Title
Prevention and control of yellow fever in the Democratic Republic of Congo: lessons learned from a recent outbreak

Author
Ghanem-Uzqueda, Angie

Publication Date
2020

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Prevention and control of yellow fever in the Democratic Republic of Congo: lessons learned from a recent outbreak

A dissertation submitted in partial satisfaction

of the requirements for the degree

Doctor of Philosophy in Epidemiology

by

Angie Ghanem-Uzqueda

2020

ABSTRACT OF THE DISSERTATION

Prevention and control of yellow fever in the

Democratic Republic of Congo: lessons learned from a recent outbreak

by

Angie Ghanem-Uzqueda

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2020

Professor Anne W. Rimoin, Chair

Yellow fever is a vaccine-preventable acute viral hemorrhagic disease. Children are vaccinated in the Democratic Republic of Congo (DRC), beginning at nine months. Yellow fever transmission can also be prevented through mosquito control and bite prevention. Nonetheless, there was an outbreak of yellow fever in DRC in 2016. The potential for yellow fever outbreaks persists due to an abundance of mosquitos and immunity gaps. Costly and logistically challenging vaccination campaigns are often needed once an outbreak is detected.

This research aims to use diverse methodologies to examine the background situation and risk factors of the 2016 DRC yellow fever outbreak and identify opportunities to effectively mitigate or prevent future outbreaks. Chapter 1 provides background about the virus, transmission, epidemiology, prevention, and health infrastructure in DRC. Chapter 2 explores the

level of childhood yellow fever vaccination in DRC, identifies demographic and behavioral factors associated with vaccination, and geographic differences in yellow fever vaccination in DRC using the Demographic and Health Survey (DHS). Vaccination coverage varied by the source of information (69.9% to 82.9%). Maternal factors, like antenatal and postnatal care and delivery at a government or public facility, were influential for childhood vaccination. Understanding these factors, specifically for yellow fever in DRC, can help guide immunization efforts. Chapter 3 identifies spatial patterns in reported yellow fever cases and analyzes the spatial relationship between sociodemographic, environmental, and organizational risk factors and yellow fever using statistical and spatial analyses. Reported yellow fever cases were clustered among certain health zones in DRC, and several factors may be associated with reported cases. Chapter 4 approximates the outbreak using a mathematical model to evaluate interventions. Many resources are needed for outbreak response, so it may be most useful to strengthen the health delivery system and integrate widespread interventions before an outbreak, which establishes capacity to detect and respond to all outbreaks.

These studies bring much-needed attention to the outbreak of yellow fever in DRC and highlight potential deficiencies in immunity, factors that may contribute to increased transmission and where cases are reported, and how outbreaks can be prevented by investing in a comprehensive disease prevention infrastructure.

The dissertation of Angie Ghanem-Uzqueda is approved.

Robert J. Kim-Farley

James O. Lloyd-Smith

Roch Arnaud Kibsa Nianogo

Anne W. Rimoin, Committee Chair

University of California, Los Angeles

2020

DEDICATION

To my family and framily, I would not have made it through this wild ride without your tremendous support

Table of Contents

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENTS

I would like to thank my advisor, Dr. Anne Rimoin, for giving me the opportunity to research emerging and reemerging diseases in the DRC and for reminding me to focus on the public health impact of my research.

Thank you to my committee mentors, Dr. Robert Kim-Farley, Dr. Roch Nianogo, and Dr. Jamie Lloyd-Smith, you have each been essential to the completion of this dissertation and I have learned so much from each of you, I'm grateful you were on my committee, and to my non-committee mentors, Dr. Sudipto Banerjee, for patiently guiding me through spatial analysis, and Dr. Eric Mossel for your insight about yellow fever, feedback, and support of my research.

A special thanks to the researchers and survey teams affiliated with UCLA-DRC, Kinshasa School of Public Health, INRB, and the Ministry of Health in DRC, some I have met but most I have not, for your efforts in collecting such useful information and allowing me to use it for my research.

Immense thanks to my parents, brothers, and sisters, for the endless support and encouraging words, to my framily, who only thought I was a little crazy for deciding to go back to school but smiled and cheered every step of the way (thanks for being there for me, Nazie and Christina, through everything), and to Riley, for being my partner and support at UCLA, my R guru, and disease modeling tutor, but mostly for always being the kindest person and a truly incredible friend!

Last, but certainly not least, to my husband, Marvin, who had no idea what he was getting himself into but has never stopped supporting me through the highs and lows, early mornings, late nights, and long working weekends of this degree. Thank you for being the best partner ever. I love you.

VITA

May 2006	Bachelor of Arts, Public Health University of California, Berkeley Berkeley, CA
May 2007 – October 2008	Program Assistant University of California, San Diego San Diego, CA
August 2010	Master of Public Health, Epidemiology San Diego State University San Diego, CA
November 2010 – May 2013	Infection Preventionist St. Vincent Medical Center Los Angeles, CA
August 2012 – Present	Certification in Infection Control (CIC) Certification Board in Infection Control and Epidemiology
June 2013 – Present	Infection Preventionist Keck Medicine of USC (Keck Hospital of USC and USC Verdugo Hills Hospital) Los Angeles, CA
September 2017 – June 2018	Graduate Research Mentorship Award University of California, Los Angeles Los Angeles, CA
April 2018 – June 2018	Teaching Assistant, Epidemiology Methods III: Analysis University of California, Los Angeles Los Angeles, CA
September 2018 – June 2020	Teaching Fellow and Spring Seminar Instructor, Biotechnology and Society Freshman Cluster University of California, Los Angeles Los Angeles, CA
June 2020 – Present	Delta Omega Honor Society in Public Health

PUBLICATIONS AND PRESENTATIONS

Garfein RS, Metzner M, Cuevas J, **Ghanem A**, Patterson T. Avoiding Risks from Meth Use: A Modular Intervention to Decrease HIV-related Risk Behaviors Among Methamphetamine-Using Men Who Have Sex with Men. National STD Prevention Conference Poster Presentation. March 2010.

Ghanem A, Little S, Liu L, Morris S, Garfein RS. Injection drug use among men who have sex with men. American Psychological Association Convention Oral Presentation. August 2010.

Ghanem A, Little SJ, Drumright L, Liu L, Morris S, Garfein RS. High-Risk Behaviors Associated with Injection Drug Use among HIV-Infected Men Who Have Sex with Men in San Diego, CA. AIDS Behav. 2011 Oct; 15(7):1561-9.

Artime C, Basconcillo A, Caceres L, Dalaly L, **Ghanem A**, Moser M. Clean or Not Clean Is the Question: Improving Patients' Perceptions of Environmental Cleanliness During Hospitalization. Association of Professionals in Infection Control and Epidemiology Annual Conference Poster Presentation. American Journal of Infection Control, Volume 42, Issue 6, S88 - S89.

Ghanem A, Artime C, Moser M, Caceres L, Basconcillo A. Holy Moley! Take Out That Foley! Measuring Compliance with a Nurse Driven Protocol for Foley Catheter Removal to Decrease Utilization. Association of Professionals in Infection Control and Epidemiology Annual Conference Poster Presentation. American Journal of Infection Control, Volume 43, Issue 6, S51.

Ghanem A, Hall S, Cologne, K, Nanda N. Enhanced colorectal surgery bundle to reduce surgical site infections. ID Week Conference Poster Presentation. October 2017.

Ghanem A, Hoff N, Sinai C, Musene K, Mukadi P, Ngoie Mwamba G, Kebella-Illunga B, Okitolonda E, Rimoin A. Health facility cold chain capacity for administering vaccines in the Democratic Republic of Congo. ASTMH Annual Meeting Poster Presentation. October 2018.

Alfonso VH, Bratcher A, Ashbaugh H, Doshi R, Gadoth A, Hoff N, Mukadi P, **Ghanem A**, Cheng A, Gerber S, Mwamba GN, et al. Changes in childhood vaccination coverage over time in the Democratic Republic of the Congo. PloS one. 2019 May 24;14(5):e0217426.

Chapter 1: Introduction and Background

Although infectious diseases now contribute to less morbidity and mortality in the United States, they still play a prominent role globally. Emerging infectious diseases (EIDs) are diseases that have newly appeared in a population or have existed but have reemerged to cause new outbreaks and increased disease burden. This is a result of pathogens being introduced into a new population from the environment, another species, or adapting from an existing human infection, then establishing further transmission within that new population.[1] A study of 335 infectious diseases from 1940 to 2004 found that the number of EID events caused by pathogens originating in wildlife (zoonotic) has increased significantly over time. Furthermore, studies estimate that zoonotic pathogens cause the majority of EID events (60%[2] - 75%[3]). Vector-borne pathogens, such as those transmitted by mosquitos, are also the most likely to be emerging.[3] As a result, zoonotic EIDs, especially those transmitted by a vector, represent an increasing and significant global health problem. In order to address EIDs, there are three factors to consider: 1) ensuring prevention strategies are implemented and public health information is effectively communicated to prevent new outbreaks, 2) earlier detection and enhanced surveillance to investigate and monitor EIDs, and 3) comprehensive response to prevent further widespread transmission. Emerging and reemerging vector-borne pathogens, such as yellow fever, are especially important public health targets globally. Yellow fever has been causing outbreaks of disease since the 15th century. Despite having several methods to prevent and control yellow fever effectively, it is still classified as a reemerging disease. Ensuring adequate use of prevention strategies and preparedness for outbreaks can significantly limit morbidity and mortality from yellow fever and other EIDs. The central purpose of this research is to use diverse methodologies to examine the background situation and contributing factors to a recent yellow

fever outbreak in the Democratic Republic of Congo (DRC) and identify opportunities to prevent future outbreaks or mitigate them more effectively.

