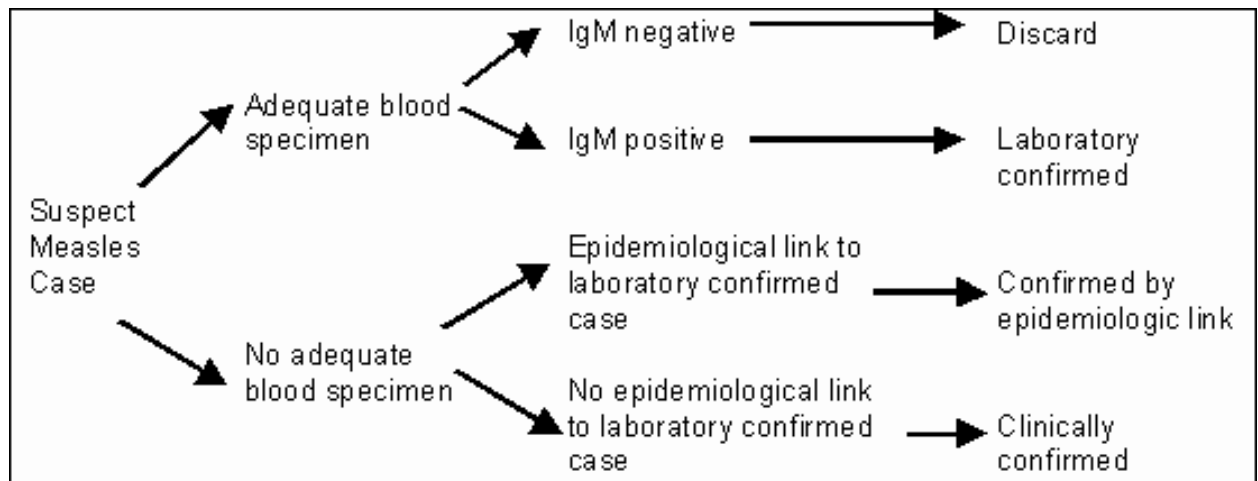
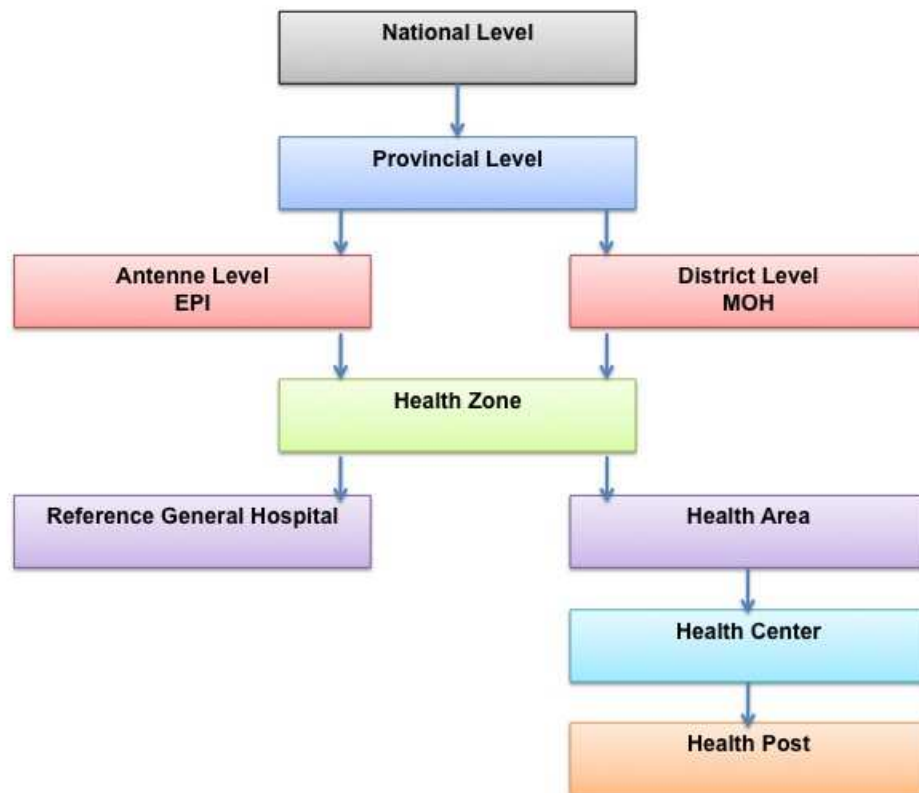


Figure 1.2: Health System Structure, Democratic Republic of Congo



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Chapter 2: The Effect of Immunization on Measles Incidence in the Democratic Republic of Congo

2.1 Abstract

Background: Measles continues to be one of the largest causes of vaccine-preventable disease mortality among children under five despite the fact that a safe and efficacious vaccine is readily available. While global vaccination coverage has improved tremendously, measles outbreaks persist throughout sub-Saharan Africa. Since 2010, the Democratic Republic of Congo (DRC) has seen a resurgence of measles outbreaks affecting all 11 provinces. These outbreaks are mainly attributed to gaps in routine immunization (RI) coverage compounded with missed supplementary immunization activities (SIAs). We utilized national passive surveillance data from DRC's Integrated Disease Surveillance and Response (IDSR) system to estimate the effect of immunization on measles incidence in DRC.

Methods: Measles case counts by health zone were obtained from the IDSR system during the period January 1, 2010 to December 31, 2013 to investigate the decline in measles incidence post-immunization (by health zone) with one dose of measles containing vaccine (MCV1) with and without the addition of Supplementary Immunization Activities (SIAs) and Outbreak Response Immunization (ORI) campaigns. The impact of measles immunization was modeled using a random effects multi-level model for count data using RI coverage levels and mass campaign activities from one-year prior.

Results: The presence of an SIA (aIRR [95% CI] 0.86 [0.60-1.25]) and the presence of an ORI (0.28 [0.20-0.39]) in the year prior were both associated with a decrease in measles incidence. When interaction terms were included, our results suggested that

the high MCV1 in the year prior and the presence of either mass campaign was associated with a decrease in measles incidence.

Conclusions: Our results highlight the importance of a two-dose measles vaccine schedule and the need for both a strong routine immunization program coupled with frequent SIAs. Repeated occurrences of large-scale outbreaks in DRC suggest that vaccination coverage rates are grossly overestimated and signify the importance of the re-evaluation of measles virus dynamics and prevention and control strategies.

2.2 Introduction

Measles is a highly contagious viral respiratory infection that can lead to deadly complications. It continues to be one of the largest causes of vaccine-preventable disease mortality among children under five, despite the fact that a safe and efficacious vaccine is readily available[1]. Prior to vaccine licensure, measles caused an estimated two million deaths and more than 15,000 cases of blindness worldwide each year [1, 2]. While global immunization has improved tremendously, in 2011 an estimated 158,000 people died from measles associated complications[1]. More than 95% of measles-related deaths occur in resource-limited countries, where health infrastructure is weak and vaccine coverage is low[1].

Between 2001 and 2008, in the World Health Organization African Region (WHO-AFRO), measles mortality was reduced more than 90% due to improvements in routine immunization and the implementation of Supplementary Immunization Activities (SIAs)[3]. Routine measles vaccination coverage increased from 54% to 73% and approximately 400 million children were vaccinated during SIAs[3]. However, in 2010, the African region saw a resurgence of measles with 28 countries reporting measles outbreaks and case-fatality rates as high as 5-10%[3]. Overall incidence in the region increased from 40 cases per million in 2009 to 165 cases per million in 2011[4]. During 2011–2012, large outbreaks continued in the AFRO region with 88% of 2012 cases from five member states (Angola, Burkina Faso, Ethiopia, Nigeria, and the Democratic Republic of Congo)[5]. Investigations in these countries indicated that the main cause was the accumulation of susceptibles due to gaps in providing all children with two doses of measles containing vaccine (MCV) through routine immunization (RI) and follow-up SIAs[5].

The Democratic Republic of Congo (DRC) has seen a number of large-scale measles outbreaks throughout the last decade. However, in 2009 suspected measles

cases counts were at a historic low likely due to reductions in susceptible children from past SIAs. DRC's Expanded Programme on Immunization (EPI) includes one dose of MCV1 at 9 to 11 months of age followed by the second dose provided through "catch-up" campaigns for children aged 6 months to 14 years and rolling "follow-up" campaigns targeting children 6 to 59 months every three years[6, 7]. Routine immunization remains sub-optimal, with WHO and United Nations Children's Fund (UNICEF) national coverage estimated at 73%, which is well below the recommended 90%[4, 8]. Decades of political instability and violent conflict have led to scattered and isolated communities, limited transportation, and a poorly functioning health system[9]. Improperly trained health care workers and limited investment in health facilities have resulted in the country's failure to implement international immunization guidelines effectively. Beginning in September 2010, reported measles cases steadily increased, particularly in provinces where SIAs had been postponed [10]. The epidemic appears to have begun in the province of Katanga, in the southeastern part of the country, where 50% of health zones had administrative RI coverage rates below the WHO recommended district level of 80%[5, 6]. Gaps in RI coverage, compounded with missed measles SIAs – largely due to limited finances and delays in mobilizing resources -- were the main factors associated with protracted measles outbreaks that affected all 11 provinces[4].

While measles vaccination has proven to have a profound effect on reducing measles incidence worldwide, repeated occurrences of measles outbreaks in DRC demonstrate the importance of the re-evaluation of measles virus dynamics, prevention, and control strategies[11]. We utilized national passive surveillance data from DRC's Ministry of Health (MOH) Integrated Disease Surveillance and Response (IDSR) system to estimate the effect on measles immunization on measles incidence in DRC between 2010 and 2013.

2.3 Data and Methods

Suspected Measles Case Counts

Measles is one of the 13 reportable diseases classified as having epidemic-potential[7]. Suspected measles cases in DRC are reported at health centers and transmitted upward to health zones, health districts, provinces, and eventually compiled at the national level in the IDSR surveillance system[10, 12]. Standard WHO case definition is used: a suspected measles case is defined as any person with fever and maculopapular rash and cough or coryza or conjunctivitis, or a person in whom a clinician suspects measles[13].

Health zone case counts were obtained from the IDSR system during the period January 1, 2010 to December 31, 2013. Suspected measles cases were included in the analysis if they occurred in children between 12 to 59 months of age and met the clinical measles case definition.

Vaccine Coverage

We used administrative RI coverage estimated at the health zone by the DRC-EPI. These rates are calculated by dividing the total number of measles vaccine doses given by the susceptible population in a health zone[8]. There were 14 (0.6%) health zones with missing RI coverage; therefore we imputed the WHO/UNICEF national RI coverage estimate of 73%. Any SIA including catch-up or follow-up campaigns are also collected and compiled by EPI. Additionally, Medecins San Frontieres (MSF) regularly conducts outbreak response immunization (ORI) campaigns to reduce transmission from outbreak zones to other areas[7, 10].

Routine immunization and SIA immunization coverage rates were obtained from EPI. Data on ORI activities was obtained directly through EPI, MSF, and a literature review.

Data Compilation

Suspected measles cases counts and RI coverage was combined with each individual observation representing the total suspected case counts in children aged 12 to 59 months in a given year in a given health zone. The final data set included 5 variables and 2,047 observations, with 5 health zones removed due to missing vaccine coverage. An indicator variable was used to represent the presence of a SIA in a given health zone in that year. A second indicator variable was used to represent the presence of an ORI in a given health zone in that year. Routine MCV1 coverage was grouped into four categories (0%–79%, 80%–89%, and 90%–100%, 100%+). Coverage categories were selected based on the standard WHO recommendation of 80% coverage in every health zone[4].

Statistical Methods

Measles case counts; incidence rates, and corresponding 95% confidence intervals (CI) were estimated by province per year. Incidence rates were defined as the total number of suspected measles cases in a year in a province divided by the total population of children 12 to 59 months in a year in a province. To assess the relationship between measles incidence and vaccine coverage, we modeled incidence using a random effects multi-level model for count data, with a negative binomial distribution to account for overdispersion. To account for measles case clustering, we included a random intercept at both the district and provincial levels. Our outcome was total suspected cases in a given year in a given health zone, with the health zone's population of children aged 12 to 59 months as an exposure offset variable. Routine immunization is a continuous event that occurs throughout the entire year and we predicted that effects might not be seen immediately. Thus, we modeled measles

incidence using vaccine coverage, SIA, and ORI data from the year prior. Our model was fit to predictor variables vaccine coverage, presence of an SIA, and presence of an ORI to determine incidence rate ratios (IRR) and corresponding 95% confidence intervals.

2.4 Results

Between January 1, 2010 and December 31, 2013 there were a total of 301,468 suspected measles cases reported; 215,590 (71.5%) of which occurred among children 12-59 months (Fig.1). Only one suspected measles case was reported in the age category 0 to 11 months (South Kivu, 2010). The highest incidence rates were seen in the provinces of Katanga, Kasai-Oriental, Orientale, and Equateur (Table 1).

Administrative vaccine coverage varied greatly across health zones, with 30.7% reporting vaccine coverage rates below 80% in 2010, 38.9% in 2011, 24.9% in 2012, and 22.7% in 2013 (Fig. 2). A large proportion of health zones also reported vaccine coverage rates above 100% (19.9-28.6%) from 2010-2013.

Incidence in the Year Coverage was Measured

Estimated measles incidence generally increased between 2010-2013 and was higher in health zones with one or more mass campaigns¹ in the same year (Table 2). Estimated incidence ranged from 8.2 to 7,705 cases/100,000/year from 2010-2013, with the lowest average incidence occurring in 2010 and the highest average incidence occurring in 2012. In 2010, estimated incidence appeared to increase in zones with higher MCV1 coverage with and without a mass campaign. In 2011, among health zones without a mass campaign, estimated incidence was lower in zones with higher MCV1 coverage. However, in health zones with a mass campaign, estimated incidence

¹ Mass campaign is defined as any SIA or ORI

was higher among zones with higher MCV1 coverage. In 2012, estimated incidence was lower in health zones reporting higher MCV1 coverage among both zones with and without a mass campaign. 2013, among health zones without a mass campaign, estimated incidence was higher in zones reporting higher MCV1 coverage. However, among zones with a mass campaign, estimated incidence decreased with higher MCV1 coverage.

Incidence in the Year after Coverage was Measured

We estimated measles incidence using MCV1 coverage, SIA, and ORI data from the year prior. Our results demonstrated a general increase in incidence from 2010-2012 followed by a slight decrease in 2013. Incidence was generally lower in zones with any campaign (Table 3). Estimated incidence ranged from 1.5-4,320 cases/100,000/year among health zones in 2010-2013 with the lowest average incidence occurring in 2010 and the highest average incidence occurring in 2013. In 2010, incidence was fairly stable across MCV1 coverage categories in health zones with and without a mass campaign the year before. In 2011, among health zones without a mass campaign, incidence increased with higher MCV1 coverage; however, among health zones with a mass campaign, incidence decreased with increased MCV1 coverage. In 2012, in health zones with and without a mass campaign, incidence generally decreased with increasing MCV1 coverage. In 2013, among health zones with and without a mass campaign, estimated incidence fluctuated among different MCV1 coverage levels.