1.1 Yellow fever background

Yellow fever is an acute viral hemorrhagic disease caused by the yellow fever virus, the prototype member of the genus *Flavivirus*, a family of positive-strand, single-strand RNA viruses, the majority of which are transmitted by mosquitoes or ticks and cause viral hemorrhagic fevers.[4] Yellow fever was one of the earliest viruses to be linked to human disease and was one of the most feared of epidemic diseases in the 15th to 19th centuries when large outbreaks occurred in port cities of North and South America, Africa, and Europe even prompting American colonies to refuse entry of ships from infected areas.[5,6] Shortly after Walter Reed discovered that yellow fever was transmitted among humans by the Aedes aegypti mosquito, it was successfully controlled in Cuba by destroying larval breeding sites. Mosquito eradication campaigns continued throughout the Americas and succeeded in reducing vector populations to almost undetectable levels.[6] The yellow fever vaccine was later developed in the 1930s, which changed the face of control efforts. Vaccination campaigns almost eliminated urban yellow fever transmission. Despite these efforts, yellow fever is still considered a reemerging disease and remains associated with significant morbidity and mortality, especially in parts of Africa. Incomplete vaccination coverage and incomplete vector control allows the virus to persist and outbreaks still occur.[6]

Despite this long history of the disease, the transmissibility of yellow fever has not been extensively studied mainly because the disease often occurs in rural parts of the world, however, most of what is known is based on an extensive description of the clinical course of the disease.

The incubation period after an initial infected bite is typically 3-6 days.[7] Most infected individuals develop only mild non-specific symptoms in the initial phase of the disease when the virus is present in the blood, such as fever, muscle pain, loss of appetite, nausea or vomiting, or asymptomatic. An individual may serve as a source of infection for mosquitos during this time.[7] Initial symptoms, if any, usually subside after approximately 2-6 days. After a brief period of symptom improvement, approximately 15-25% of individuals progress to a more severe form of the disease ("period of intoxication") which includes the signature symptoms such as high fever, liver and kidney failure leading to jaundice, dark urine, abdominal pain with vomiting, and bleeding that can occur from the mouth, nose, eyes, or stomach. During this severe phase, antibodies appear in the blood and the virus disappears.[4,7,8] Approximately 20-50% of patients who have severe symptoms die within 7-10 days.[4] Figure 1.1 from Monath (2001) outlines the clinical course of the disease and highlights the duration of different disease stages and the early viremic stage.[7]

1.2 Yellow fever transmission

Yellow fever is transmitted by infected mosquitoes, primarily the Aedes or Haemoagogus species.[9] Yellow fever has three transmission cycles: jungle/sylvatic (transmission of the virus between non-human primates, mosquitos, and humans visiting the jungle), intermediate/savannah in Africa (transmission between mosquitos and non-human primates and humans living or working in jungle border areas), and the urban cycle (transmission only between humans and urban mosquitos once the virus is brought to urban areas by an infected human) (Figure 1.2).[10]

The sylvatic transmission cycle facilitates ongoing transmission between non-human primates and mosquitos and places humans at continuous risk of infection in the absence of vaccination and other protective behavior.[11] The urban transmission cycle is responsible for most recent outbreaks of yellow fever in Africa and is, therefore, the most concerning from a public health perspective.[6,12]

1.3 Risk factors of yellow fever infection

Unprotected exposure of an unvaccinated individual to mosquitoes in an endemic area is the major risk factor for yellow fever. Mosquito burden is mediated mainly by environmental and geographic factors, such as climate.[13] Severe or prolonged rainy seasons are associated with increased numbers of vectors and may be implicated in increased transmission.[4] The dry season in DRC generally only lasts from June to August, leaving the rest of the year to support the breeding of mosquitos during the rainy season (September to May).[14] The *Aedes* mosquito is capable of breeding in small amounts of water that accumulates in artificial containers inside or near dwellings or in natural reservoirs such as tree holes. This is especially exacerbated in urban areas where overcrowding is possible and low-income housing, inadequate water supply, and poor sanitation and waste removal practices result in open containers becoming inadvertently filled with rainwater (or intentionally used to store drinking water) and serve as breeding sites for mosquitos.[15] This, along with overcrowding and limited health facilities, helps support disease transmission on resulting outbreaks in urban settings.[4,13] These mosquito breeding opportunities and the fact that vertical transmission can occur in mosquitoes allow yellow fever to persist through the dry season in countries with a high vector burden.[4]

Certain ecosystems also support vector abundance such as the low-lying rain forests and forest-savanna ecotones in both South America and Africa.[4] One study showed that deforestation, especially for agricultural use or cattle grazing, may be associated with increased ground-level biting activity of previous canopy-dwelling vectors, subsequent yellow fever cases and potential outbreaks.[4] Land use changes in general may reduce the availability of mosquito breeding sites in tree holes or reduce populations of non-human primates altering yellow fever exposure potential.[16] Farming, woodcutting, bush clearing and other human activities such as washing and bathing in rivers or collecting water from rivers for domestic purposes, travel, and commerce may also increase exposure opportunities.[13]s

Mosquito and human population size and density determine exposure rates contributing to urban outbreaks and rapid transmission.[16,17] The rate of urban growth in Africa is the most rapid in the world and it is estimated that the proportion of urban populations will reach 63% by 2020.[15] Increasingly dense urban populations and lower than desired immunization rates result in an increased chance of virus transmission. Yellow fever risk is also dynamic as a result of many of the factors mentioned. Changes in climate, abnormal rainfall that deviates from standard patterns, and human factors, such as migration and air travel, can change yellow fever risk over time.[16] Studies that have estimated yellow fever risk and burden consider factors such as rainfall, surface or air temperature, vegetation index, land cover classification, longitude, latitude, and altitude typically based on satellite imagery as well as existing patterns of cases to create global risk maps.[6,16–18]

1.4 Yellow fever vaccine and other prevention measures

There is no specific antiviral treatment for yellow fever, however, new infections and outbreaks of widespread transmission of yellow fever can be prevented. The current yellow fever vaccine is especially effective[9] and is part of the childhood vaccination schedule in several countries in Africa, including the DRC which began vaccinating all children at nine months of age in 2003.[19] Routine immunization occurs throughout the country, however, the schedule for yellow fever is distinct from most other vaccines and requires contact with the health care system specifically for the measles and yellow fever vaccine (Table 1.1).

The vaccine is a live-attenuated virus vaccine that has been available since the 1930s and officially replaced a previous version of the vaccine in the 1980s. It is recommended for people aged nine months or older with a few exceptions, such as individuals with allergies to components of the vaccine, organ transplant recipients, and individuals with immune system disorders or deficiencies.[20] The seroconversion rate is greater than 91% and no lower than 81% in most uncontrolled studies. Furthermore, 90% of subjects seroconverted within ten days and 100% within 14 days in two separate clinical trials.[21] Seroconversion was observed in 98.6% of individuals who were given the UK manufactured and in 99.3% of those who were given the US manufactured vaccine in a randomized, double-blind outpatient study of 1,440 healthy adults comparing the two manufacturers of the yellow fever vaccine.[22]

In 2015, the CDC Advisory Committee on Immunization Practices and the World Health Organization issued new recommendations that a single dose of the vaccine provides long-lasting protection, although some countries at increased risk for yellow fever still require a booster dose every ten years.[20] However, some recent studies have indicated that seroconversion among children may be lower than in adults (approximately 86-95% depending on age group and brand

of vaccine[23]), especially among children who received the vaccination against measles, mumps, and rubella at the same time (69% with MMR).[24] Furthermore, a recent study from DRC estimated the seroprevalences of neutralizing antibodies against yellow fever to be as low as 6.0% (95% confidence interval [CI] = 4.6–7.5%); much lower than expected based on the yellow fever vaccine schedule. The authors also established that results from both ELISA and neutralization tests correlated poorly with reported vaccine history on vaccine cards using the Demographic and Health Survey (DHS).[25] These findings may be potentially attributed to inaccurate vaccine cards or idiopathic lack of seroconversion in children in the DRC.

The yellow fever vaccine must be stored between 2 to 8ºC (35-46ºF) and never frozen. The half-life is reduced from approximately 14 days when stored at 35ºF to 37ºF to 3-4.5 days when stored at a slightly higher temperature of 45ºF to 47ºF.[21] Furthermore, the shelf-life of the vaccine was found to be approximately three years and potency is maintained if stored at 4ºC continuously.[26] It has long been recognized that factors such as temperature, repeated freezing and thawing, and exposure to light have adverse effects on the stability of vaccines.[27] To ensure that a vaccination campaign is effective and efficient, vaccines must be stored properly from the time they are manufactured until they are administered. Exposure to temperatures outside the recommended ranges can reduce vaccine potency and increase the risk that the recipient will not actually be protected from the vaccine-preventable disease. The system that ensures these proper temperatures are maintained is known as the cold chain and it has three main components: transport and storage of equipment, trained personnel, and efficient management procedures.[28] A malfunctioning cold chain can result in vaccine waste and unnecessary costs as well as unintentional human harm.

Problems with the cold chain have been implicated in outbreaks of vaccine-preventable disease but few studies have examined this issue, especially not in the DRC. Studies in other African countries such as Nigeria, the setting of large yellow fever outbreaks in the 1970s and 80s,[29–31] have investigated factors associated with vaccine handling and storage and found that knowledge and practice gaps existed despite training and that the most common barriers to effective vaccine handling were related to electricity and refrigerator availability.[32] In another study, only 53% of vaccines tested met the WHO recommended virus titer level for a potent measles vaccine and vaccines were found to be less potent than expected despite being far from the expiration date.[33] In Ethiopia, health facilities were found to be lacking temperature recordings and vaccine storage was not proper, putting vaccines at risk for losing potency before they reach the community.[34] In Cameroon, 20% of surveyed health facilities with functioning thermometers had abnormal temperature readings at the time of the survey and 24% had recorded abnormal readings within two months. The absence of an alternative power source was a predictor of having abnormal temperature readings.[35] Cold chain deficiencies may be ubiquitous in Africa and a substantial barrier to effective vaccination campaigns.