Random Effects Multi-level Model

We modeled measles incidence using vaccine coverage rates, presence of an SIA, and the presence of ORI from the year prior (Table 4). MCV1 coverage was associated with an increase in measles incidence when compared to low vaccine

coverage (0-79%). The highest MCV1 (100+) coverage level had the lowest rate ratio, followed by MCV1 coverage level; 90-100%, and the 80-89% coverage level having the highest rate ratio (aIRR [95% CI] 100%+: 1.35 [1.02-1.78] 90-99%: 1.37 [1.02-1.78] 80-89%: 1.61 [1.24-2.12]. The presence of an SIA (aIRR [95% CI]), 0.86 [0.60-1.25] and the presence of an ORI, 0.28 [0.20-0.39] in the year prior, were both associated with a decrease in measles incidence. When interaction terms were included in our model, our results suggested that the high MCV1 in the year prior and the presence of either mass campaign was associated with a decrease in measles incidence (Table 4). The effect of an SIA the year before increased with higher MCV1 coverage (aIRR [95% CI] 100%+: 0.17 [0.07-0.39] 90-100%: 0.40 [0.18-0.90] 80-89%: 0.35 [0.16-0.76] <80%: 1.11 [0.65-1.90]). The effect of an ORI in the year before was associated with a decrease in measles incidence and became stronger with higher MCV1 coverage (aIRR [95% CI] 100%+: 0.21 [0.13-0.35] <80%: 0.52 [0.25-1.06]).

In Kinshasa, there were no ORIs, however the presence of an SIA was significant (aIRR [95% CI] 0.18 [0.08-0.45]. While the overall interaction between MCV1 and presence of SIA was not significant, we did notice a decrease in IRR when MCV1 coverage was reduced.

2.5 Discussion

In DRC, routine immunization remains sub-optimal. Alternating provincial SIAs were too infrequent to provide sustained immunity to those not accessing routine health services and follow-up and catch-up campaigns failed to prevent the large-scale measles outbreaks that began in 2010 [6]. Estimated incidence in health zones with an SIA in the same year was higher when compared to health zones without an SIA. These results are reflective of the follow-up SIAs, which had been planned in a number of provinces in 2010, however, were delayed due to funding and resource availability[4].

Four to five year gaps in SIAs in a number of provinces led to high numbers of susceptible children and large outbreaks throughout the country. Missed SIAs were eventually carried out after the start of the outbreak and ORIs were used to reduce transmission from outbreak zones to other areas [7,10, 11]. The high incidence may also be partially explained by active case searching and increased reporting during mass campaigns.

Our findings indicate that measles immunization in DRC is associated with a decrease in incidence specifically in zones with mass campaigns in the year before incidence was measured. This suggests that immunization effects are not necessarily seen immediately. Our model predicted a reduction in measles incidence in the presence of a mass campaign in the year prior. These results are not surprising given that vaccination campaigns are heavily advertised, with house-to-house mobilization, target wider age groups, and generally have more accessible vaccination sites. While we were unable to look at the effect of MCV1 coverage and the presence of a campaign two and three years prior, it is likely we would have seen a stronger protective effect.

The effect of increasing MCV1 coverage in the same year incidence was measured is likely to be biased; therefore we lagged MCV1 coverage one year. Using MCV1 coverage levels from the year before, we were able to see a more substantial decrease in incidence with higher MCV1 coverage in health zones with a mass campaign. RI coverage varies greatly among provinces and across health zones[10]. We were able to account for provincial and district level case clustering in our multi-level model, nevertheless the high heterogeneity seen across the country suggests the need to account for case clustering on a smaller scale. Estimated health zone population's range from 27,000 to more than 650,000 people, which includes varying numbers of communities and villages, resulting in differing degrees of susceptibility. While we were not able to look at each province alone due to sample size restrictions, we were able to

look at the province of Kinshasa. Our results generally showed a protective effect with increasing MCV1 coverage, which is not surprising given that the province is smaller geographically with improved accessibility and health infrastructure. While our model with all provinces showed an increase in risk when compared to the lowest vaccination level (<80%), the lowest IRR was seen in the highest MCV1 coverage level. Superior functioning health zones with higher MCV1 coverage located in denser, urban areas, facilitating the transmission of disease may partly explain these results. Residual confounding across provinces and poor administrative coverage estimates are likely to be additional factors. We did see a significant interaction between MCV1 coverage from the year before and the presence of an SIA and/or ORI. These results highlight the synergistic effect of two doses of MCV and the importance of second opportunity for MCV provided by a mass campaign in a country with a weak routine immunization system.

Our analyses are subject to a number of limitations and the variation seen in our results may be partially explained by data quality. The measles surveillance system has not been fully implemented in DRC and the sensitivity has not been evaluated[6]. Completeness of data is poor and little information is collected beyond aggregate age data. Case reporting occurs at the health center and is then transmitted to the health zone, where it is aggregated and sent to the national level. Case reporting is likely to be severely underestimated, with the true statistics up to 10-20 times greater[5, 14]. While more than 10,000 health centers are required to report weekly case counts to the zone's central office, only a small proportion actually participate [6]. Despite the fact that reporting "0" cases is part of the country's surveillance protocol, inconsistencies are common and 17-42% of health zones remain "silent" (do not report) each year[6]. Additionally, traditional healers, prayer houses, and privately run clinics are not always required to participate.

The IDSR system is not fully integrated into the case-based measles surveillance system. Between 2010 and 2013, only 3.7% of all cases were reported to the case-based system. And only 40% of suspected cases reported to the case-based system were confirmed measles positive by either IgM or epidemiologic linkage.² Of those negative, 11% were confirmed rubella cases due to concurrent outbreaks in some areas of the country suggesting that the measles clinical case definition may be non-specific.

While we would expect health zones with higher MCV1 coverage to have lower reported incidence, this was not reflected in our data. This is most likely an artifact of inaccurate population estimates based on a 1984 census with a 3% annual growth rate[10]. Between 2010 and 2013, 19.9 to 28.6% of health zones reported MCV1 coverage rates above 100% indicating that true vaccine coverage rates are largely unknown in DRC and frequently overestimated. These population problems are extended to SIA vaccine coverage rates and national vaccination rates. National administrative coverage was estimated at 88% compared to the WHO/UNICEF estimate of 73%[15, 16]. The Multiple Indicator Cluster Survey (MICS) 2010 estimated measles coverage at 67% and the most recent Demographic and Health Survey (DHS) conducted in 2013 estimated coverage at 71.6%[17, 18]. A 2013 serosurvey conducted on children aged 6-59 months indicated that only 66% were seropositive for measles antibodies [unpublished data]. While the researchers were unable to determine whether the presence of antibodies were vaccine induced or natural immunity, these results indicate that vaccine coverage in DRC is dramatically overestimated.

Measles vaccine efficacy is expected to be 85% at 9-11 months of age and increases to 95% after a second dose given at ≥ 12 months[19, 20]. In a country where

² IgM positive defined as Individuals confirmed as a recent infection through Siemens Enzygnost® indirect enzyme immunoassay (EIA) for measles IgM antibody; epidemiologic linkage defined as a case that meets the measles clinical case definition and had contact with a lab-confirmed case with rash onset within the preceding 30 days or living in same district

complications such as heavy rain, limited transportation options, and inadequate roads make a large majority of the country inaccessible, ensuring a well-functioning cold chain is challenging. Our findings may be explained by a reduction in vaccine efficacy caused by improper training in vaccine administration, fuel shortages, and the inaccessibility of many areas in the routine immunization system.

The use of surveillance data limits our ability to make causal inferences about an individual's risk of disease. Ecologic bias, misclassification within groups, temporal ambiguity, and an inability to control for all confounders can lead to significant bias[21]. We did not have data on all confounders, particularly the nutritional status of each child. Malnourishment is strongly associated with more severe cases of measles and may reduce vaccine uptake. Furthermore, measles cases in malnourished children are more likely to be reported. Additionally, insufficient communication with mothers, vaccine stock-outs, poorly motivated staff, and the expense and difficulty of travel to a health center may have biased our results. Furthermore, our ORI data is likely to be incomplete. Unfortunately, MSF does not regularly provide EPI with their ORI summaries and coverage estimates.

Our results highlight the importance of a two-dose measles vaccine schedule and the need for both a strong routine immunization program coupled with frequent SIAs. Preventing another measles resurgence will require reaching $\geq 95\%$ of children with 2 MCV doses and WHO does not recommend adding a second dose of MCV to the routine immunization schedule in countries with low vaccine coverage[22]. In the meantime, DRC should prioritize the improvement of their routine immunization program and continue to follow-up with regular SIAs every two or three years [23]. Ensuring high MCV1 coverage with well-conducted SIAs will certainly be the most effective way to prevent future measles outbreaks.

Table 2.1: Measles suspected case counts and incidence rates among children aged 12-59 months Incidence (per 100,000) by province and year, Democratic Republic of Congo, 2010-2013

	2010		2011		2012		2013	
	No. Cases	Incidence (95% CI)	No. Cases	Incidence (95% CI)	No. Cases	Incidence (95% CI)	No. Cases	Incidence (95% CI)
Province								
<i>Bandundu</i>	33	2.20 (0.31-16.40)	496	32.80 (4.60-233.00)	4012	257.62 (36.30-1829.00)	3510	218.82 (30.80-1554.00)
<i>Bas-Congo</i>	24	3.80 (0.51-28.10)	448	68.81 (9.70-489.50)	462	68.89 (9.70-490.10)	347	50.24 (7.10-357.60)
<i>Equateur</i>	134	7.65 (1.10-54.70)	200	11.08 (1.60-79.10)	6524	351.02 (49.40-2492.00)	15170	765.79 (107.90-5437.00)
<i>Kasai-Occ</i>	30	2.21 (0.30-16.20)	736	52.60 (7.40-373.90)	2436	169.04 (23.80-1200.00)	8170	550.41 (77.50-3908.00)
<i>Kasai-Ori</i>	138	8.23 (1.20-58.80)	27743	1605.39 (226.10-1140.00)	4070	228.66 (32.20-1624.00)	797	43.47 (6.10-309)
<i>Katanga</i>	2567	118.04 (16.60-838.30)	58136	2595.41 (365.60-18430.00)	7076	306.70 (43.20-2178)	6652	279.92 (39.40-1987.00)
<i>Kinshasa</i>	54	3.73 (0.52-27.00)	291	19.52 (2.70-139.00)	738	48.05 (6.80 (341.60)	443	28.00 (3.90-199.20)
<i>Maniema</i>	16	4.12 (0.55-31.00)	7639	1907.52 (268.70-13540.00)	1241	300.86 (42.30-2138.00)	1295	304.81 (42.90-2166.00)
<i>North-Kivu</i>	73	5.92 (0.82-42.60)	65	5.12 (0.71-36.90)	493	37.71 (5.30-268.20)	729	51.88 (7.30-368.80)
<i>Orientale</i>	160	8.49 (1.20-61.40)	2560	133.49 (18.80-948.00)	23594	1194.43 (168.2-8480.00)	20972	1030.7 (145.20-7318.00)
<i>South-Kivu</i>	752	73.2 (10.30-520.60)	2913	275.4 (38.80-1956.00)	451	41.4 (5.80-294.50)	1199	106.9 (15.00-759.20)
Total	3981		101227		51097		59284	

Figure 2.1: Incidence rates (per 100,000) among children aged 12-59 months by province and year, Democratic Republic of Congo, 2010-2013

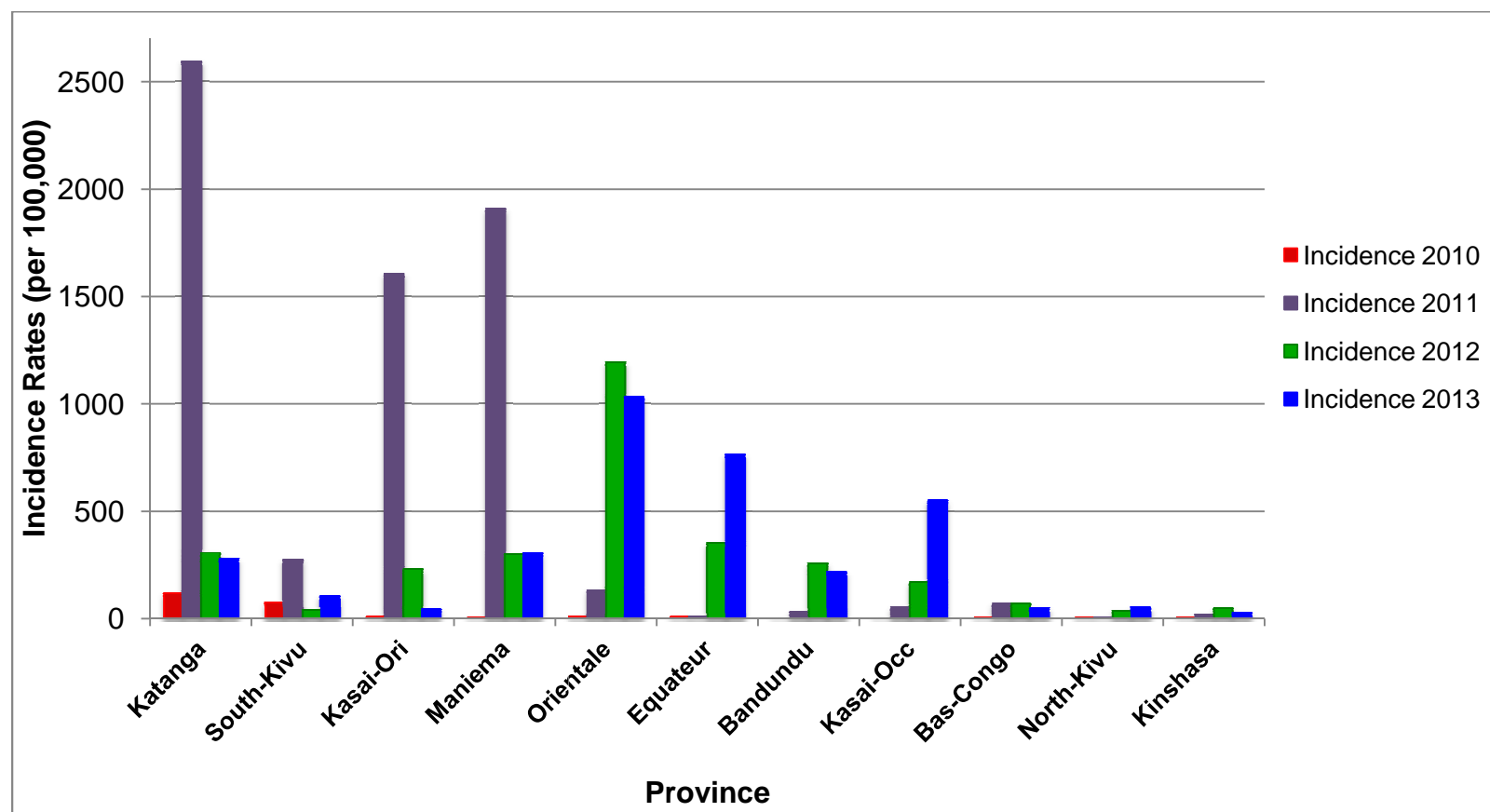


Table 2.2: Estimated measles incidence (per 100,000) in the same year coverage was measured by MCV1 coverage and mass vaccination campaign, Democratic Republic of Congo, 2010-2013