Other yellow fever prevention methods include mosquito control efforts such as eliminating potential breeding sites using larvicides and insecticide spraying to kill adult mosquitoes.[9] Individuals can use methods to avoid mosquito bites such as using insect repellant and wearing long sleeve or insecticide-treated clothing. The *Aedes aegypti* mosquito feeds during the daytime, therefore caution from early daytime hours until the evening is essential for bite prevention.[36] In conjunction with vaccination, these methods can further reduce the risk of infection, especially in areas where vaccination coverage may be low or in populations that are hard to target with vaccination campaigns such as marginalized and vulnerable populations.

1.5 Predictors of vaccination in DRC and throughout Africa

Estimates of yellow fever vaccination in DRC vary by source. The WHO and UNICEF estimate that coverage for yellow fever vaccination was approximately 66% in 2015, 67% in 2016, and 76% in 2017. These estimates are slightly lower than the official estimates (as reported by national authorities reflecting a combination of administrative coverage, survey-based data and other data sources) of 88% in 2015, 78% in 2016, and 87% in 2017. However, the WHO/UNICEF estimates demonstrate a low grade of confidence in the data since there is no direct supporting data for these estimates.[37] Additionally, Shearer et al. estimated that children in DRC (less than age 14) were 50-70% vaccinated (depending on specific age group), however after age 15 the vaccination coverage is estimated at approximately 10-20% with overall vaccination between 30-40%. Furthermore, depending on simulated vaccination campaign strategies from optimistic to conservative, anywhere from 30.3 to 34.9 million people would need to be vaccinated in 2016 to achieve the 80% WHO coverage goal. DRC had the fifth highest population needing vaccination in Africa in their estimates and simulations.[38]

As mentioned, improving vaccination coverage is an essential tool for preventing outbreaks of yellow fever. Identifying factors that can be modified or targeted for intervention can provide opportunities to improve baseline vaccination coverage and allow for more efficient vaccination campaigns outside of routine programs. Few studies have assessed predictors of yellow fever vaccination in DRC or other parts of Africa. However, information can be gleaned from studies of other routine immunizations or immunization in general, which are becoming prevalent among African countries. In Eastern DRC, all children under five years of age who were found to have an incomplete immunization status had not received the measles and yellow fever vaccine. Child and parental factors were determinants of incomplete immunization,

including the child's age and gender, school status, the parent's education (literacy) level, marital status, and the mother's age.[39] In a household survey in 12 high-risk health zones in Kinshasa Province, DRC, 71% of children were up to date with all vaccinations for their age and 84% had received the yellow fever vaccine. Factors associated with access to a health facility and length of time in the residence were associated with differences in being up to date for all vaccinations appropriate for the child's age.[40] A recent study in DRC found that immunization coverage varied by province and that higher maternal education and richest wealth quintile along with modifiable factors such as antenatal care, delivery location, and postnatal visits all had a positive effect on full immunization with BCG, DPT, polio, and measles vaccine. Maternal autonomy, exposure to mass media, occupation, and rate of institutional delivery were also investigated.[41] Lastly, predictors of measles vaccination in the DHS survey among children 6-59 months consisted mainly of socioeconomic and geographic aspects where children in urban areas born to educated mothers were more likely to have received their vaccine. Differences were also observed by birth order in the family.[42]

A few studies have examined adherence to the vaccination schedule and timely vaccination in Burkina Faso. Factors such as mothers' education, poverty, seasonality of birth (where children born in the dry season were less likely to have timely vaccination), and geography were associated with timely vaccination, however, urban children were less likely to have timely vaccination for some vaccines and vaccination coverage of the core vaccinations by 12 months of age, possibly a result of enhanced outreach programs in rural areas.[43,44] Overall, timely adherence to vaccines varied by the type of vaccine from 46% for measles to 70% for BCG and adherence to the yellow fever vaccine was not reported.[43] Similarly, timely vaccination was a more significant problem than overall 1-year coverage in a study from Ghana except for

measles/yellow fever, which showed one of the only differences in overall coverage at one year. There were also differences among all socioeconomic factors, such as SES, level of education, and urban/rural status, in terms of vaccine timeliness.[45] Mother's age, marital status, religion, and child's sex were associated with complete vaccination in another Ghanaian study.[46] Overall maternal education level, maternal knowledge specifically regarding vaccination, retention of immunization cards, as well as receiving vaccines at a privately funded and supported health center were all predictors of complete and timely vaccination in Nigeria.[47] In an assessment of 13 countries in West Africa, full immunization was defined as receiving BCG, the full course of DPT and OPV vaccines, and the measles vaccine. Maternal education, delivery at a health facility, having a vaccine card, and recent visits to a health facility post-delivery were common predictors of complete vaccination among the countries. Additionally, as much as 20% drop out was observed between the first DPT vaccine and the measles vaccine among children 12-23 months.[48] Maternal occupation (being a government employee) has also been found to be a predictor of full vaccination in Nigeria and if the child was born in a government hospital. Furthermore, maternal knowledge of the vaccine schedule for children helped ensure full vaccination with BCG, Hepatitis B, measles, yellow fever, the four doses of OPV, and three does of pentavalent vaccine. .[49]

Several studies have used multilevel logistic regression models to elucidate both individual and community-level factors associated with immunization. A prospective cohort study in six clinics in Kinshasa found that geographic location (i.e., the clinic visited) was strongly associated with incomplete and untimely immunization specifically the tuberculosis, polio, and diphtheria, pertussis, and tetanus vaccines. Furthermore, maternal education level and socioeconomic status were predictive of complete and timely immunization.[50] One study used

the Demographic and Health Survey (DHS) data from 24 countries in sub-Saharan Africa, including the 2007 DRC survey, and uncovered similar findings where child's age, mother's age, wealth index, and parental education as well as geography and illiteracy rate in the area were associated with child immunization. However, they also found significant variation across countries and communities, so more country-specific assessments would further elucidate these findings.[51] Another multilevel analysis of individual and contextual factors in Togo found that mothers' education, household income, having an immunization card, parent's knowledge that immunizations were free of charge, and shorter distances required to walk to a healthcare center all decreased the likelihood of incomplete immunization coverage.[52] Being born in a health facility, higher maternal education, exposure to mass media, fewer children in the household aged less than five years, as well as residing in a community with higher utilization of maternal antenatal care services were associated with full immunization in a multilevel assessment of individual and community level determinants using the Ethiopian DHS data.[53]

In a review of low and middle-income countries, issues associated with the immunization system, like poor access and distance, vaccine supply, availability and knowledge of health care workers, were found to be associated with non-vaccination and under-vaccination in 32% and 45%, respectively, of the studies, examined. Parental attitude and knowledge contributed more to non-vaccination than under-vaccination.[54] Caretakers knowledge about vaccines and vaccine-preventable diseases and attitudes towards vaccination are also important factors associated with vaccination coverage[55,56]

These studies, taken together, indicate that there are identifiable predictors of immunization, some that can be targets of interventions. Clarifying these factors, specifically for

yellow fever in DRC, can help guide immunization efforts to prevent future outbreaks and improve protection against this vaccine-preventable disease.

1.6 Yellow fever epidemiology and global distribution

Yellow fever had a major burden on global health in the 18th to 20th Centuries, but the introduction of the vaccine through routine immunization of children and various mass vaccination and catch-up campaigns helped control the disease in many countries.[4,12] Now it is endemic in all or parts of 34 countries in Africa where 90% of cases are reported, including the DRC, and tropical parts of South America with over 50 countries worldwide at risk.[12] Forty-four countries in Africa, South and Central America are considered part of the modern yellow fever endemic zone and almost 900 million people are at risk of infection.[57] Yellow fever is currently the only infectious disease that requires proof of vaccination for travelers from or into endemic areas under the WHO International Health Regulations due to its high potential to spread to other areas with the A. aegypti mosquito and cause outbreaks.[58]

Estimates of the burden of yellow fever vary by source; anywhere from 5,000 to 200,000 cases annually have been reported in the tropical regions of Africa, South America, and Central America.[7–9,57] Early symptoms of yellow fever are mild and non-specific and many individuals remain asymptomatic, making yellow fever challenging to diagnose. Additionally, cases often occur in rural areas, so reported cases collected through passive surveillance likely greatly underestimate the true incidence.[4] WHO reported 1,111 reported cases in 2016, which represents a substantial increase over previous years, but a modeling study based on African data sources estimated 84,000–170,000 severe cases and 29,000–60,000 deaths in 2013.[9]

The sylvatic transmission cycle sustains sporadic cases of yellow fever, usually in male forestry workers, in the tropical rainforests of Africa and South America where the virus can be transmitted between local species of monkeys and humans by mosquitoes found in the forest.[57] Since the 1980s, sporadic outbreaks of yellow fever have occurred throughout Africa and South America, including in Nigeria, which had numerous cases in several outbreaks from 1986-1994, and more recently in Uganda, Sudan, Ethiopia, and currently in Brazil.[4,7,59] The intermediate and urban transmission cycles are most responsible for recent outbreaks of yellow fever.[6,12,15,57] Although environmental factors such as changing patterns in rainfall and high temperatures may generally play a role in increased mosquito-borne disease transmission, it is likely that vaccine-induced or natural immunity to yellow fever in these areas is lower than required.[4]

1.7 A recent outbreak of yellow fever in DRC

In March 2016, the DRC began reporting yellow fever cases in connection with an outbreak occurring in neighboring Angola[60] and the outbreak was officially declared in April 2016. Cases associated with the outbreak are recorded as early as February 2016. Local transmission was quickly observed in three provinces (Kwango, Kinshasa, and Kongo Central) due to frequent travel between the two countries, inadequate vaccination coverage, and high vector (mosquito) density in both countries.

Between January 1 and August 11, 2016, 2,269 suspected cases were reported, and ultimately, 78 (4%) were confirmed. Patients presenting with acute onset of fever followed by jaundice within 14 days were considered suspect. Blood samples from all suspected cases were sent for laboratory confirmation. They were considered confirmed when anti-yellow fever IgM antibodies or YF viral RNA was detected in serum and if the patient was not immunized against

yellow fever. Virus-specific enzyme-linked immunosorbent assay (ELISA) tests were used to rule out other flavivirus infections and confirmed by demonstrating a four-fold increase in yellow fever neutralizing antibodies or by plaque reduction neutralization test. Most cases were among adult males who traveled or worked in Angola, but 19% of cases were locally transmitted and there were 18 deaths among confirmed cases (23% case fatality).[61]

In response to the outbreak, disease control and surveillance measures were implemented, including reactive vaccination campaigns starting in May 2016 and cross border interventions to avoid further spread of the disease.[62] In DRC, the first vaccination campaign ultimately began 4-5 months after the outbreak was declared due to limited vaccine supply. The CDC estimates that approximately 1.5 million doses were administered during two mass vaccination campaigns in the Kongo Central province alone and the campaigns were estimated to have reached 99% administrative vaccination coverage.[63] In total, the WHO reports that approximately 9.4 million doses were approved and sent to DRC for four vaccination campaigns and all were seemingly administered, including using a fractional dose scheme in Kinshasa to maximize vaccination coverage.[64] The government had planned a ten day campaign to target 7.6 million people,[65] and ultimately, a fractional dose (one-fifth of the standard dose) was used to efficiently use vaccine supply. Follow-up at one month and one year after vaccination revealed that 98% and 97% of participants, respectively, had detectable antibodies.[66] This vaccination effort in combination with the vaccination campaigns in Angola (30 million vaccines total), while exhausting the global stockpile several times, succeeded in stopping the outbreaks in both countries.

It was ultimately determined that significant delays occurred in detecting cases due to delays in reporting and the use of a case definition with low accuracy. The median time to

hospitalization for severe cases was 17 days, too late for effective supportive care, or other prevention strategies such as using vector control measures around confirmed cases homes.[61] At the time of the outbreak, neither Angola nor DRC were categorized as high-risk countries and were not targeted under the previous Yellow Fever Initiative for preventive vaccination campaigns (see below).[11]

1.8 WHO Eliminate Yellow Fever Epidemics (EYE) Global Strategy

A collaborative initiative between WHO and UNICEF called the Yellow Fever Initiative was first launched in 2006 after a re-emergence of outbreaks in West Africa. Yellow fever vaccination was incorporated into routine child immunizations, preventive vaccination campaigns were conducted in high-risk areas, and a global stockpile of the vaccine was established. However, after the outbreaks of yellow fever in Angola and DRC and an ongoing outbreak in Brazil, the strategic framework was revised and the Eliminate Yellow Fever Epidemics (EYE) Global Strategy for 2017-2026 was developed. The three primary objectives are global and comprehensive, including: 1) To protect at-risk populations, 2) To prevent international spread of the disease, and 3) To contain outbreaks rapidly. Briefly, the main approaches include, first and foremost, vaccination activities where countries are risk classified and recommended to include routine immunization of children, preventive vaccination campaigns nationwide or for specific age groups, and targeted or catch-up campaigns depending on the risk level. With these campaigns, the documentation of vaccination needs to be improved in order to capture the coverage level in the community accurately, therefore, revising vaccination certificates should be a priority and vaccine registers should also be maintained at health facilities to be able to validate historical vaccination information. The EYE Global

Strategy also includes prevention through early detection of cases by ensuring a functioning Integrated Disease Surveillance and Response (IDSR) system that applies a standard definition and follows-up on suspect cases with laboratory testing and interviews. Vector surveillance and control and emergency management plans to reduce the risk of international spread are also recommended and incorporated in the plan.[11] Under this new strategy, DRC is considered high-risk and a combination of all the strategic options is recommended including three-pronged vaccination approach (with preventive vaccination campaigns for all age groups since routine immunization has already been established), monitoring of population immunity, case-based surveillance and laboratory testing, rapid response to outbreaks, targeting travelers to improve entry and departure adherence to vaccination, and readiness and health systems strengthening.[11]

1.9 DRC infrastructure for outbreak detection and response

The DRC is the largest country in sub-Saharan Africa. Most of the population lives in rural and isolated communities that are extremely difficult to access due to poor road infrastructure and challenging landscape. This results in difficulty in detecting and controlling disease outbreaks throughout the country. In 2014, DRC was among the top 10 countries with the highest number of unimmunized children.[67] Communicable, maternal, neonatal, and nutritional diseases still contribute to the most death and disability combined and cause significantly more premature death than similar regions.[68]

Briefly, the DRC is currently made up of 26 provinces (previously 11 provinces before 2015), each of which is broken into health zones (approximately 516 in total) (Figure 1.3). On average, 10 – 15 health zones make up a health district. Most programs regarding disease prevention and surveillance are coordinated at this level then carried out throughout the health

zones. Within each health zone, smaller health areas may have health centers or posts that support local populations. Nurses or sometimes community-based volunteers at each health facility are responsible for all operations of the facility, including vaccination activities and submitting weekly disease surveillance reports to the health zone.

The DRC has implemented an Integrated Disease Surveillance and Response (IDSR) system, a comprehensive regional framework for strengthening national public health surveillance and response systems in Africa.[69] The DRC currently reports 17 diseases of epidemic potential or that are targeted for eradication or elimination weekly and has reported a combination of 24 diseases for the last 17 years (Table 1.2). The system consists of vertical reporting from the local level to the national level. At the national level, surveillance activities are managed by the Ministry of Health, Direction of Disease Control (aka. 4th Direction). The health zone collects surveillance information from the health centers and transmits that data ideally to the district (in functioning districts) or the provincial level. The provincial 4th Direction office ultimately collects the data and reports them at the national level each week. Specimens are also collected as part of disease surveillance. The goal is to transmit all specimens to the national public health laboratory at the Institut National de Recherche Biomedicale (INRB) in Kinshasa for testing. The INRB is the central laboratory service for all DRC, focusing on surveillance and research with extensive laboratory capacity. They are a WHO collaborating center for Human African Trypanosomiasis testing, a WHO AFRO lab for polio testing, they can rapidly test for Ebola using GeneXpert technology,[70] and can perform initial serology tests for yellow fever diagnosis. However, yellow fever specimens are sent to the Institut Pasteur de Dakar in Senegal for confirmation using neutralizing assays.

DRC is a vast country with many rural communities. Surveillance information must travel from individual health posts to the central health zone monitoring centers and ultimately reach the national level for the disease to be recognized. This type of information in the DRC can be sent via the Internet or using cellular telephones but may also be by radio communication or on paper transferred from one location to another on foot when motorcycles or bicycles are not available or if sub-standard roads make the area inaccessible by motor vehicle. Additionally, the health care system outside major cities has limited support from the government and compensation for health care workers can be sporadic and inconsistent, reducing motivation to perform certain activities, including disease surveillance. Furthermore, due to the increasing burden on healthcare workers to manage all functions of the health center, including primary health care and administrative tasks, surveillance is often not the top priority. Unfortunately, this can result in delays in reporting, or in worst case scenarios, the report may never arrive at the higher level. Indeed throughout West Africa, surveillance for yellow fever likely suffers from under-recognition, underreporting, and underestimation secondary to limitations with diagnostic capabilities and health infrastructure.[13]

The DRC also has a functioning National Expanded Program on Immunization (EPI) responsible for overseeing and monitoring vaccination activities in the country. At the national level, EPI seeks to strengthen routine immunization by overseeing all immunization activities and coordinating community-based campaigns, vaccine-preventable disease surveillance, cold chain maintenance, and delivery of new and traditional vaccines. The EPI reassesses vaccine need, cold chain supplies, and other immunization-related equipment necessities every five years as part of their comprehensive multi-year plan. UNICEF assists with the procurement of traditional vaccines and immunization supplies. Quantifying of needs for the comprehensive plan

is challenging due to the large rural areas in DRC as lack of monitoring or data systems in part of the country.[71]

The EPI still experiences challenges due to the vast country size and existence of remote health districts and health centers where immunization activities are conducted and immunization data is collected. As a result, DRC has been a target of efforts to strengthen the quality of surveillance data to facilitate prioritizing and planning for the immunization program. Projects such as the Strengthening the Quality and Use of Immunization Data, or SQUID team, from WHO, UNICEF, and CDC in 2012 have sought to foster ownership of childhood immunization data and teach national leaders systematic ways to monitor their program data in order to make the system more effective and cost-efficient.[67]

The DRC also receives support from the Global Alliance for Vaccines and Immunizations (GAVI),[72] a public-private partnership aiming to improve childhood vaccination coverage in developing countries and accelerate access to new vaccines. GAVI provides direct and indirect support to improve vaccination coverage by providing the actual vaccines themselves, particularly new vaccines, but also supporting initiatives such as cold chain equipment optimization, health system strengthening, and infection safety devices. GAVI has been supporting EPI immunization efforts since 2002 by providing various vaccines, including tetravalent, pentavalent, pneumococcal, and yellow fever, as well as injection safety and strengthening health systems.[71,73] While funding from GAVI has been abundant ($806.4 million disbursed since 2002[72]) making up almost half of the immunization funding in DRC,[71] successfully implementing immunization programs continues to be a challenge in DRC.[73] New vaccine introduction has suffered from concerns regarding insufficient cold chain capacity, increased cost of vaccine distribution, and stock-outs of vaccines. After introduction, delays in

training and delivery of injection material and actual vaccine continued to be problems.[74] Recruiting, training, and maintaining skilled health workers and supply chain staff is also a problem at the provincial and health facility levels. Even supervisors and leaders may not be equipped with the knowledge to oversee the delivery and distribution of vaccines and may not be familiar with health policies and planning priorities regarding immunizations.[71]