MCV1 Coverage %				
No Campaign				
	<80%	80-89%	90-100%	> 100%
2010	14.9 (2.1-106.3)	18.0 (2.5-128.0)	37.1 (5.2-263.7)	26.4 (3.7-186.8)
2011	67.2 (9.5-477.4)	16.0 (2.2-113.9)	48.6 (6.8-345.4)	8.2 (1.1-58.6)
2012	315.1 (44.4-2237.0)	196.6 (27.7-1396.0)	344.4 (48.5-2445.0)	202.0 (284.0-1434.0)
2013	70.5 (9.9-500.4)	139.0(19.6-986.7)	151.2 (21.3-1070.3)	226.1 (31.8-1605.0)
≥ 1 Mass Campaign				
2010	245.8 (34.3-1763.0)	-	-	1353.0 (190.2-9630.0)
2011	416.5 (58.7-2957.0)	920.7 (129.7-6536.0)	1355.0 (190.9-9621.0)	1565.0 (220.5-11110.0)
2012	2102.0 (296.0-14930.0)	7706.0(1085.0-54720.0)	2433.0 (342.7-17280.0)	695.3 (97.9-4370.0)
2013	925.0(130.3-6567.0)	994.6 (140.1-7061.0)	183.7 (25.9-1305.0)	296.3 (41.7-2104.0)

* > 1 Mass Campaign includes either a provincial SIA or an Outbreak Response Immunization (ORI) Campaign

Table 2.3: Estimated measles incidence (per 100,000) in the following year coverage was measured by MCV1 coverage and mass vaccination campaign, Democratic Republic of Congo, 2010-2013

MCV1 Coverage %				
No Campaign				
	<80%	80-89%	90-100%	> 100%
2010	29.7 (4.2-210.8)	18 (2.5-128.0)	76.5 (10.8-543.3)	34.2 (4.8-243.2)
2011	355.3 (50.0-2522)	624.4 (88.0-4433.0)	773.6 (109.0-5492.0)	990.7 (139.5-7033.0)
2012	1274.0 (179.4-9045.0)	1205 (169.6-8554.0)	4.4 (0.6-34.4)	40.4 (5.7-288.0)
2013	552.1 (77.8-3920.0)	230.6 (32.5-1637.0)	228.6 (32.3-1623.0)	379.7 (53.5-2695.0)
≥ 1 Mass Campaign				
2010	3.8 (0.5-27.6)	5.0 (0.7-36.1)	1.5 (0.2-11.3)	6.1 (0.8-44.2)
2011	187.9 (26.1-1352.0)	-	-	92.7 (12.6-681.0)
2012	358.5 (50.5-2545.0)	490.8 (69.1-3485)	295.6 (41.6-2099.0)	172.6 (24.3-1226.0)
2013	1332.0 (187.4-9466.0)	158.4 (21.8-1153)	4320 (608.1-30690.0)	115.6 (15.9-839.7)

* > 1 Mass Campaign includes either a provincial SIA or an Outbreak Response Immunization (ORI) Campaign

Table 2.4. Incidence Rate Ratio of Measles Predictors in a Negative Binomial Random Effects Model of the Impact of Increasing Coverage with Measles-Containing Vaccine (MCV), Kinshasa vs. All Provinces, Democratic Republic of Congo, 2010-2013

	Kinshasa		All Provinces	
	Model 1 ^a IRR (95% CI)	Model 2 ^b IRR (95% CI)	Model 1 ^a IRR (95% CI)	Model 2 ^b IRR (95% CI)
MCV1 % Coverage				
<80	Ref	Ref	Ref	Ref
80-90	0.87 (0.53-1.45)	0.95 (0.45-2.02)	1.61 (1.24-2.12)	1.04 (0.60-1.82)
90-100	0.38 (0.20-0.71)	0.33 (0.09-1.15)	1.37 (1.02-1.85)	0.73 (0.39-1.36)
>100	0.54 (0.24-1.17)	0.70 (0.23-2.19)	1.35 (1.02-1.78)	0.48 (0.26-0.89)
SIA in Health Zone				
No SIA	Ref	Ref	Ref	Ref
≥ 1 SIA	0.18 (0.08-0.45)	0.17 (0.08-0.39)	0.86 (0.60-1.25)	0.40 (0.26-0.62)
ORI in Health Zone				
No ORI	-	-	Ref	Ref
≥ 1 ORI	-	-	0.28 (0.20-0.39)	0.39 (0.28-0.55)
MCV1 % < 80				
No SIA	-	Ref	-	Ref
≥ 1 SIA	-	0.14 (0.05-0.41)	-	1.11 (0.65-1.90)
MCV1 % 80-89				
No SIA	-	Ref	-	Ref
≥ 1 SIA	-	0.20 (0.08-0.50)	-	0.35 (0.16-0.76)
MCV1 % 90-100				
No SIA	-	Ref	-	Ref
≥ 1 SIA	-	0.09 (0.01-0.84)	-	0.40 (0.18-0.90)
MCV1 % > 100				
No SIA	-	Ref	-	Ref
≥ 1 SIA	-	0.34 (0.05-2.29)	-	0.17 (0.07-0.39)
MCV1 % < 80				
No ORI	-	-	-	Ref
≥ 1 ORI	-	-	-	0.52 (0.25-1.06)
MCV1 % 80-89				
No ORI	-	-	-	Ref
≥ ORI	-	-	-	0.83 (0.41-1.68)
MCV1 % 90-100				
No ORI	-	-	-	Ref
≥ 1 ORI	-	-	-	0.31 (0.17-0.56)
MCV1 % > 100				
No ORI	-	-	-	Ref
≥ 1 ORI	-	-	-	0.21 (0.13-0.35)

Abbreviations: IRR=incidence rate ratio; CI=confidence interval; MCV1=measles containing vaccine (dose 1); SIA=supplementary immunization activities; ORI=outbreak response immunization

^a Model 1 without interactions

^b Model 2 with interactions between 1) SIA and MCV1 coverage 2) ORI and MCV1 coverage

p-value for product term between MCV1 cover and SIA = 0.008 (all provinces)

p-value for product term between MCV1 and ORI = 0.0005 (all provinces)

p-value for product term between MCV1 and SIA = 0.7659 (Kinshasa)

Figure 2.2: Percentage of suspected measles cases by IDSR age category, province and year, Democratic Republic of Congo, 2010-2013

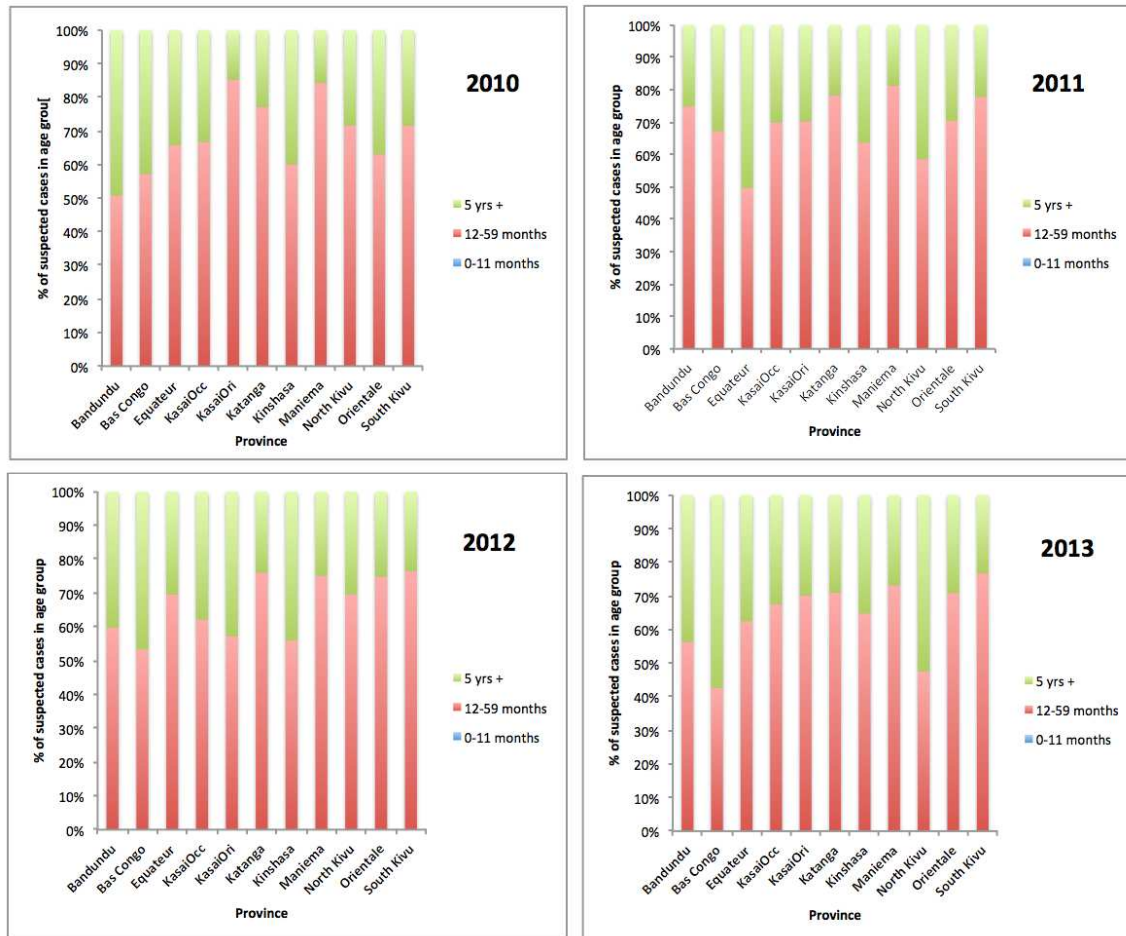
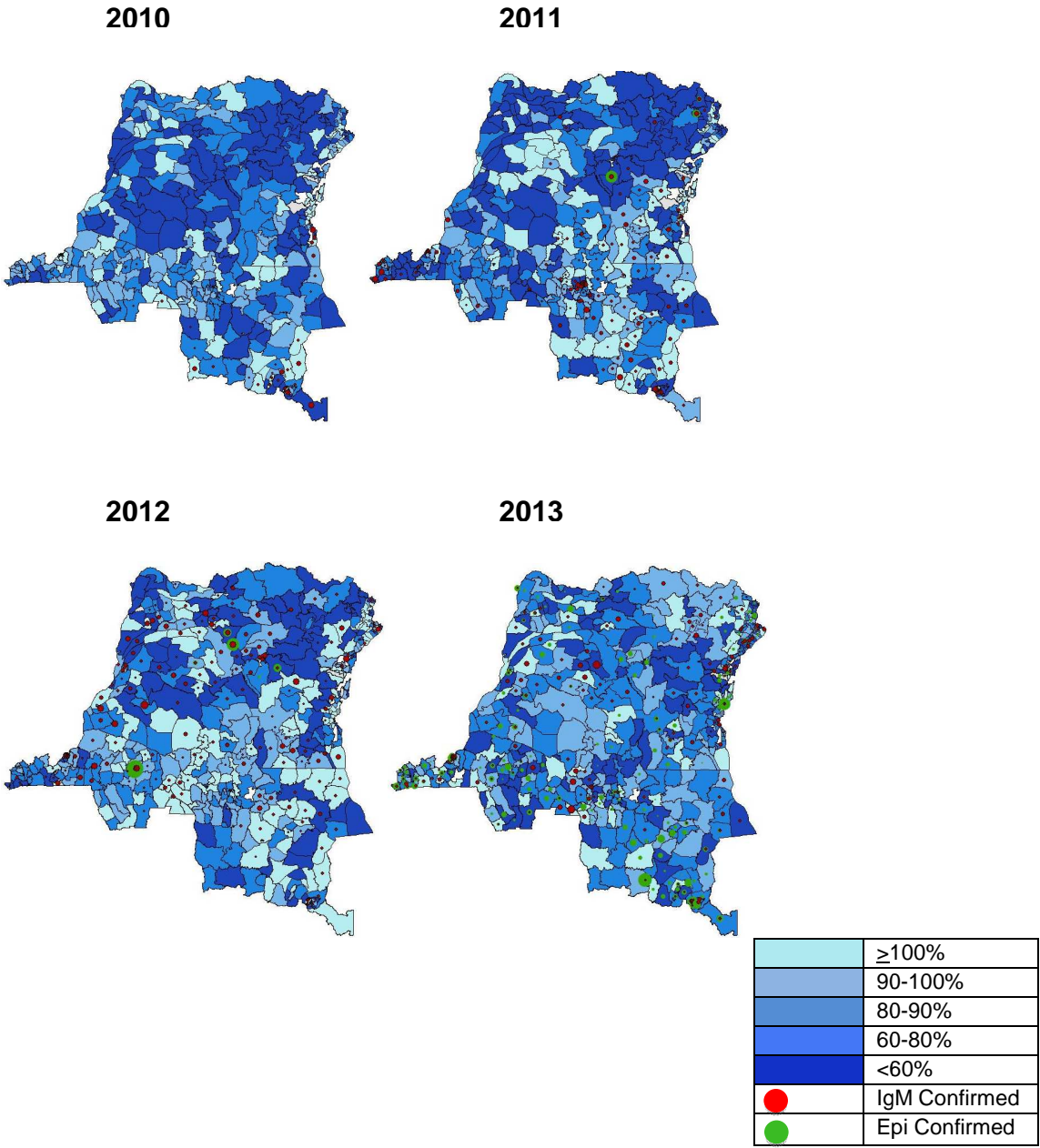


Figure 2.3: Administrative MCV1 coverage, IGM confirmed and Epi Linked measles case by Health Zone and year



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Chapter 3: Field Evaluation of Measles Vaccine Effectiveness Among Children in the Democratic Republic of Congo

3.1 Abstract

Background: We estimated measles Vaccine Effectiveness (VE) among children aged 12-36 months in the Democratic Republic of Congo (DRC) using laboratory surveillance data from 2010-2012.

Methods: We used the case-based surveillance system with laboratory confirmation to conduct a case-control study using the test negative design. Cases and controls were selected based on presence (n=628) or absence (n=847) of measles specific antibody IgM or epidemiologic linkage, and matched by year of illness and province. Risk factors for measles were assessed using conditional logistic regression. An unmatched analysis was performed, stratifying by year of measles diagnosis.

Results: Vaccination was protective against measles in the matched analysis [aMOR (95% C)], 0.19 (0.12-0.31) and estimated VE was 80% (95% CI 69-88%). In the unmatched analysis [aOR (95% C)], year of diagnosis, 2011: 6.10 (4.03-9.24) and 2012; 8.33 (5.32-13.04) was a risk factor for measles. Compared to Kinshasa, children in Bas-Congo, Kasai-Oriental, Katanga and South Kivu provinces all had higher odds of developing measles. Measles VE was 81% (95% CI, 60-91%) in 2010, 77% (95% CI, 63-85%) in 2011 and 81% (95% CI, 67-89%) in 2012.

Conclusions: Repeated occurrences of measles outbreaks and lower than expected VE estimates suggest the need to further evaluate measles vaccine efficacy and improve vaccine delivery strategies in DRC

3.2 Introduction

It is estimated that 1.5 million deaths among children less than five are attributed to vaccine preventable diseases[1, 2]. Measles is one of the most infectious diseases, associated with complications such as encephalitis, pneumonia, and blindness[3]. Despite the availability of a safe and effective vaccine, measles continues to be one of the largest causes of vaccine-preventable disease mortality among children under five, in resource-limited countries, with as many as five out of every hundred measles cases leading to death[3]. Globally, measles immunization coverage has improved tremendously over the last ten years and measles has been eliminated in most high and middle-income countries. In 2012, there were 122,000 estimated deaths worldwide, over 95% of which occurred in resource-limited settings[4].

In the African region, increased routine vaccination coverage coupled with Supplementary Immunization Activities (SIAs) has led to significant reductions in incidence and mortality[5]. Between 2000 and 2010, measles related mortality was reduced by more than 85%[6]. One of the key strategies specified for the reduction of childhood morbidity and mortality in the Millennium Development Goals (MDG) is increasing measles immunization coverage to 90% in all countries by 2015 [7]. However, at the end of 2010, the African Region was not on track to achieve this goal due to low vaccination coverage[7]. Throughout the region, deficiencies in routine immunization persist. Of the 28 countries reporting measles outbreaks in 2009-2010, 18 reported <90% vaccine coverage with the first dose of Measles Containing Vaccine (MCV)[8]. Additionally, 13 had held SIAs with <90% coverage, less than 24 months before the outbreak[8]. These occurrences of measles outbreaks post campaigns have raised concerns about the loss of vaccine effectiveness (VE) in conditions where vaccine storage, handling, distribution, and cold chain requirements are difficult to maintain. VE is of particular concern in resource-limited settings, where refrigeration and electricity is

limited, and cold chain maintenance represents a substantial economic and logistical burden[9].

Since 2004, the Democratic Republic of Congo's (DRC) effort to reduce measles mortality has consisted of a 3-pronged approach; 1) increasing routine immunization coverage of MCV1, given at 9-11 months of age, 2) implementing SIAs to provide second dose of MCV, and 3) expanding epidemiologic surveillance[2, 7]. Despite these efforts, in 2010, DRC saw a resurgence of measles with large scale outbreaks throughout the country[7].

As the second largest country in Africa by land mass, DRC struggles to recover from a devastating multi-year conflict, resulting in mass population displacement, and extreme violence[10]. The country continues to suffer from inadequate roads and limited electricity and water, coupled with a lack of human resources. These challenges have hindered development efforts and contributed to the collapse of existing public health infrastructure, resulting in the country's inability to implement international vaccination guidelines effectively, including maintaining and monitoring an effective cold chain. Despite these problems, reported administrative vaccine coverage levels are high, with 223 of 513 health zones reporting >90% coverage in 2010 and SIA coverage reportedly at 100% in many health zones[11].

Monitoring of measles vaccine effectiveness is a useful measure of quality control in immunization programs. It can provide insight into areas of weakness and help in the evaluation of new policy decisions [12-14]. The effectiveness of a vaccine is dependent both on its potency and proper administration[12, 13]. In addition to serologic studies, which assess vaccine uptake, laboratory-based techniques test the potency of the measles vaccine; unfortunately, the complexity and associated expense of these studies make implementation in resource-limited countries infeasible. [12]. However, vaccination success in the field can be monitored through the use of epidemiologic

studies[12-15].

One approach that has been proven effective at estimating Vaccine Effectiveness (VE) is the test-negative case-control study, which has been used in studies assessing the VE of influenza and rotavirus[14-19]. This design selects cases and controls from a pool of subjects with “measles-like illness”, which are subsequently laboratory-confirmed positive or negative. It is a non-traditional case-control study in that the marginal ratio of cases to controls is unknown during enrollment, however its ease and elegant way of mitigating selection bias due to health seeking behavior make it a useful way of measuring VE[16, 20]. Using this approach, we conducted a case-control study to estimate VE using case-based measles surveillance data among children in DRC collected between 2010 to 2012.

3.3 Methods

Case-Control Study

We utilized data from the Case-Based (CB) measles surveillance system with laboratory confirmation collected from January 1, 2010 through December 31, 2012. The system was first implemented in 2002 to coincide with the start of SIAs. Individuals presenting to health centers with measles like illness (MLI), or found through active case searching are reported to the Integrated Disease Surveillance and Response (IDSR) and CB surveillance systems. Suspected measles cases are reported and a blood specimen is collected and tested for measles specific antibodies (IgM). We determined that among the population of children reported to the surveillance system with MLI, a proportion of children tested positive and another proportion tested negative for measles IgM.

We performed a matched and unmatched case-control study using the available data. The Human Subjects Protection boards at both the Kinshasa School of Public Health and the UCLA Fielding School of Public Health approved the study protocol.

Case Definition: Individuals reported to the CB measles surveillance system are persons presenting with MLI, defined as any person with fever and maculopapular rash and cough or coryza or conjunctivitis, or a person in whom a clinician suspects measles[21]. Individuals were confirmed as a recent infection through either 1) Siemens Enzygnost® indirect enzyme immunoassay (EIA) for measles IgM antibody or 2) by epidemiologic linkage, defined as a case that meets the clinical case definition and had contact with a lab-confirmed case with rash onset within the preceding 30 days or living in same district[21]. All laboratory analyses were conducted at the National Institute for Biomedical Research in Kinshasa, part of the Global Measles and Rubella Laboratory.

Case Selection: Case patients were selected if they met the case definition (confirmed infection) and were 12-36 months of age, living in DRC and reported to the CB measles surveillance system, with available vaccination history.

Controls: Individuals were eligible to be a control if they were 12-36 months of age, living in DRC, reported to the CB measles surveillance system because of MLI, and testing IgM negative for measles virus with available vaccination history. In the matched analysis, controls were matched to cases based on the year of diagnosis and province of residence.

Vaccination Status Ascertainment: Measles vaccination history was obtained through maternal recall when vaccination cards were unavailable. All subjects were considered vaccinated if a vaccination date was recorded and occurred >1 month prior to disease onset. Children were also considered vaccinated if two or more doses of vaccine were recorded.

Age Calculation: We calculated age (in months) when birthday was available; the date of birth was subtracted from the date of specimen collection to calculate the age in months. If an exact birthday was unavailable, then the variable “age in years” was converted to months and added to “age in months” to create an overall age (in months).

Statistical Analyses: All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC). Conditional and unconditional multivariate logistic regression was used to assess possible risk factors for recent measles infection for children aged 12-36 months who were included in the VE estimation. Factors included in the multivariate analyses were vaccination status, sex, age, year of diagnosis, province, and whether health zone of residence was considered rural or urban.

VE Estimation: VE was estimated using the standard case-control protocol, with the formula $VE = (1 - \text{odds vaccinated} / \text{odds unvaccinated}) * 100$, where the odds vaccinated/odds unvaccinated was the adjusted matched or unmatched odds ratio for receiving ≥ 1 dose of measles vaccine compared with no doses[12]. Cases were matched to controls by year of reporting and province to account for year-to-year measles vaccine differences and province specific epidemics. The attack rates in each province were low (<10%), satisfying the rare disease assumption and the odds ratio was used to approximate the risk ratio[12, 13, 22]. An unmatched analysis was

performed to assess year-to-year variation in VE estimates and look at year and province as possible risk factors for measles. Children with unknown vaccination history were not included in any of the multivariate models used to estimate VE.

3.4 Results

In 2010, there was a resurgence of measles cases in DRC. By 2011, the number of cases increased dramatically to 134,041 reported cases, with more than 70% occurring in children under five years of age[23]. The epidemic may have started in Katanga province and proceeded to spread throughout the country, with the highest incidence rates in province Orientale, Equateur and Kasai Orientale[7, 23].

Since 2004, 16,789 samples have been tested for measles specific antibodies, with 28.51% confirmed positive by measles IgM and 11.19% confirmed by epidemiologic linkage. For the purposes of VE estimation, we used the data from January 1, 2010 to December 31, 2012. Of the 8,650 samples in this timeframe, 4,208 (48.6%) were considered measles positive, 1,734 (41.2%) of which were additionally confirmed through epidemiologic linkage while 4,379 (50.6%) tested negative.

Matched Case-Control Study

In total, 714 case-control pairs were eligible for the analysis. Median age for cases was 24 months, while median age for controls was 25 months (Table 1). Cases were more likely to be unvaccinated than controls (MOR [95% CI] 0.17 [0.11-0.27]), and the odds of measles among those living in rural areas compared to those living in urban areas (MOR [95% CI] 1.40 [0.79-2.49]) was non-significant. In the multivariate analysis (Table 2), vaccination status remained significantly associated with measles (aMOR [95% CI] 0.19 [0.12-0.31]), while living in a rural area remained non-significant (aMOR [95% CI] 1.22 [0.64-2.34]).

Unmatched Case-Control Study

In total, 628 cases and 847 controls were available for the analysis (fig. 2). Cases were more likely to be unvaccinated (OR [95% CI] 0.16 [0.13-0.20] than controls (Table 3). Compared to 2010, children in 2011 had 8.42 (OR [95% CI] 8.42 [5.96-11.88] times the odds and in 2012, 6.23 [4.39-8.82] times the odds of developing measles. Compared to the province of Kinshasa, children in Bas-Congo (OR [95% CI] 3.67 [2.12-6.39], Kasai-Oriental 5.50 [3.04-9.97], Maniema 3.68 [1.97-6.88], Orientale 7.22 [4.79-10.89] and South Kivu 7.16 [3.56-14.42] all had higher odds of developing measles (Table 2). Those living in rural areas had 1.68 (OR [95% CI] 1.68 [1.18-2.39] times the odds of developing measles compared to those living in urban areas.

In the multivariate analysis (table 2), measles vaccination (aOR [95% CI] 0.19 [0.14-0.26]) and year of diagnosis, 2011 6.10 [95% CI, 4.03-9.24] and 2012; 8.33 [95% CI, 5.32-13.04] remained significant. Compared to Kinshasa, children in Bas-Congo, Kasai-Oriental, Katanga, and South Kivu all had higher odds of developing measles. We also investigated risk factors for measles in 2010, 2011, and 2012 individually (Table 4).

Vaccine Effectiveness (VE)

VE for any measles vaccination was calculated for both matched and unmatched case-control studies. VE in the matched analysis was 81% (95% CI, 69-88%), and VE in the unmatched analysis was also 81% (95% CI, 74-86%). VE was also calculated individually for 2010, 2011 and 2012, and was 81% (95% CI, 60-91%), 77% (95 CI, 63-85%), and 81% (95% CI, 67-89%) respectively.

3.5 Discussion

Despite the fact that DRC has a country specific measles control strategy and target elimination date of 2020, large-scale measles outbreaks have persisted throughout the country since 2010 [7]. This suggests the immediate need to re-evaluate

the country's immunization program in terms of immunization strategy, control and prevention. In settings where accessibility to health services is limited, efforts to estimate VE of delivered vaccine can have an important impact.

Routine immunization coverage remains sub-optimal throughout the country. In 2012, WHO/UNICEF estimated that national measles vaccine coverage was only 73%, well below the WHO measles mortality reduction strategy which calls for $\geq 90\%$ coverage [24, 25]. Additionally, when de-aggregating the data at the health zone level, between 25-40% of health zones were below the WHO recommended 80% for routine immunization[26]. Provincial SIAs, follow-up immunization activities, and catch-up campaigns were too infrequent to provide sustained immunity to those not accessing routine health services and therefore failed to prevent the recent measles epidemics[7]. While our analyses for VE were restricted to a younger age group, a large proportion of the confirmed measles cases were seen in older age categories (Fig, 1), suggesting a history of immunization deficiencies in DRC.

Measles vaccine efficacy is expected to be 85% following the first dose at 9 to 11 months of age and 95% after the second dose at ≥ 12 months[25, 27]. Given the study population of children aged 12 to 36 months; the subjects were more likely to be exposed to more than one dose of MCV either through routine immunization and/or SIAs, suggesting that failure rates should be low. While the available data did not allow for stratification by number of doses, we present an overall estimate of VE by combining subjects receiving one or more doses. While we were able to control for provincial differences, our VE estimates represent national averages. With the large diversity seen across the country, additional stratified studies are needed, to tease out differences between provinces and health zones.

Calculated VE estimates are lower than expected regardless of year. Extensive rain, inadequate transport, impassable roads, population movement, and insecure

regions make a large majority of the country inaccessible. Furthermore, improper staff training and fuel shortages have resulted in an unreliable cold chain in many areas. The measles vaccine requires a 4–8°C cold chain until use; then after reconstitution, the vaccine faces the risk of bacterial contamination and loss of potency with exposure to high temperatures and light after only 6 hours[8]. Using a vaccine with reduced effectiveness, coupled with a 15% vaccination failure rate at 9 to 11 months of age, will lead to lower vaccine-induced immunity in the population[28, 29]. Additionally, past SIA's have included children as young as 6 months and vaccine failure may occur due to competing maternal antibodies[24, 30, 31].