Although EPI monitors vaccination coverage and estimates are reported by agencies such as GAVI and WHO, published reports typically rely on vaccination records that may be unavailable or incomplete, national household surveys, such as the Demographic Health Survey, or rely on maternal recall. Maternal recall is known to be subject to bias,[75] however, household surveys such as the DHS may provide more reliable information to measure changes in vaccine coverage over time as compared to official WHO/UNICEF health delivery reported statistics.[76] Furthermore, some studies have found that maternal recall is accurate compared to vaccine card information in a similar setting and that these two information sources can be used together to compile accurate surveillance data.[77,78] Of note, the sensitivity of maternal recall is much higher than the specificity.[47] Recall bias was not observed in DHS surveys by comparing overlapping data from consecutive surveys.[76] The WHO has recommended and utilized household surveys for decades to ascertain immunization coverage where homes are visited, immunization records are examined, and parents or caretakers are interviewed about immunization.[79]

The success of vaccination activities in DRC is further complicated by conflict and unrest, leading to prolonged interruptions in vaccination programs that have resulted in immunity gaps over the last decade. Additionally, conflict has a deleterious effect on children's nutritional status resulting in stunted growth, emaciation, and weight inadequacy, which has implications on immune status and vaccine immunity uptake. DRC experiences conflict in six of the eleven old

provinces: Equateur, Orientale, North Kivu, South Kivu, Maniema, and Katanga, resulting in poverty and displacement of populations. In fact, 81.4% of internally displaced persons (IDPs) in DRC were displaced because of armed conflict and an additional 16.3% because of conflict-related insecurity.[80] Indeed, political unrest also creates challenges for yellow fever control. Population movement and migration of non-immune people from non-endemic areas to areas with ongoing sylvatic transmission to escape violence, such as in Sudan and Uganda, resulted in yellow fever outbreaks.[13,81,82]

Many villages in DRC are also isolated from nearby health centers due to poor infrastructure and challenging landscape. Furthermore, health centers may be isolated from the nearest health zone center due to similar reasons creating deficiencies in vaccine storage during transport. Lastly, the burden of poverty contributes to challenges in achieving adequate vaccination coverage.[5,73,83] As mentioned, interruptions in the cold chain have also been implicated in outbreaks of vaccine-preventable diseases due to compromised vaccine.
When an outbreak is detected in DRC, current interventions typically only consist of reactive vaccination campaigns and sporadic vector control, which are supported by outside organizations such as CDC or WHO. Vaccine availability is facilitated by the International Coordinating Group (ICG) for the Provision of Vaccines.[84] Vaccination campaigns can be costly and logistically challenging to implement and, as a result, are often implemented after an outbreak has already begun to decline. The campaigns typically seek to vaccinate as many people as possible and may not pause to distinguish individuals that may already be vaccinated or maybe have gotten the disease and either do not have symptoms or have already recovered. This may potentially contribute to vaccine waste. While the ICG maintains stockpiles of vaccine for use during outbreak response, an example such as the yellow fever outbreak in Angola and DRC in

2016 illustrates that these stockpiles may not be sufficient to blanket vaccinate all individuals indiscriminately.

1.10 Modeling yellow fever and vector-borne diseases

There is a paucity of literature regarding modeling the dynamics of yellow fever in general and few published articles regarding any aspect of the recent outbreak in the DRC and Angola. One study that investigated the recent yellow fever outbreak in the DRC used a statistical logistic model to estimate the geographic expansion of yellow fever in the DRC and Angola to predict the future spread and estimate the areas that could be prioritized for vaccination. They highlighted the need to incorporate factors related to vector ecology and demographic factors when modeling the spread of yellow fever. They estimated the reproductive number (R_0) of yellow fever in the outbreak as 4.8, which may have been overestimated due to an increase in early reporting but indicated a critical vaccination coverage of about 80%. They suggested that their findings needed to account for constraints such as vaccine supply and delivery to translate any findings into policy.[85] Other recent studies used a mathematical model and likelihood-based statistics techniques to analyze the epidemiological processes of the outbreak in Angola. They used a more complex vector-host model to account for transmission dynamics, including separating stages of the yellow fever disease then studied the impact of the vaccination campaigns versus several delayed vaccination scenarios. This study also extrapolated several of their parameters for mosquitos from previous literature on dengue transmission and used a partially observed Markov process (POMP) to fit the data and maximum likelihood estimation to model the parameters. They estimated that the Angola outbreak had an R_0 of 2.6-3.4 and concluded that the vaccination campaigns were timely and saved approximately five-fold

more people from death and 5.6 fold of the observed 941 cases.[86] The outbreak in Angola was also used as an example to demonstrate a derived formula for the effective reproductive number (R_{eff}) for vector-borne diseases using a compartmental mathematical model, however, the study did not seek to study the outbreak itself or explore interventions.[87] More generally, Yusuf and Daniel used a deterministic mathematical model to investigate transmission dynamics of yellow fever and various control measures and concluded that measures to reduce the mosquito biting rate, the human to vector and vector to human transmission rates, and increase the vaccination success rate would be most effective for preventing the spread of disease.[88] Lastly, another study which used a mathematical model to explore the transmission of yellow fever in the presence of a vaccine by modeling the human, adult mosquito, and egg populations similarly found that if the mortality rate of mosquitos is high enough, yellow fever is naturally eradicated from the population, further emphasizing the need for vector control.[89]

Several previously published studies have modeled the dynamics of dengue virus, another vector-borne disease,[90,91] and recommend incorporating aspects of vector control and vaccination to prevent diseases transmitted by vectors,[90–92] especially strategies to decrease the actual number of mosquitos rather than just bite protection.[93] Dengue has a very similar transmission mode, including the same mosquito species, so these studies can be used to guide modeling efforts for yellow fever.

1.11 Conceptual model of prevention of urban transmission of yellow fever

This research focuses on the prevention and control of the transmission of yellow fever associated with the urban transmission cycle. Extrapolating from the CDC model for yellow fever transmission (Figure 1.2),[10] prevention strategies and risk factors of infection are outlined

in this model (Figure 1.4). Although not all pathways will be explored, some of the crucial determinants of yellow fever infection and prevention will be assessed.

1.12 Tables and Figures

Figure 1.1 Clinical course of yellow fever disease and stages of infection

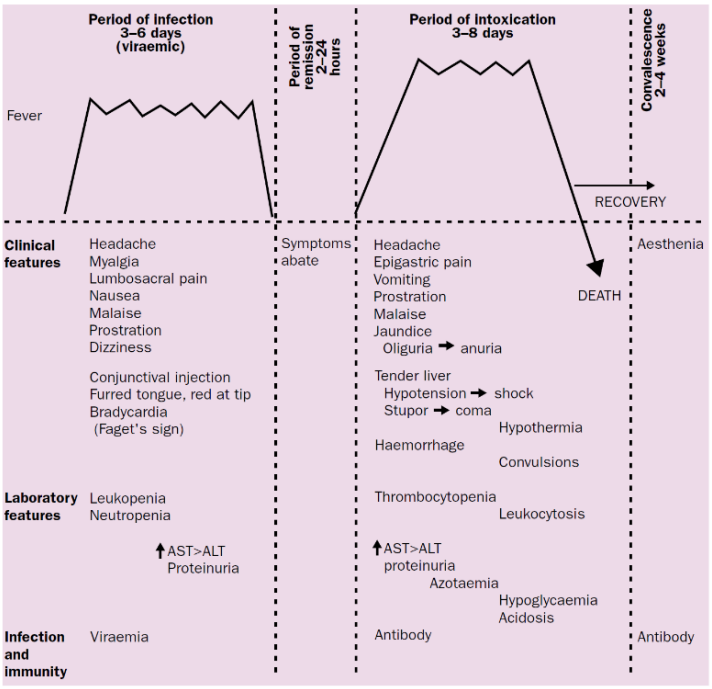


Figure 1.2 Yellow fever transmission cycles[10]

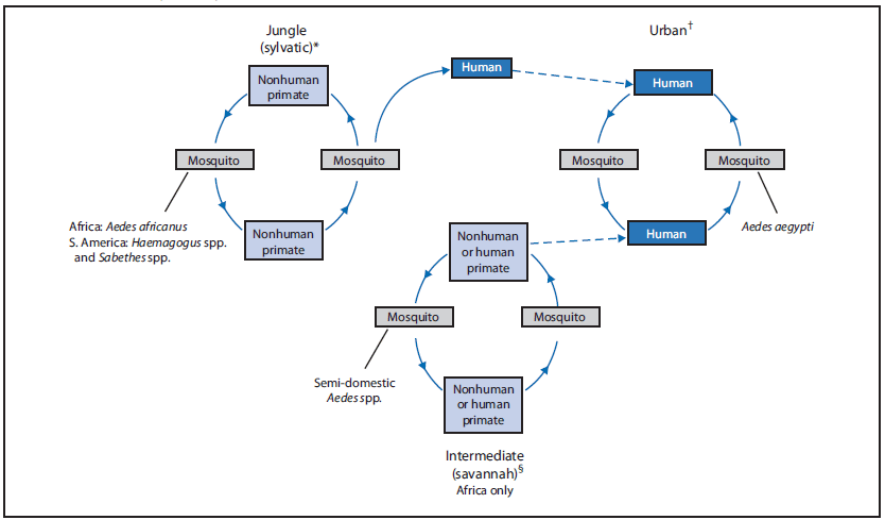


Table 1.1 Childhood immunization schedule for the Democratic Republic of the Congo[19]

Vaccine	Birth	6 weeks	10 weeks	14 weeks	9 months	
Bacille Calmette-Guérin vaccine (BCG)	X					
Diphtheria and Tetanus and Pertussis and Haemophilus influenzae and Hepatitis B vaccine (DTwPHibHepB)		X	X	X		
Inactivated polio vaccine (IPV)				X		
Measles					X	
Oral polio vaccine (OPV)	X	X	X	X		
Pneumococcal conjugate vaccine (Pneumo_conj)		X	X	X		
Rotavirus			X	X		Since May 2018
Vitamin A						Every 6 months until 59 months
Yellow fever					X	

Figure 1.3 Provinces (new and old) and health zones of the Democratic Republic of Congo (DRC)

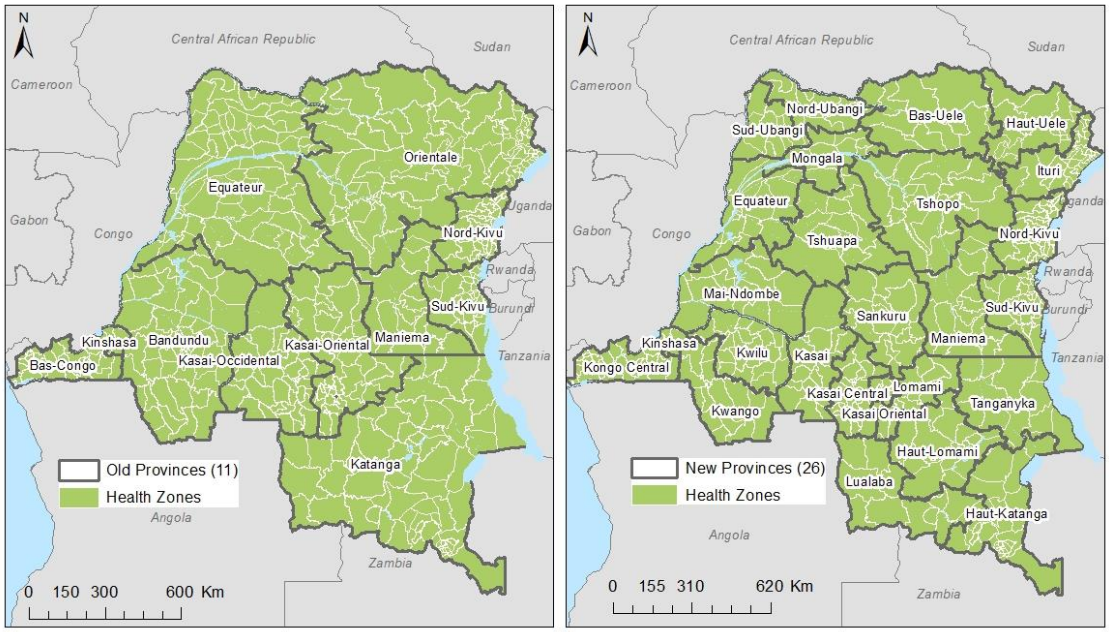
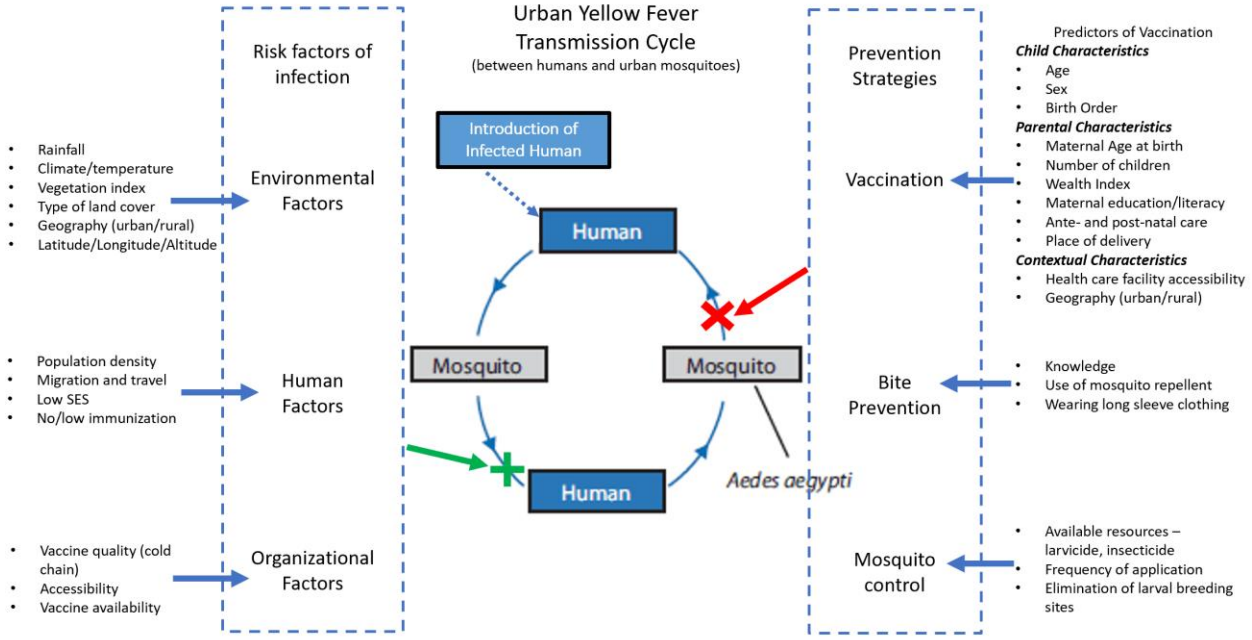


Table 1.2 Diseases reported to IDSR, DRC (* indicates currently reported since 2015)

AFP*	Meningitis*
Avian Influenza	Monkey Pox*
Bacillary dysentery/Shigellosis	Neonatal Tetanus*
Bloody Diarrhea*	Pertussis*
Cholera*	Plague*
Dracunculiasis*	Rabies*
Gastroenteritis	Simple Diarrhea
Influenza	Typhoid Fever*
Influenza H1N1	Typhus
Malaria*	URI*
Maternal Death*	Viral hemorrhagic fever (VHF)*
Measles*	Yellow fever*

Figure 1.4 Conceptual Model of prevention of urban transmission of yellow fever



1.13 References

1. Morse SS. Factors in the Emergence of Infectious Diseases. *Emerg Infect Dis*. 1995;1(1):7-15. doi:10.3201/eid0101.950102
2. Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature*. 2008;451(7181):990-993. doi:10.1038/nature06536
3. Woolhouse MEJ. Population biology of emerging and reemerging pathogens. *Trends Microbiol*. 2002;10(10 Suppl):S3-7. http://www.ncbi.nlm.nih.gov/pubmed/12377561. Accessed January 22, 2019.
4. Monath TP, Vasconcelos PFC. Yellow fever. *J Clin Virol*. 2015;64:160-173. doi:10.1016/j.jcv.2014.08.030
5. Bryant JE, Holmes EC, Barrett ADT. Out of Africa: A Molecular Perspective on the Introduction of Yellow Fever Virus into the Americas. *PLoS Pathog*. 2007;3(5):e75. doi:10.1371/journal.ppat.0030075
6. Rogers DJ, Wilson AJ, Hay SI, Graham AJ. The global distribution of yellow fever and dengue. *Adv Parasitol*. 2006;62:181-220. doi:10.1016/S0065-308X(05)62006-4
7. Monath TP. Yellow fever: an update. *Lancet Infect Dis*. 2001;1(1):11-20. doi:10.1016/S1473-3099(01)00016-0
8. Barnett ED. Yellow Fever: Epidemiology and Prevention. *Clin Infect Dis*. 2007;44(6):850-856. doi:10.1086/511869
9. World Health Organization. Yellow fever Fact Sheet. http://www.who.int/mediacentre/factsheets/fs100/en/. Published 2016.
10. Centers for Disease Control and Prevention. Transmission | Yellow Fever | CDC. http://www.cdc.gov/yellowfever/transmission/. Published 2015. Accessed June 11, 2017.
11. World Health Organization. Eliminate Yellow fever Epidemics (EYE): a global strategy, 2017-2016. *Wkly Epidemiol Rec*. 2017;92(16):193-204. https://www.who.int/wer/2017/wer9216/en/. Accessed August 13, 2018.
12. Barrett ADT. Yellow fever live attenuated vaccine: A very successful live attenuated vaccine but still we have problems controlling the disease. *Vaccine*. 2017;35(44):5951-5955. doi:10.1016/J.VACCINE.2017.03.032
13. Baba MM, Ikusemoran M. Is the absence or intermittent YF vaccination the major contributor to its persistent outbreaks in eastern Africa? *Biochem Biophys Res Commun*. 2017;492(4):548-557. doi:10.1016/j.bbrc.2017.01.079
14. Southern African Development Community. Democratic Republic of Congo Country Profile. https://www.sadc.int/member-states/dr-congo. Accessed February 17, 2019.
15. World Health Organization. Emergencies preparedness, response - Increased risk of urban yellow fever outbreaks in Africa. *WHO*. 2015. https://www.who.int/csr/disease/yellowfev/urbanoutbreaks/en/. Accessed January 20, 2019.
16. Jentes ES, Poumerol G, Gershman MD, et al. The revised global yellow fever risk map

and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. *Lancet Infect Dis*. 2011;11(8):622-632. doi:10.1016/S1473-3099(11)70147-5

17. Garske T, Van Kerkhove MD, Yactayo S, et al. Yellow Fever in Africa: Estimating the Burden of Disease and Impact of Mass Vaccination from Outbreak and Serological Data. Hay SI, ed. *PLoS Med*. 2014;11(5):e1001638. doi:10.1371/journal.pmed.1001638

18. Hamrick PN, Aldighieri S, Machado G, et al. Geographic patterns and environmental factors associated with human yellow fever presence in the Americas. Barker CM, ed. *PLoS Negl Trop Dis*. 2017;11(9):e0005897. doi:10.1371/journal.pntd.0005897

19. World Health Organization. Emergencies preparedness, response - Yellow fever in the Democratic Republic of the Congo. *WHO*. 2015. https://www.who.int/csr/don/2010_07_19a/en/. Accessed November 13, 2018.