Our analyses are subject to a number of limitations. The measles surveillance system has not been fully implemented in DRC. Case reporting occurs at the health center level and is then transmitted to the health zone, where it is aggregated and sent to the national level. The CB surveillance system and the Integrated Disease Surveillance and Response (IDSR) system are still not fully integrated. The CB surveillance system represents just a small percentage (3.7%) of those cases reported via the IDSR, and likely only represents only a small proportion of all measles cases. Furthermore, since confirmed outbreaks only require three³ measles confirmed IgM positive cases, it is probable that a health zone may not have sent additional samples for laboratory confirmation. Despite the fact that reporting “0” cases is part of the country's surveillance protocol, inconsistencies are common and 17-42% of health zones remain “silent” (do not report) each year[7]. Depending on their true measles and vaccination statuses, these missed cases may have led to biased VE estimates. A majority of the vaccination information was obtained through maternal recall (68.9% in both cases and controls), however bias is likely to be non-differential because both cases and controls

³ Health zones must send a minimum of five samples, however an outbreak is confirmed when 3 samples are IgM positive

were tested based on measles-like symptoms, leading to an underestimate of vaccine efficacy. The high proportion of subjects with unknown vaccination status (43.3%) may have led to biased VE estimates.

We did not have data on important confounders, particularly the nutritional status of each child. Malnourishment is strongly associated with more severe cases of measles and therefore measles cases in malnourished children are more likely to be reported [31-33]. Additionally, nutritional status and malaria infection has been associated with reduced vaccine uptake and may partially explain lower VE estimates in a malaria endemic country where a majority of children are malnourished[34]. Children in Bas-Congo, Kasai-Oriental, Maniema, and Orientale, and all had higher odds of developing measles and a higher prevalence of malaria (44.1-49.1%)[35].

The indirect ELISA used to confirm measles generally works well and has high sensitivity (89.9%–97.4%; higher after the first week of rash onset) and specificity (92.8%–100%) for samples collected within 3-28 days after rash onset[36, 37]. However, even a test that is 90% specific can result in a large number of non-measles MLI cases being attributed to measles and in equal proportions among the vaccinated and unvaccinated, resulting in an underestimate of VE[15].

The validity of a case control study is dependent on the control group representing the exposure distribution of the source population. This design provides some reassurance that our controls did emerge from the source population that gave rise to the cases, considering that all subjects present with a measles-like illness[14]. However, vaccination status is likely to be associated with improved health seeking behaviors and obtaining care at a health center, thus limiting the generalizability of our results to the entire population of DRC.

Large-scale outbreaks in DRC and other African countries demonstrate the virus's ability to easily re-enter communities lacking sustained levels of population

immunity[5]. These outbreaks underscore the importance of re-evaluating measles virus dynamics and determining the elements necessary to attain global targets for reducing measles transmission and mortality. Accurate vaccination coverage data must be collected and reasons why vaccination was not received should be assessed in order to inform new and improved vaccination strategies. Additional studies assessing measles VE should be conducted, specifically in inaccessible areas, to further refine prevention and control strategies in DRC. Heavily monitored program scale-up and financial commitment will be essential as we push forward, toward measles elimination goals.

Table 3.1: Characteristics associated with measles in children aged 12-36 months, case-control study, Democratic Republic of Congo, 2010-2013 (matched analysis)

	Cases (n=357) n (%)	Controls (n=357) n (%)	MOR (95% CI)
Measles Vaccination			
<i>Unvaccinated</i>	203 (56.86)	88 (24.65)	Ref
<i>Vaccinated</i>	154 (43.14)	269 (75.35)	0.17 (0.11-0.27)
Sex			
<i>Male</i>	200 (56.02)	195 (54.62)	Ref
<i>Female</i>	157 (43.98)	162 (45.38)	0.94 (0.70-1.27)
Age (months) at diagnosis			
Median age in years (IQR)	24 (22-36)	25 (19-36)	1.00 (0.98-1.02)
Year of Diagnosis*			
<i>2010</i>	39 (10.92)	39 (10.92)	-
<i>2011</i>	175 (49.02)	175 (49.02)	
<i>2012</i>	143 (40.06)	143 (40.06)	
Province*			
<i>Kinshasa</i>	41 (11.48)	41 (11.48)	-
<i>Bandundu</i>	13 (3.64)	13 (3.64)	
<i>Bas-Congo</i>	24 (6.72)	24 (6.72)	
<i>Equateur</i>	16 (4.48)	16 (4.48)	
<i>Kasai-Occidental</i>	22 (6.16)	22 (6.16)	
<i>Kasai-Oriental</i>	14 (3.92)	14 (3.92)	
<i>Katanga</i>	111 (31.09)	111 (31.09)	
<i>Maniema</i>	24 (6.72)	24 (6.72)	
<i>North-Kivu</i>	7 (1.96)	7 (1.96)	
<i>Orientale</i>	69 (19.33)	69 (19.33)	
<i>South-Kivu</i>	16 (4.48)	16 (4.48)	
Health Zone			
<i>Urban</i>	43 (13.56)	53 (16.01)	Ref
<i>Rural</i>	274 (86.44)	278 (83.99)	1.40 (0.79-2.49)

* Matched variables

Figure 3.1: Age and vaccination status of MLI cases in measles case-based surveillance system with laboratory confirmation, Democratic Republic of Congo, January 1, 2010 - December 31, 2012

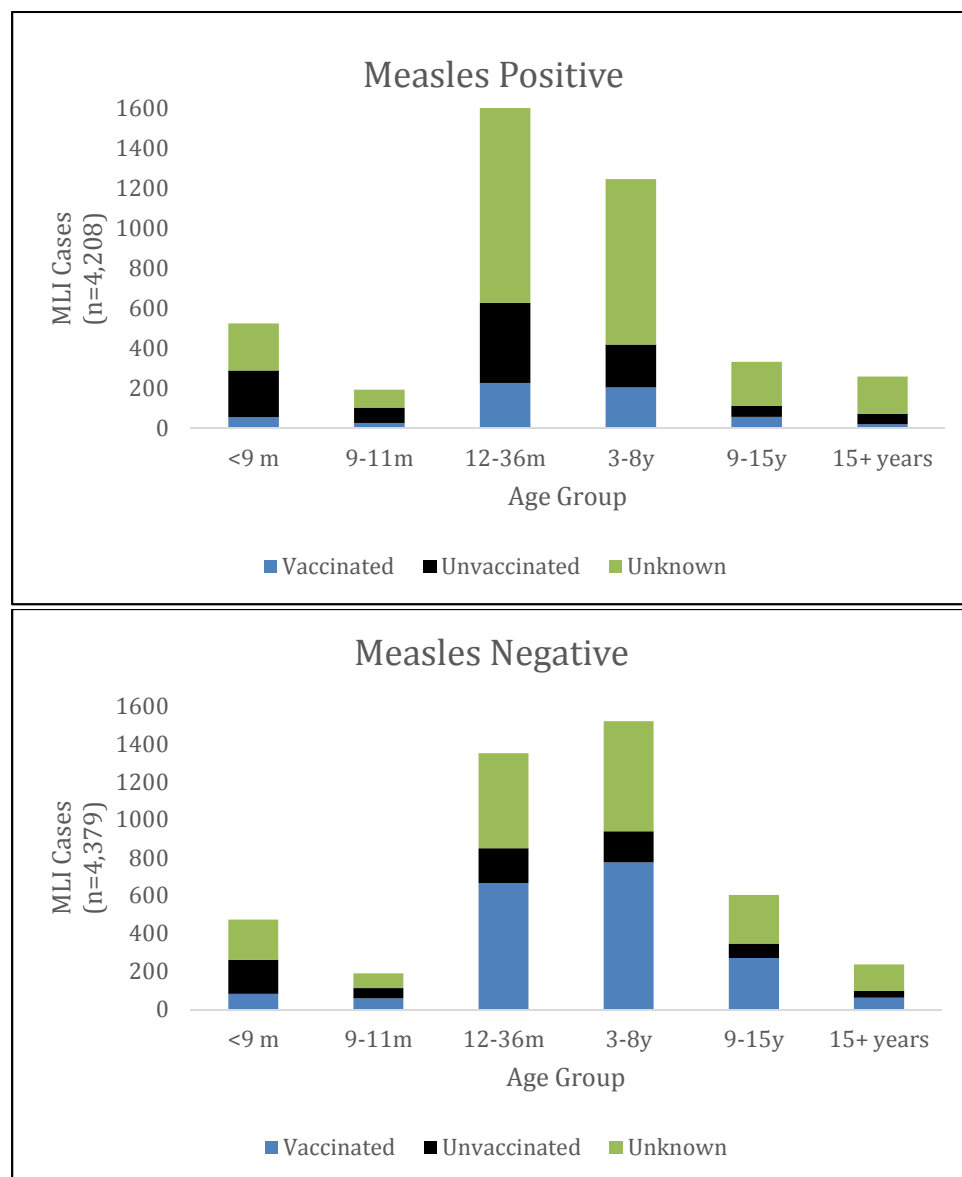


Figure 3.2: Study population selection, case-control study, Democratic Republic of Congo, 2010-2013

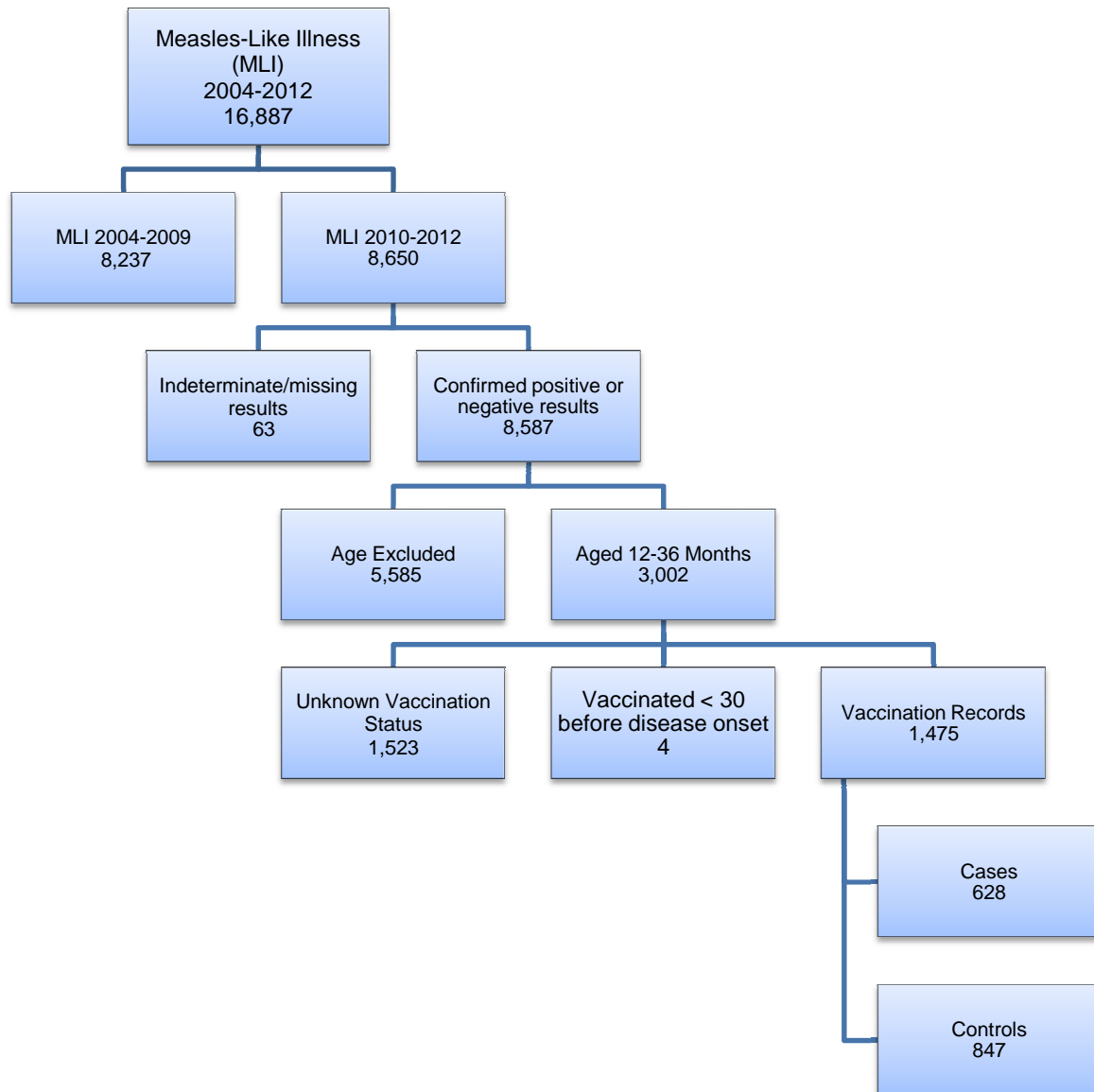


Table 3.2: Results of multivariate analyses of risk factors associated with measles in children aged 12-36 months of age, case-control study, Democratic Republic of Congo, 2010-2013 (matched and unmatched)

	Adjusted OR (95% CI)	mAdjusted OR (95% CI)
Measles Vaccination		
<i>Unvaccinated</i>	Ref	Ref
<i>Vaccinated</i>	0.19 (0.14-0.26)	0.19 (0.12-0.31)
Sex		
<i>Male</i>	Ref	Ref
<i>Female</i>	0.85 (0.64-1.12)	0.82 (0.57-1.18)
Age (months) at diagnosis	0.99 (0.98-1.01)	1.00 (0.98-1.02)
Year of Diagnosis		
<i>2010</i>	Ref	-
<i>2011</i>	6.10 (4.03-9.24)	
<i>2012</i>	8.33 (5.32-13.04)	
Province		
<i>Kinshasa</i>	Ref	-
<i>Bandundu</i>	0.83 (0.34-2.04)	
<i>Bas-Congo</i>	3.51 (1.70-7.24)	
<i>Equateur</i>	1.96 (0.90-4.30)	
<i>Kasai-Occidental</i>	1.62 (0.75-3.47)	
<i>Kasai-Oriental</i>	4.28 (1.97-9.32)	
<i>Katanga</i>	1.91 (1.08-3.35)	
<i>Maniema</i>	2.02 (0.92-4.48)	
<i>North-Kivu</i>	1.90 (0.65-5.55)	
<i>Orientale</i>	1.56 (0.83-2.93)	
<i>South-Kivu</i>	8.30 (3.53-19.54)	
Health Zone		
<i>Urban</i>	Ref	Ref
<i>Rural</i>	1.04 (0.62-1.73)	1.22 (0.64-2.34)

Table 3.3: Characteristics associated with measles in children aged 12-36 months, case-control study, Democratic Republic of Congo, 2010-2013 (unmatched)