20. Centers for Disease Control and Prevention. Vaccine Information | Yellow Fever | CDC. https://www.cdc.gov/yellowfever/healthcareproviders/vaccine-info.html. Accessed October 8, 2018.

21. Sanofi Pasteur. *YF-VAX ® LE6103-LE6104 Yellow Fever Vaccine YF-VAX ®*.; 2016. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142831.pdf. Accessed October 8, 2018.

22. Monath TP, Nichols R, Archambault WT, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. *Am J Trop Med Hyg*. 2002;66(5):533-541. doi:10.4269/ajtmh.2002.66.533

23. Belmusto-Worn VE, Sanchez JL, McCarthy K, et al. Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru. *Am J Trop Med Hyg*. 2005;72(2):189-197. http://www.ncbi.nlm.nih.gov/pubmed/15741556. Accessed August 20, 2018.

24. Collaborative Group for Studies of Yellow Fever Vaccine CG for S of YF. A randomised double-blind clinical trial of two yellow fever vaccines prepared with substrains 17DD and 17D-213/77 in children nine-23 months old. *Mem Inst Oswaldo Cruz*. 2015;110(6):771-780. doi:10.1590/0074-02760150176

25. Willcox AC, Collins MH, Jadi R, et al. Seroepidemiology of Dengue, Zika, and Yellow Fever Viruses among Children in the Democratic Republic of the Congo. *Am J Trop Med Hyg*. 2018;99(3):756-763. doi:10.4269/ajtmh.18-0156

26. Perraut R, Girault G, Moreau J-P. Stability-related studies on 17D yellow fever vaccine. *Microbes Infect*. 2000;2(1):33-38. doi:10.1016/S1286-4579(00)00288-4

27. Peetermans J. Factors affecting the stability of viral vaccines. *Dev Biol Stand*. 1996;87:97-101. http://www.ncbi.nlm.nih.gov/pubmed/8854006. Accessed August 14, 2018.

28. Rogers B, Dennison K, Adepoju N, Dowd S, Uedoi K. Vaccine Cold Chain Part 1. Proper Handling and Storage of Vaccine. *AAOHN J*. 2010;58(8). doi:10.3928/08910162-20100716-02

29. Monath TP, Wilson DC, Lee VH, Stroh G, Kuteyi K, Smith EA. The 1970 yellow fever epidemic in Okwoga District, Benue Plateau State, Nigeria. I. Epidemiological observations. *Bull World Health Organ*. 1973;49(2):113-121. http://www.ncbi.nlm.nih.gov/pubmed/4545318. Accessed August 15, 2018.

30. De Cock KM, Nasidi A, Enriquez J, et al. EPIDEMIC YELLOW FEVER IN EASTERN NIGERIA, 1986. *Lancet*. 1988;331(8586):630-633. doi:10.1016/S0140-6736(88)91425-0

31. Nasidi A, Monath TP, DeCock K, et al. Urban yellow fever epidemic in western Nigeria, 1987. *Trans R Soc Trop Med Hyg*. 1989;83(3):401-406. doi:10.1016/0035-9203(89)90518-X

32. Dairo DM, Osizimete OE. Factors affecting vaccine handling and storage practices among immunization service providers in Ibadan, Oyo State, Nigeria. *Afr Health Sci*. 2016;16(2):576-583. doi:10.4314/ahs.v16i2.27

33. Oyefolu AO, Nwaeke AC, Audu RA, et al. Evaluation of measles vaccine cold chain in Lagos State, Nigeria. *African J Clin Exp Microbiol*. 2007;8(1). doi:10.4314/ajcem.v8i1.7457

34. Berhane Y, Demissie M. Cold chain status at immunisation centres in Ethiopia. *East Afr Med J*. 2000;77(9):476-479. doi:10.4314/eamj.v77i9.46692

35. Yakum MN, Ateudjieu J, Pélagie FR, Walter EA, Watcho P. Factors associated with the exposure of vaccines to adverse temperature conditions: the case of North West region, Cameroon. *BMC Res Notes*. 2015;8:277. doi:10.1186/s13104-015-1257-y

36. Centers for Disease Control and Prevention. Prevention | Yellow Fever | CDC. https://www.cdc.gov/yellowfever/prevention/index.html. Published 2015. Accessed May 19, 2017.

37. WHO and UNICEF. *Democratic Republic of the Congo: WHO and UNICEF Estimates of Immunization Coverage: 2017 Revision*.; 2018. https://www.who.int/immunization/monitoring_surveillance/data/cod.pdf. Accessed March 10, 2019.

38. Shearer FM, Moyes CL, Pigott DM, et al. Global yellow fever vaccination coverage from 1970 to 2016: an adjusted retrospective analysis. *Lancet Infect Dis*. 2017;17(11):1209-1217. doi:10.1016/S1473-3099(17)30419-X

39. Kabudi AM, Mukobelwa P, Kazadi JM, Bardella IJ. Prevalence and associated factors of partially/non-immunization of under-five in Goma city, Democratic Republic of Congo: a community-based cross-sectional survey. *Pan Afr Med J*. 2015;20(38). doi:10.11604/pamj.2015.20.38.4483

40. Mwamba GN, Yoloyolo N, Masembe Y, et al. Democratic Cite this: The Pan African Medical Journal. 2017;27:7. doi:10.11604/pamj.supp.2017.27.3.11930

41. Acharya P, Kismul H, Mapatano MA, Hatløy A. Individual- and community-level determinants of child immunization in the Democratic Republic of Congo: A multilevel analysis. Ali M, ed. *PLoS One*. 2018;13(8):e0202742. doi:10.1371/journal.pone.0202742

42. Ashbaugh HR, Hoff NA, Doshi RH, et al. Predictors of measles vaccination coverage among children 6–59 months of age in the Democratic Republic of the Congo. *Vaccine*.

2018;36(4):587-593. doi:10.1016/j.vaccine.2017.11.049

43. Schoeps A, Ouédraogo N, Kagoné M, Sié A, Müller O, Becher H. Sociodemographic determinants of timely adherence to BCG, Penta3, measles, and complete vaccination schedule in Burkina Faso. *Vaccine*. 2013;32(1):96-102. doi:10.1016/J.VACCINE.2013.10.063

44. Kagoné M, Yé M, Nébié E, et al. Vaccination coverage and factors associated with adherence to the vaccination schedule in young children of a rural area in Burkina Faso. *Glob Health Action*. 2017;10(1):1399749. doi:10.1080/16549716.2017.1399749

45. Gram L, Soremekun S, ten Asbroek A, et al. Socioeconomic determinants and inequities in coverage and timeliness of early childhood immunisation in rural Ghana. *Trop Med Int Heal*. 2014;19(7):802-811. doi:10.1111/tmi.12324

46. Adokiya MN, Baguune B, Ndago JA. Evaluation of immunization coverage and its associated factors among children 12–23 months of age in Techiman Municipality, Ghana, 2016. *Arch Public Heal*. 2017;75(1):28. doi:10.1186/s13690-017-0196-6

47. Odusanya OO, Alufohai EF, Meurice FP, Ahonkhai VI. Determinants of vaccination coverage in rural Nigeria. *BMC Public Health*. 2008;8(1):381. doi:10.1186/1471-2458-8-381

48. Kazungu JS, Adetifa IMO. Crude childhood vaccination coverage in West Africa: Trends and predictors of completeness. *Wellcome Open Res*. 2017;2:12. doi:10.12688/wellcomeopenres.10690.1

49. Tagbo B, Omotowo B, Onyeka B, et al. Vaccination Coverage and Its Determinants in Children Aged 11-23 Months in an Urban District of Nigeria Article in World Journal of Vaccines · October. *World J Vaccines*. 2014;4:175-183. doi:10.4236/wjv.2014.44020

50. Zivich PN, Kiketa L, Kawende B, Lapika B, Yotebieng M. Vaccination Coverage and Timelines Among Children 0–6 Months in Kinshasa, the Democratic Republic of Congo: A Prospective Cohort Study. *Matern Child Health J*. 2017;21(5):1055-1064. doi:10.1007/s10995-016-2201-z

51. Wiysonge CS, Uthman OA, Ndumbe PM, Hussey GD. Individual and Contextual Factors Associated with Low Childhood Immunisation Coverage in Sub-Saharan Africa: A Multilevel Analysis. Moormann AM, ed. *PLoS One*. 2012;7(5):e37905. doi:10.1371/journal.pone.0037905

52. Ekouevi DK, Gbeasor-Komlanvi FA, Yaya I, et al. Incomplete immunization among children aged 12–23 months in Togo: a multilevel analysis of individual and contextual factors. *BMC Public Health*. 2018;18(1):952. doi:10.1186/s12889-018-5881-z

53. Abadura SA, Lerebo WT, Kulkarni U, Mekonnen ZA. Individual and community level determinants of childhood full immunization in Ethiopia: a multilevel analysis. *BMC Public Health*. 2015;15(1):972. doi:10.1186/s12889-015-2315-z

54. Rainey JJ, Watkins M, Ryman TK, Sandhu P, Bo A, Banerjee K. Reasons related to non-vaccination and under-vaccination of children in low and middle income countries: Findings from a systematic review of the published literature, 1999-2009. *Vaccine*. 2011;29(46):8215-8221. doi:10.1016/j.vaccine.2011.08.096

55. Meleko A, Geremew M, Birhanu F. Assessment of Child Immunization Coverage and Associated Factors with Full Vaccination among Children Aged 12-23 Months at Mizan Aman Town, Bench Maji Zone, Southwest Ethiopia. 2017. doi:10.1155/2017/7976587

56. Wemakor A, Kofi Helegbe G, Abdul-Mumin A, Amedoe S, Zoku JA, Dufie AI. Prevalence and factors associated with incomplete immunization of children (12-23 months) in Kwabre East District, Ashanti Region, Ghana. doi:10.1186/s13690-018-0315-z

57. Gardner CL, Ryman KD. Yellow fever: a reemerging threat. *Clin Lab Med*. 2010;30(1):237-260. doi:10.1016/j.cll.2010.01.001

58. World Health Organization. *International Health Regulations (2005) Third Edition*. http://apps.who.int/iris/bitstream/handle/10665/246107/9789241580496-eng.pdf;jsessionid=2364F192E51614CB18932A353AAFECFF?sequence=1. Accessed August 21, 2018.