	Cases (n=628) n (%)	Controls (n=847) n (%)	OR (95% CI)
Measles Vaccination			
<i>Vaccinated</i>	227 (36.15)	663 (78.28)	0.16 (0.13-0.20)
<i>Unvaccinated</i>	401 (63.85)	184 (21.72)	
Sex			
<i>Male</i>	341 (54.30)	457 (53.96)	Ref
<i>Female</i>	287 (45.30)	390 (46.06)	0.99 (0.80-1.21)
Age (months) at diagnosis			
Median age in years (IQR)	24 (22-36)	26 (19-36)	0.99 (0.98-1.00)
Year of Diagnosis			
<i>2010</i>	48 (7.64)	319 (37.66)	Ref
<i>2011</i>	328 (52.23)	259 (30.58)	8.42 (5.96-11.88)
<i>2012</i>	252 (40.13)	269 (31.76)	6.23 (4.39-8.82)
Province			
<i>Kinshasa</i>	41 (6.53)	162 (19.13)	Ref
<i>Bandundu</i>	13 (2.07)	31 (3.66)	1.66 (0.80-3.45)
<i>Bas-Congo</i>	39 (6.21)	42 (4.96)	3.67 (2.12-6.39)
<i>Equateur</i>	87 (13.85)	38 (4.49)	9.05 (5.42-15.10)
<i>Kasai-Occidental</i>	22 (3.50)	45 (5.31)	1.93 (1.05-3.57)
<i>Kasai-Oriental</i>	39 (6.21)	28 (3.31)	5.50 (3.04-9.97)
<i>Katanga</i>	111 (17.68)	320 (37.78)	1.37 (0.91-2.06)
<i>Maniema</i>	27 (4.30)	29 (3.42)	3.68 (1.97-6.88)
<i>North-Kivu</i>	8 (1.27)	20 (2.36)	1.58 (0.65-3.84)
<i>Orientale</i>	212 (33.76)	116 (13.70)	7.22 (4.79-10.89)
<i>South-Kivu</i>	29 (4.62)	16 (1.89)	7.16 (3.56-14.42)
Health Zone			
<i>Urban</i>	47 (11.60)	146 (18.05)	Ref
<i>Rural</i>	358 (88.40)	663 (81.95)	1.68 (1.18-2.39)

Table 3.4: Results of multivariate analyses of risk factors associated with measles in children aged 12-36 months of age, stratified by year of diagnosis, case-control study, Democratic Republic of Congo, 2010-2013 (unmatched)

	2010 aOR* (95% CI)	2011 aOR (95% CI)	2012 aOR (95% CI)
Measles Vaccination			
<i>Unvaccinated</i>	Ref	Ref	Ref
<i>Vaccinated</i>	0.19 (0.09-0.40)	0.23 (0.15-0.37)	0.19 (0.11-0.33)
Sex			
<i>Male</i>	Ref	Ref	Ref
<i>Female</i>	0.92 (0.44-1.92)	0.84 (0.54-1.30)	0.77 (0.48-1.23)
Age (months) at diagnosis	0.98 (0.93-1.02)	1.01 (0.98-1.04)	0.98 (0.96-1.01)
Province			
<i>Kinshasa</i>	Ref	Ref	Ref
<i>Bandundu</i>	0.22 (<. 001->999.9)	0.24 (0.02-2.46)	1.33 (0.45-3.96)
<i>Bas-Congo</i>	0.35 (<. 001->999.9)	4.49 (1.54-13.08)	2.87 (0.94-8.71)
<i>Equateur</i>	0.16 (<. 001->999.9)	0.74 (0.15-3.60)	4.12 (1.43-11.84)
<i>Kasaï-Occidental</i>	>999.9 (<. 001->999.9)	1.20 (0.37-3.86)	2.22 (0.74-6.68)
<i>Kasai-Oriental</i>	0.12 (<. 001->999.9)	6.77 (2.24-20.50)	1.70 (0.26-11.18)
<i>Katanga</i>	>999.9 (<. 001->999.9)	1.68 (0.69-4.06)	1.29 (0.56-3.00)
<i>Maniema</i>	-	2.40 (0.75-7.62)	1.63 (0.50-5.33)
<i>North-Kivu</i>	0.19 (<. 001->999.9)	2.12 (0.43-10.48)	4.58 (0.67-31.33)
<i>Orientale</i>	0.24 (<. 001->999.9)	0.77 (0.26-2.26)	3.21 (1.35-7.64)
<i>South-Kivu</i>	>999.9 (<. 001->999.9)	2.20 (0.62-7.74)	4.54 (0.73-28.35)
Health Zone			
<i>Urban</i>	Ref	Ref	Ref
<i>Rural</i>	2.73 (0.35-21.07)	1.05 (0.47-2.36)	0.90 (0.42-1.91)

*Sparse data

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Chapter 4: Assessing the Cost-effectiveness of Different Vaccination Strategies for Children in the Democratic Republic of Congo

4.1 Abstract

Introduction: The reduction in childhood mortality is one of the key Millennium Development Goals set in 1990, with routine measles vaccination coverage representing an indicator for its success. While, measles mortality has been reduced more than 78%, the disease remains one of the major causes of childhood vaccine preventable diseases globally. Measles immunization requires a two-dose schedule and only countries with strong, stable immunization programs have been able to rely on routine services to deliver the second measles dose. In the Democratic Republic of Congo, the second dose of measles vaccine is administered via supplementary immunization activities (SIAs), due to inadequately low vaccine coverage.

Methods: We used a decision analysis with a Markov model based on published and unpublished data to compare the cost-effectiveness of two different strategies for the second dose of Measles Containing Vaccine (MCV) to one dose of MCV through routine immunization services over a 15-year time period for a hypothetical birth cohort of 3 million children.

Results: Compared to strategy 1, strategy 2 (MCV2 by SIA) would prevent a total of 279,110 measles cases and 6,795 deaths and save U.S. \$2.26 million. Compared to strategy 1, strategy 3 (MCV2 by RI) would prevent a total of 207,996 measles cases and 5,074 measles-related deaths and save U.S. \$0.71 million. Strategy 2 was both cost-saving and dominated the other two strategies, yielding the fewest deaths and the lowest total program costs over the 15-year time period for the hypothetical cohort.

Discussion: Vaccination recommendations should be tailored to each country, offering a framework where countries can adapt to local epidemiological and economical circumstances in the context of other health priorities. Our results reflect the synergistic effect of two doses of

MCV and demonstrate that the most cost-effective approach to measles vaccination in DRC is to continue the administration of the second dose by mass campaign.

4.2 Introduction

The reduction in childhood mortality is one of the key Millennium Development Goals set in 1990, with routine measles vaccine coverage representing an indicator for its success[1]. Since 2000, vaccination has led to a 78% reduction in measles mortality[1]. Yet the disease remains one of the major causes of childhood vaccine preventable diseases globally, despite the fact that an effective and inexpensive vaccine exists. In 2012, there were still an estimated 122,000 measles-related deaths, mostly among children under the age of five[1]. More than 95% of these deaths occur in resource-limited countries with weakened public health infrastructures[1].

In Sub-Saharan Africa, measles remains a major public health problem, with an estimated 28,000 deaths still occurring yearly[2]. Measles deaths generally occur due to complications, with infants and young malnourished children at highest risk of death[3] . Measles immunization requires a two-dose schedule due to vaccine efficacy and competing maternal antibodies at younger ages[1]. While in principle, the first dose of measles-containing vaccine (MCV) is always offered through Routine Immunization (RI) services, only countries with strong, stable immunization programs are able to rely on routine services to deliver the second vaccine dose. Countries unable to achieve high and homogenous vaccine coverage through their routine systems must deliver the second dose in the form of supplementary immunization activities (SIAs) [4]. In these countries, special efforts must be undertaken to ensure that children missed during routine services are immunized, especially in hard-to-reach, poor communities[4].

The Democratic Republic of Congo (DRC) is struggling to recover from a devastating multi-year conflict. DRC continues to suffer from limited roads, electricity and water, leaving a significant portion of the country inaccessible. Coupled with a lack of human resources, these challenges have led to limited improvements in health infrastructure, including an inability to implement international vaccination guidelines effectively. In 2010, DRC saw a resurgence of measles with large scale outbreaks occurring throughout the country[5]. In 2013, national RI

coverage was still estimated at 71.6%, well below the WHO recommended 90%[6, 7].

The country's effort to reduce measles mortality currently consists of 3 strategies; 1) increase routine immunization coverage of MCV1, administered at 9 to 11 months of age, 2) implement SIAs to provide a second opportunity for MCV, and 3) expand epidemiologic surveillance[5, 8]. In 2012, DRC's Expanded Program on Immunization (EPI) committed to measles elimination by 2020. This plan proposed a shift in administration of MCV2 from SIAs to the routine immunization schedule.

While a number of studies have assessed the cost-effectiveness of measles elimination or eradication, few studies have addressed the cost-effectiveness of differing vaccination strategies. The diversity of both measles epidemiology and health system infrastructure across countries make analyses context specific. A comparison of the costs and benefits of providing the second doses of measles vaccine through routine immunization services and SIAs can guide the selection of the most appropriate measles vaccination strategy in DRC.

Vaccination recommendations should be tailored to each country, offering a framework where countries can adapt to local epidemiological and economical circumstances in the context of other health priorities[9]. In DRC, interpretable data on what strategies are needed to effectively and efficiently control measles is critical. We utilized cost specific data from a DRC health care perspective to analyze and compare the costs and benefits of providing two opportunities for measles immunization using two different strategies, to one dose of measles containing vaccine (MCV).

4.3 Methods

We used a decision analysis based on published and unpublished data to compare the cost-effectiveness of two different strategies for the second dose of MCV to one dose of MCV1 through routine immunization services (Fig. 1) All analyses were completed using TreeAge Pro 2014, R2.1. *TreeAge Software, Williamstown, MA.*

Strategy 1 (baseline): One dose of measles vaccine delivered through the routine immunization services at 9 months of age at the current reported coverage rate.

Strategy 2: One dose of measles vaccine delivered through routine immunization services at 9 months of age with multiple opportunities for immunization through national SIAs up to the age of five years (SIAs doses are independent of the dose received through the routine system).

Strategy 3: Two doses of measles vaccine delivered through routine immunization services at 9 months and 18 months of age.

Decision Tree

Our decision tree is designed based on the probability that a measles event occurs in a hypothetical birth cohort of 3,000,000 (Fig. 1). We utilized a Markov structure to model the number of measles events over a 15-year timeframe. During our simulations, cohort members transitioned into different health states: no measles (no immunity), no measles (vaccine induced immunity), measles (natural immunity), and death. Individual simulations were run for each of the three vaccination strategies to estimate the number of projected cases and deaths.

Annual Birth Cohort

We used DRC's estimated annual birth cohort of 3,000,000 in our decision analysis [10].

Vaccination Coverage

We utilized the most recent vaccine coverage survey conducted by the Demographic and Health Survey (DHS), which estimated measles RI coverage at 71.6%[6]. Reported SIA coverage is variable across health zones, thus we assumed SIA coverage to be 80% based on published and unpublished MOH data[11].

Vaccine Efficacy

Measles vaccine efficacy is expected to be 85% at 9-11 months of age and increases to 95% when administered at ≥ 12 months, therefore a percentage of children will always remain susceptible even after vaccination[12-15].

Wastage Factor

The wastage factor represents the proportion of vaccine not used in a program. Generally, SIAs have a smaller wastage factor than routine immunization. In DRC, the SIA wastage factor was estimated to be 1.15 for SIAs and 3.43 (based on data from other countries) for routine immunization[16].

Adverse Events Post Vaccination

Minor adverse events post vaccination occur in 5-15% of individuals[17]. We assumed that only 5% of those vaccinated would suffer an adverse event requiring a health center visit. This was determined based on literature published in other countries[16].

Adjusted Measles Incidence

In 2013, national incidence was estimated at 14.88 per 1000 persons. We calculated an adjusted incidence rate for children aged 6 to 59 months. To correct the denominator (susceptible population), we multiplied the population of children aged 6 to 59 months by the vaccine coverage (71.6%) and expected vaccine efficacy (95%)[11]. Our adjusted attack rate was 21.87 per 1000 persons.

Medical Care

The DRC-DHS 2013 estimated that 40% of mothers would seek medical care for

children sick with diarrhea, fever, or a respiratory illness[18]. Based on this information we assumed that the proportion seeking medical care for measles was similar due to shared symptoms.

Case-Fatality Rate

We assumed the case-fatality rate to be 2.6%. This was based on assessments during measles outbreaks between 2010 and 2013[19].

Costs

Cost determinants were identified through unpublished data from the DRC-EPI office, reviews of the literature, and interviews with key stakeholders and local health workers.

Vaccine costs

Costs of routine immunization and SIAs were estimated using an *ingredients* approach by assigning a value to each dose of MCV administered through either routine services or an SIA [20]. Costs associated with routine immunization were incorporated into each of the 3 strategies. Injection equipment included the cost of auto-disable syringes and safety boxes. Cold chain costs include vaccine carriers, cold boxes, ice packs, refrigerator parts and fuel. Transportation represented the distribution of vaccines, repair of vehicles, and other logistical considerations between the district, health zone, and health centers. Personnel included health workers and other vaccinators, while stationary represented the use of printing supplies for vaccination documentation.

For vaccine administered through an SIA, additional costs were included to complement the routine immunization program. Social mobilization was divided into personnel (mobilizers) and supplies, which included printed materials, megaphones, and radio announcements. Supervision, planning and training included the use of workshops, meetings, training of staff,

and printing of vaccination tools. Finally, additional costs for personnel and transportation were added because SIAs target hard-to-reach populations generally missed by routine services.

Disease Costs

We estimated the average costs of hospitalization and medical care for measles cases. Information was collected using interviews with local health care workers. Mild cases of measles were estimated at \$30, while cases with complications were estimated at \$110. Severe cases requiring an average 4-day hospital stay were estimated at \$290 including hospitalization and medication costs.

4.4 Results

Cost-Effectiveness

Strategy 2 was the most cost-effective scenario and dominated strategy 1 and 3. Strategy 1 would result in 331,466 measles cases, 13,259 hospitalizations and 8,128 deaths (Table 3). Compared to strategy 1, strategy 2 would prevent a total of 279,110 measles cases, 11,165 hospitalizations, and 6,795 deaths (Table 4). Compared to strategy 1, strategy 3 would prevent a total of 207,996 measles cases, 8,320 hospitalizations, and 5,074 deaths.

A single dose vaccination program (strategy 1) would cost a total of \$11.67 million: \$4.48 million in vaccination costs and \$7.19 million in disease expenses. A vaccination program using strategy 3 would result in \$8.30 million in vaccination costs and \$2.68 million in medical expenses, resulting in a 15-year savings of \$0.69 million compared to strategy 1. A vaccination program using strategy 2 would result in a total of \$7.27 million in vaccination costs and \$1.14 million in disease expenses, resulting in a total savings of \$2.81 million compared to strategy 1. Comparing strategy 2 and strategy 3, strategy 2 would result in a total savings of \$2.12 million and 71,115 measles cases and 1,721 deaths over a 15-year period. Therefore, strategy 2 dominated both other strategies, yielding the fewest deaths at the lowest total program costs.

Sensitivity Analysis

MCV1 Coverage

We performed a sensitivity analysis, varying rates of MCV1 coverage. In all strategies, effectiveness increased with higher rates of MCV1 coverage (Fig 2a). Even with 100% MCV1 coverage, strategy 1 would be unable to provide the measles control that strategy 2 or 3 could achieve with lower MCV1 coverage.

A decrease in MCV1 resulted in increased numbers of measles cases in all 3 strategies. At extremely low MCV1 coverage, the number of cases averted over 15 years would be more than 4,000 with strategy 3 and more than 5,000 with strategy 2.

Wastage Factor

We varied the RI wastage factor from no wastage (1.0) to extreme wastage (6.0) (Fig. 3). As the wastage factor increased, the total vaccination costs increased for both strategies 2 and 3. Strategy 2's total vaccination costs were higher than strategy 3, until the wastage factor reached 3.5, where the two strategies yielded similar costs. In programs with high wastage factors, strategy 3 would result in greater total vaccination costs.

Cold Chain

We measured the impact of varying cold chain costs on both two-dose vaccination strategies. Strategies 2 and 3 yielded similar total vaccination costs when cold chain expenses were less than \$0.25 (Fig. 4) When the cost of the cold chain increased, strategy 2 was associated with lower total vaccination costs compared to strategy 3.

4.5 Discussion

Our results reflect the synergistic effect of two doses of MCV and demonstrate that the most cost-effective approach to measles vaccination in DRC is to continue the administration of the second dose by mass campaign. Vaccination with a single dose of MCV has resulted in substantial reductions in disease incidence and mortality from the pre-vaccination era; however,

countries using a single dose of MCV are required to maintain high levels of vaccine coverage to achieve true herd immunity. While past studies have yielded high benefit-cost ratios from a single MCV dose, our simulations indicated that the number of projected measles cases and deaths were lower with a second dose of MCV by either routine or SIA services when compared to one dose of MCV [16, 21, 22]. The accumulation of susceptibles in areas of low vaccine coverage coupled with a 15% vaccine failure rate at younger ages has resulted in outbreaks worldwide[12]. These outbreaks underscore the importance of a two-dose vaccination program, particularly in DRC, where vaccine coverage remains low.

In DRC, routine immunization remains sub-optimal and the most recent survey estimated coverage at 71.6%[6, 23]. A 2013 serosurvey conducted among children aged 6-59 months indicated that only 66% were seropositive for measles antibodies [unpublished data, DRC Expanded Programme on Immunization, Ministry of Health]. While our assumption of RI (71.6%) and SIA (80%) coverage may represent overestimates, sensitivity analyses with varying RI coverage estimates demonstrated that strategy 2 would prevent more measles cases compared to strategy 3, even with 100% MCV1 coverage (Fig 2b, strategy 3a). When coverage rates for both routine doses were the same, strategy 3 was not as effective in preventing measles cases as strategy 2 until vaccine coverage reached above 85% (Fig 2b, strategy 3b). And with 100% coverage, strategy 1 would never prevent as many measles cases as strategy 3 with 20% vaccine coverage for both doses. WHO recommends that countries with weak routine immunization systems implement targeted SIAs every 3 years to ensure high coverage among new birth cohorts[7]. This strategy should be adopted until RI coverage exceeds 80% in each health zone[24, 25].

In terms of projected advantages, cost savings and/or improved health outcomes, strategy 2 outweighs the projected advantages of strategy 3 [26]. Strategy 2 would result in an estimated savings of \$2.12 million preventing 71,115 measles cases and 1,721 deaths when compared to strategy 3. While our results assumed that SIA vaccine coverage was higher than

RI coverage and offered two opportunities for vaccination up to the age of 5, these are realistic assumptions. During SIAs, children of different age ranges, who may not have access to regular health services, are targeted regardless of their previous vaccination history. These should be implemented every 2-4 years to prevent the build-up of susceptibles[25]. This methodology frequently results in higher vaccine coverage among populations. The Pan American Health Organization (PAHO) has successfully implemented SIAs since the 1990s, which significantly contributed to the elimination of endemic measles in most Latin American countries[27]. The use of SIAs has been adapted to sub-Saharan African countries and may partially explain recent drops in measles cases and deaths in that region[2, 28, 29]. SIAs often incorporate the delivery of other health interventions including vitamin A supplementation, the distribution of deworming medicines, other vaccines, and insecticide-treated bed nets (ITNs)[30]. In DRC, immunization resource allocation is heavily focused on SIAs. SIAs can provide an opportunity to increase community awareness of good health practices and strengthen and build capacity within RI programs through improvements in the cold chain, logistics, and local partnerships with stakeholders[31].

Vaccination program costs include a number of variables, some of which represent more substantial expenses. While one dose of measles vaccine costs only \$0.30, additional vaccine must be available to account for wastage. While we estimated the wastage factor to be 1.14 for SIAs and 3.42 for RI services we found that strategy 3 was only more expensive than strategy 2 when the RI wastage factor was high. When the wastage factor was below 3, strategy 2 resulted in lower vaccination program costs. In countries planning to incorporate the second dose into the routine system, targeting a reduction in RI waste can result in substantial decreases in costs.

A review of the literature suggests a wide range of cold chain costs, thus for the purpose of our analyses, we assumed the cost in DRC to be \$0.57 per dose of vaccine, with an additional \$0.02 per dose during an SIA[32, 33]. Other countries have estimated cold chain

costs to be substantially lower; therefore, our assumption may be an overestimate. However, the limited supply of resources in DRC result in higher costs for the majority of health activities[34]. Our sensitivity analysis demonstrated that reducing cold chain costs could lead to substantial reductions in overall vaccination program costs, especially in strategy 3. In strategy 2, the population is provided with 3 opportunities for vaccination, most of which are provided in the form of SIAs, therefore the reduction in cost was not as prominent in this strategy.

Our analyses are subject to a number of limitations. While our simulations were based on DRC specific costs and probabilities, our data represents a national average. Accurate information on cold chain costs specific to DRC was not available. We included additional costs for transportation and personnel for vaccine administered through SIAs using 2013 EPI budgets, however accessibility across health zones varies and there may be increased costs associated with travel to more remote areas that we were unable to account for. Disease costs were obtained through interviews with local health workers, but the large heterogeneity seen across provinces, health zones, and villages cannot be accounted for in our model. We estimated that 40% of measles cases seek some form of treatment; however, the availability of medications and health services in rural areas is often insufficient and maybe overestimated[6]. We were unable to include all costs associated with measles complications including rare and severe complications such as encephalitis or sub-acute sclerosing panencephalitis, which would have increased the overall disease costs and increased the cost-effectiveness of strategy 2. Moreover, there are a number of additional costs that may be difficult to quantify and include in this analysis. For example, implementation of a vaccination campaign could detract attention and resources from other health programs, leading to inaccurate disease costs.

The model assumes independence of vaccine doses, although they are not independent of each other and there is no specific country-level data to determine the probability of an individual receiving a second dose of vaccine[35]. Additionally, the effect of vaccination on the epidemiology is difficult to model accurately and we were unable to account for the change in

age structure across the 15-year period of analysis, resulting in possible overestimates in the reduction of measles cases and deaths[16]. Our model assumed a closed population, and a dynamic population would introduce new birth cohorts leading to changes in attack rates over time. The higher attack and death rates we utilized throughout the 15-year time period may have resulted in overestimates of measles cases and deaths in each strategy.

Continuing to offer the second dose in the form of an SIA is the most cost effective strategy in DRC and our results mirror that of other studies[16]. SIAs provide, children unable to access routine immunization services, the opportunity to obtain the vaccine, especially in hard-to-reach areas. Regardless of the chosen strategy, targeted efforts focused on reaching previously unvaccinated children are needed to ensure high coverage in RI services and through SIAs.

Figure 4.1: Simplified version of decision tree used to model the cost-effectiveness of three strategies

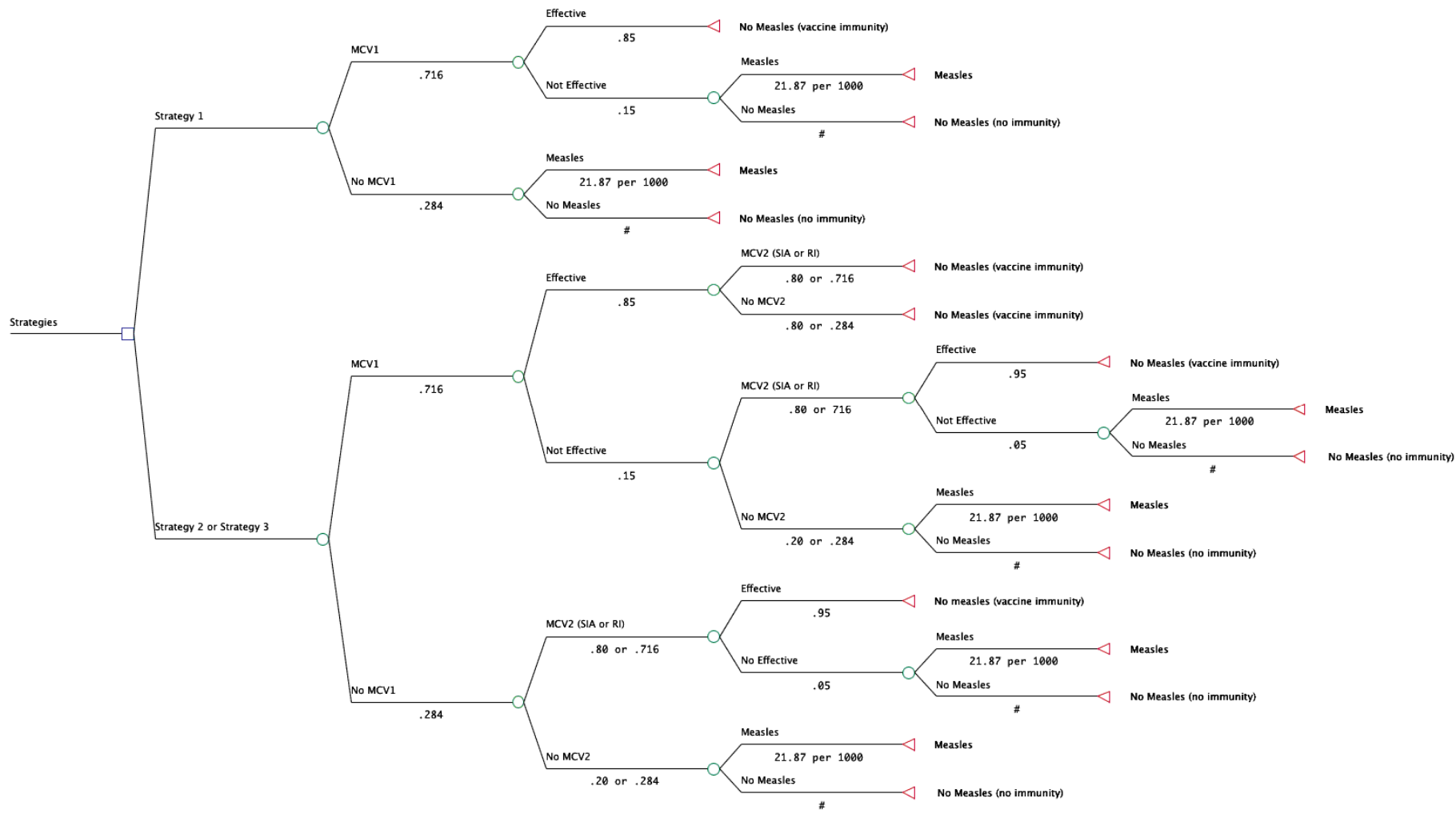


Table 4.1: Variables included in the decision analysis with sources

Variable	Value	Source
Annual birth cohort	3,000,000	[10]
Vaccine Coverage		
Routine	71.6%	[36]
SIAs	80.0%	Assumption
Vaccine Efficacy		
MCV at 9-11 months	85%	[14, 15]
MCV at ≥ 12 months	95%	[14, 15]
Wastage Factor		
RI	3.42	[37]
SIAs	1.15	[38, 39]
Adverse events	5%	[17]
Measles attack rate	21.87 per 1000	[11]
Proportion of cases seeking care ¹	40%	[18]
Hospitalization Rate	10%	Assumption
Duration of hospital stay	4 days	Assumption
Number of Hospital visits	1	Assumption
Case-Fatality ratio	2.7%	[11]

¹Fever, malaria, diarrhea, and respiratory illness reporting rates are were estimated at 40%

²Assumptions are based on surveys of key organizations and health care personnel interviewed throughout DRC

Table 4.2: Vaccination program costs by routine immunization and Supplementary immunization activities

Variables	Cost per Dose	Source
Routine Immunization		
Vaccine w/ freight	.30	[38, 40]
Injection Equipment ^a	.17	[38, 41]
Cold Chain	.57	[33]
Transportation	0.11	[42]
Personnel	0.04	[42]
Stationary	0.02	[39]
<i>Total costs RI</i>	<i>1.21</i>	
Supplementary Immunization Activities		
Transportation	.13	[39]
Cold Chain ^b	.02	[32]
Personnel	.20	[38]
Social Mobilization		
Supplies	0.02	[39]
Personnel	0.03	[39]
Planning/Training	.07	[39]
Supervision	.04	[39]
<i>Total Additional Costs (SIAs)</i>	<i>0.51</i>	

^aInjection equipment includes syringes, biosafety boxes, and measles vaccine diluent

^bCold chain costs for additional support were assumed to be .5 the cost of the RI program

^cTotal costs include routine immunization, additional costs of SIAs through routine system, excluding wastage

^dBased on costs in 2013

Table 4.3: Summary of costs associated with three vaccination strategies^{1, 2}, Democratic Republic of Congo

	Strategy 1	Strategy 2	Strategy 3
No. Of Cases	331,446	52,356	123,470
No. Of Deaths	8,128	1,333	3,054
Hospitalizations	13,259	2,094	4,939
Avg. Hospitalization Days	53,035	8,377	19,755
Avg. number of adverse events	16,572	2,618	6,174
Disease Costs (US\$)			
Hospitalization	3,845,006	607,330	1432,252
General Medication	3,341,177	527,749	1,244,578
<i>Total Disease Costs</i>	<i>7,186,184</i>	<i>1,135,079</i>	<i>2,676,830</i>
Vaccination Costs (US\$)			
Vaccine	2,203,848	3,613,214	4,407,696
Injection Equipment	365,160	1,065,722	727,194
Cold Chain	1,224,360	1,319,842	2,438,239
Transport	236,280	689,583	470,537
Personnel	85,920	250,758	171,105
Stationary	365,160	125,379	85,552
SIA social mobilization	0	206,048	0
SIA supervision	0	164,838	0
SIA planning/training	0	288,467	0
<i>Total Vaccination Costs</i>	<i>4,480,728</i>	<i>7,273,851</i>	<i>8,300,323</i>
Total Costs	\$11,666,911	\$8,858,930	\$10,977,153

¹Strategy 1: one dose at 9 to 11 months old, Strategy 2: MCV1 through RI services, MCV2 through SIA, Strategy 3: two doses

²All costs were rounded to the nearest dollar

Table 4.4: Results of the cost-effectiveness analysis comparing strategies 2 and 3 to strategies 1 over 15 years

Strategy	Costs in 2013 (US\$)				Effectiveness				
	Disease Costs	Vaccination Costs	Total (Disease + Vaccination)	Additional costs	Measles Cases	Cases prevented	Measles Deaths	Deaths prevented	QALYs
1	7,186,183	4,480,728	11,666,911	0	331,466	0	8,128	0	36,158,596
2	1,135,078	7,273,853	8,858,930	-2,807,981	52,356	279,110	1,333	6,795	36,306,214
3	2,676,830	8,300,323	10,977,153	-689,758	123,470	207,996	3,054	5,074	36,269,745

Figure 4.2: Cost-effectiveness analysis graph, strategies 1-3

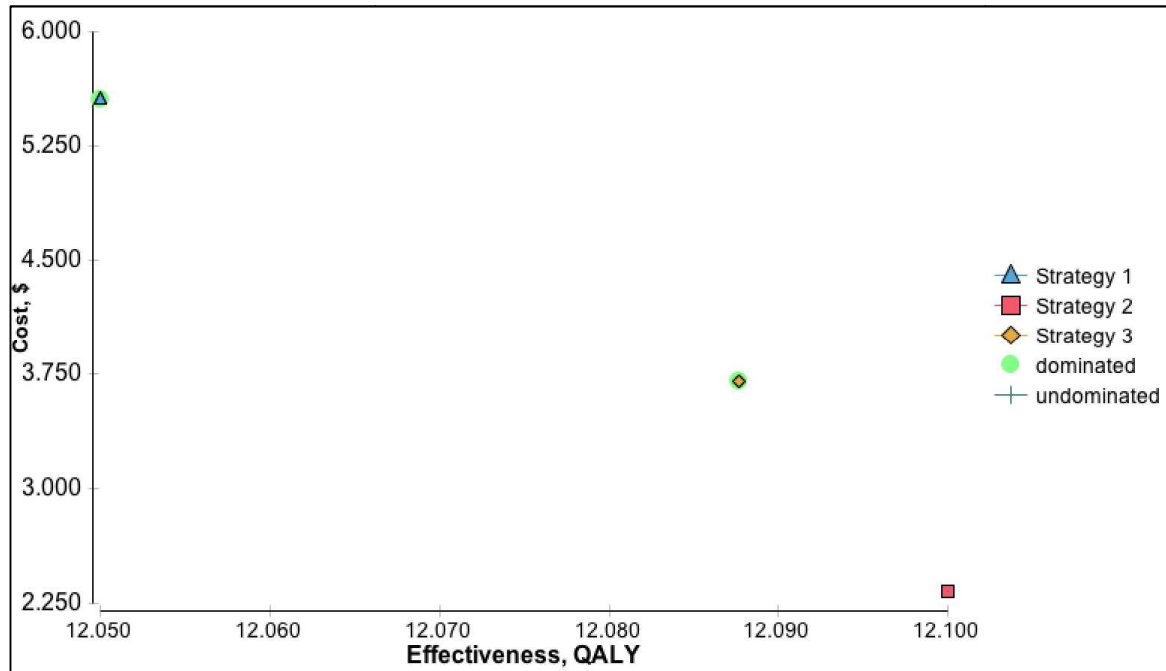
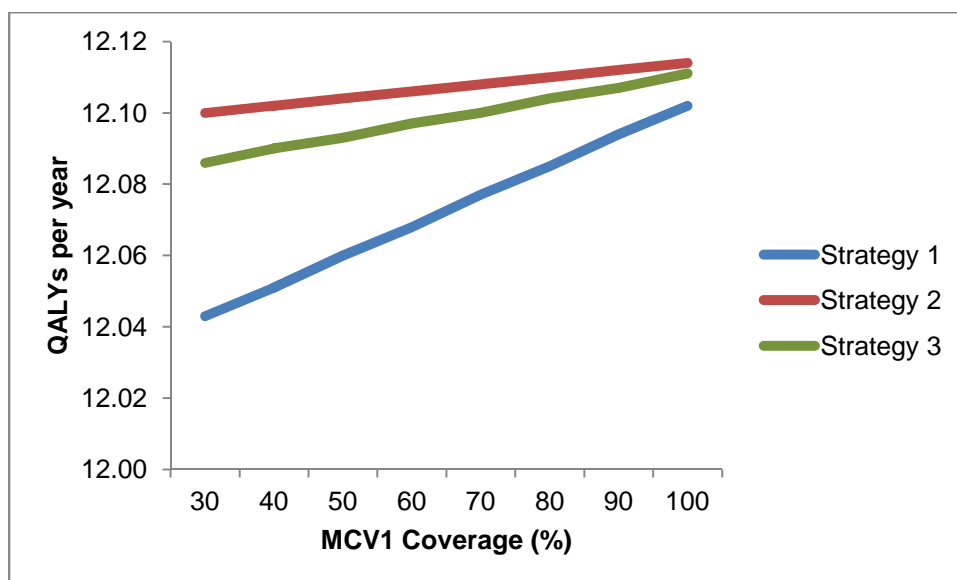
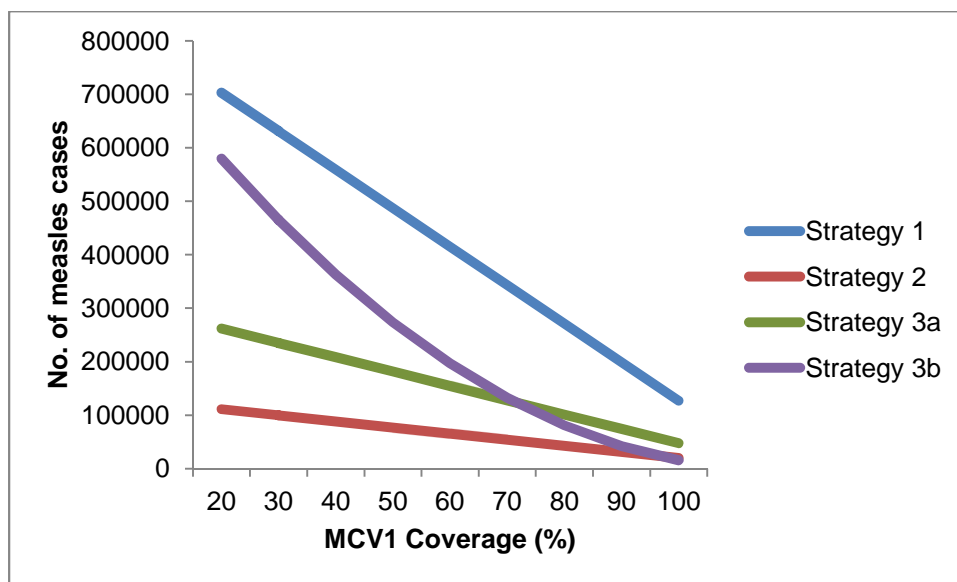


Figure 4.3: Sensitivity analysis with varying rates of MCV1 coverage

a) Sensitivity analysis with MCV1 and Effectiveness (QALYs per year)



b) Sensitivity analysis with MCV1 and projected measles cases



¹ Strategy 3a: MCV1 coverage rates varied, strategy 3b: MCV1 and MCV2 rates are always the same value and varied together

Figure 4.4: Sensitivity analysis with varying routine immunization wastage factor

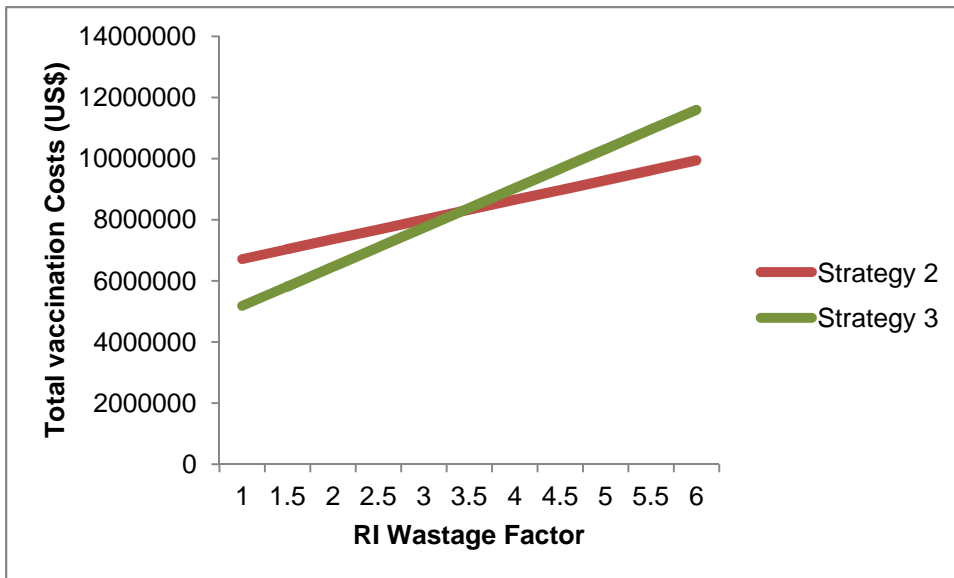
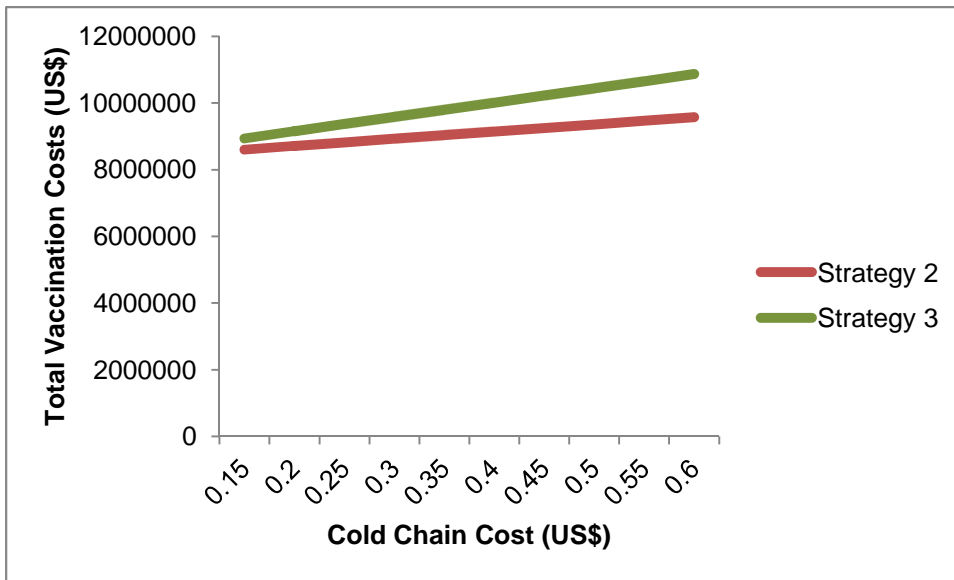


Figure 4.5: Sensitivity Analysis with varying cost of the routine immunization cold chain



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Chapter 5. Conclusions and Implications

5.1 Conclusion

Measles is one of the most contagious diseases and continues to be an important cause of vaccine preventable disease death in DRC. In the last 10 years the country has seen tremendous improvements in immunization coverage, which have led to significant reductions in measles mortality.

After the number of measles cases reached a historic low in 2009, the country experienced outbreaks in all 11 provinces, beginning at the end of 2010. A majority of the cases were children under 5 years of age, suggesting continuous measles endemicity[1]. Analyses of this period of outbreak magnify the country's weak immunization program. Lack of health infrastructure, poor access to care, and political instability, have led to a long history of low immunization coverage. While, DRC's national administrative coverage was 88%, recent surveys suggest that DRC's measles RI coverage is grossly overestimated[2]. The Multiple Indicator Cluster Survey (MICS) 2010 estimated measles coverage at 67% and the most recent Demographic and Health Survey (DHS), conducted in 2013, estimated coverage at 71.6%[3, 4]. A 2013 serosurvey conducted on children aged 6-59 months indicated that only 66% were seropositive for measles antibodies [unpublished data]. Given this coverage, it is likely that older children and adults are likely to be protected by natural measles from past exposure to circulating measles[1].

Our analyses indicate that measles immunization in DRC is associated with a decrease in incidence specifically in zones with mass campaigns in the year before incidence was measured. These results highlight the importance of frequent SIAs in a resource-limited setting, where the routine immunization system is poor. Postponed SIAs led to 4 to 5 year gaps between campaigns and were unable to provide sustained immunity to those not accessing routine health services[2]. Our cost-effective analysis

highlighted the ability of mass campaigns to reach more children and avert more measles cases and deaths over a 15-year period.

In addition, vaccine effectiveness (VE) is lower than the expected 95%, which is likely a function of DRC's routine immunization program[5]. A weak immunization program leads to difficulties in monitoring and maintaining an effective cold chain. Furthermore, complications such as heavy rain, limited transportation, and inadequate roads make a large majority of the country inaccessible. Logistical challenges compounded by high malnutrition rates and endemic malaria throughout the country may partially explain reduced VE.

In order to achieve measles elimination by 2020, DRC must achieve and maintain high levels of population immunity through two doses of MCV. Efforts should focus on building capacity within the routine immunization program. A strong well-functioning routine immunization program will complement the rolling SIA's, which must be conducted every two years to ensure high levels of immunity.

Measles elimination will depend on the ability to monitor disease effectively through a strong surveillance program[6, 7]. Currently, a large number of health centers are not required to report to the national system. Incorporation of traditional healers and private clinics will be needed to identify all cases of measles before the disease spreads to neighboring villages and towns. Strengthening data collection methodology by reviews of health registers and monitoring data completeness could be applied in future responses to ensure the most effective strategy. Outbreak preparedness will provide the ability to respond and contain measles outbreaks before they spiral out of control.

Finally, increasing population level immunity will require community involvement. Building public confidence and demand for immunization services by strengthening advocacy, communication, and social mobilization, as well as building trust in local health workers will enhance participation in immunization programs[7].

Large-scale outbreaks in DRC demonstrate the virus's ability to easily re-enter communities lacking sustained levels of population immunity[8]. Preventing another measles resurgence will require reaching $\geq 95\%$ of all children. While, WHO does not recommend introducing a second dose of MCV into the routine immunization schedule in countries with low RI coverage, frequent well conducted SIAs throughout the country will ensure high measles immunity. And mass campaigns are certainly the most cost-effective way to prevent future measles outbreaks [9-11]. Heavily monitored program scale-up and financial commitment will be essential as we push forward, toward measles elimination goals.

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