59. World Health Organization. Emergencies preparedness, response - Yellow fever – Brazil. *WHO*. 2019. https://www.who.int/csr/don/11-february-2019-yellow-fever-brazil/en/. Accessed March 11, 2019.

60. World Health Organization. Emergencies preparedness, response, Yellow Fever – Democratic Republic of the Congo, 11 April 2016. WHO. http://www.who.int/csr/don/11-april-2016-yellow-fever-drc/en/. Published 2016. Accessed May 19, 2017.

61. Ingelbeen B, Weregemere NA, Noel H, et al. Urban yellow fever outbreak—Democratic Republic of the Congo, 2016: Towards more rapid case detection. Beasley DWC, ed. *PLoS Negl Trop Dis*. 2018;12(12):e0007029. doi:10.1371/journal.pntd.0007029

62. World Health Organization. Emergencies preparedness, response, Yellow fever – Democratic Republic of the Congo, 2 June 2016. WHO. http://www.who.int/csr/don/02-june-2016-yellow-fever-drc/en/. Published 2016. Accessed May 19, 2017.

63. Otshudiema JO, Ndakala NG, Mawanda E-TK, et al. Yellow Fever Outbreak - Kongo Central Province, Democratic Republic of the Congo, August 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(12):335-338. doi:10.15585/mmwr.mm6612a5

64. World Health Organization. *Situation Report - Yellow Fever - 28 October 2016.*; 2016. http://apps.who.int/iris/bitstream/handle/10665/250661/yellowfeversitrep28Oct16-eng.pdf?sequence=1. Accessed June 19, 2018.

65. World Health Organization (WHO). *Yellow Fever Mass Vaccination Campaign Using Fractional Dose in Kinshasa, DRC.*; 2016. https://www.who.int/immunization/sage/meetings/2016/october/4_Yellow_fever_mass_vaccination_campaign_using_fractional_dose_in_Kinshasa.pdf?ua=1. Accessed May 6, 2020.

66. Casey RM, Harris JB, Ahuka-Mundeke S, et al. Immunogenicity of Fractional-Dose Vaccine during a Yellow Fever Outbreak — Final Report. *N Engl J Med*. 2019;381(5):444-454. doi:10.1056/NEJMoa1710430

67. Centers for Disease Control and Prevention. Fostering Ownership of Childhood Immunization Data in Democratic Republic of Congo. https://www.cdc.gov/globalhealth/immunization/stories/child-immunization-drc.htm.

Published 2014. Accessed January 20, 2019.

68. Institute for Health Metrics and Evaluation. Democratic Republic of the Congo. http://www.healthdata.org/democratic-republic-congo. Accessed January 20, 2019.

69. Centers for Disease Control and Prevention. Integrated Disease Surveillance and Response: About Us | Division of Global Health Protection | Global Health | CDC. https://www.cdc.gov/globalhealth/healthprotection/idsr/about.html. Published 2017. Accessed October 15, 2018.

70. World Health Organization. New technology allows for rapid diagnosis of Ebola in Democratic Republic of the Congo | WHO | Regional Office for Africa. https://afro.who.int/news/new-technology-allows-rapid-diagnosis-ebola-democratic-republic-congo. Accessed January 22, 2019.

71. PATH. *Immunization in the Democratic Republic of the Congo: Landscape Analysis and Policy Recommendations*. Seattle; 2016. https://path.azureedge.net/media/documents/APP_drc_landscape_rpt.pdf. Accessed January 19, 2019.

72. Global Alliance for Vaccines and Immunization. Gavi country factsheet : The Democratic Republic of the Congo. https://www.gavi.org/country/drc/. Accessed October 13, 2018.

73. Ferrinho P, Mohammed M. Barriers to immunization coverage in DRC: An analysis of the GAVI-Alliance cash-based support. *Ann Trop Med Public Heal*. 2013;6(4):401. doi:10.4103/1755-6783.127773

74. Le Gargasson J-B, Breugelmans JG, Mibulumukini B, Da Silva A, Colombini A. Sustainability of National Immunization Programme (NIP) performance and financing following Global Alliance for Vaccines and Immunization (GAVI) support to the Democratic Republic of the Congo (DRC). *Vaccine*. 2013;31(15):1886-1891. doi:10.1016/J.VACCINE.2013.02.024

75. Valadez JJ, Weld LH. Maternal recall error of child vaccination status in a developing nation. *Am J Public Health*. 1992;82(1):120-122. doi:10.2105/AJPH.82.1.120

76. Murray CJL, Shengelia B, Gupta N, Moussavi S, Tandon A, Thieren M. Validity of reported vaccination coverage in 45 countries. *Lancet (London, England)*. 2003;362(9389):1022-1027. doi:10.1016/S0140-6736(03)14411-X

77. Ndirangu J, Bland R, Bärnighausen T, Newell M-L. Validating child vaccination status in a demographic surveillance system using data from a clinical cohort study: evidence from rural South Africa. *BMC Public Health*. 2011;11(1):372. doi:10.1186/1471-2458-11-372

78. Binyaruka P, Borghi J. Validity of parental recalls to estimate vaccination coverage: evidence from Tanzania. *BMC Health Serv Res*. 2018;18(1):440. doi:10.1186/s12913-018-3270-z

79. World Health Organization. *VACCINATION COVERAGE CLUSTER SURVEYS: REFERENCE MANUAL*.; 2015. https://www.who.int/immunization/monitoring_surveillance/Vaccination_coverage_cluster_survey_with_annexes.pdf?ua=1. Accessed March 11, 2019.

80. Conflicts in the Democratic Republic of Congo: Causes, impact and implications for the

Great Lakes region | United Nations Economic Commission for Africa. https://www.uneca.org/publications/conflicts-democratic-republic-congo-causes-impact-and-implications-great-lakes-region. Published 2015. Accessed May 3, 2020.

81. Onyango CO, Ofula VO, Sang RC, et al. Yellow fever outbreak, Imatong, Southern Sudan. *Emerg Infect Dis*. 2004;10(6):1064-1068. doi:10.3201/eid1006.030738

82. Wamala JF, Malimbo M, Okot CL, et al. Epidemiological and laboratory characterization of a yellow fever outbreak in northern Uganda, October 2010-January 2011. *Int J Infect Dis*. 2012;16(7):e536-e542. doi:10.1016/j.ijid.2012.03.004

83. Demographic and Health Survey. *Democratic Republic of the Congo Demographic and Health Survey (DRC-DHS II 2013-2014) Supplemental Vaccine-Preventable Diseases Report*.; 2015. https://dhsprogram.com/pubs/pdf/FR300/FR300.vpd.pdf. Accessed October 27, 2018.

84. World Health Organization. International Coordinating Group (ICG) on Vaccine Provision. WHO. https://www.who.int/csr/disease/icg/qa/en/. Published 2016. Accessed October 15, 2018.

85. Kraemer MUG, Faria NR, Reiner RC, et al. Spread of yellow fever virus outbreak in Angola and the Democratic Republic of the Congo 2015–16: a modelling study. *Lancet Infect Dis*. 2016. doi:10.1016/S1473-3099(16)30513-8

86. Zhao S, Stone L, Gao D, He D. Modelling the large-scale yellow fever outbreak in Luanda, Angola, and the impact of vaccination. Rodriguez-Barraquer I, ed. *PLoS Negl Trop Dis*. 2018;12(1):e0006158. doi:10.1371/journal.pntd.0006158

87. Zhao S, Musa SS, Hebert JT, et al. Modelling the effective reproduction number of vector-borne diseases: The yellow fever outbreak in Luanda, Angola 2015-2016 as an example. *PeerJ*. 2020;2020(2). doi:10.7717/peerj.8601

88. Yusuf TT, Daniel DO. Mathematical Modeling of Yellow Fever Transmission Dynamics with Multiple Control Measures. *Asian Res J Math*. May 2019:1-15.

89. Raimundo SM, Amaku M, Massad E. Equilibrium Analysis of a Yellow Fever Dynamical Model with Vaccination. 2015. doi:10.1155/2015/482091

90. Andraud M, Hens N, Marais C, Beutels P. Dynamic Epidemiological Models for Dengue Transmission: A Systematic Review of Structural Approaches. *PLoS One*. 2012. doi:10.1371/journal.pone.0049085

91. Nishiura H. Mathematical and Statistical Analyses ofthe Spread of Dengue. *Dengue Bull*. 2006;30:51-67. message:%3C4D8040D1.2000800@emory.edu%3E%5Cnpapers2://publication/uuid/41B30B48-DE61-4646-AB72-E3FF8190566F.

92. Luz PM, Struchiner CJ, Galvani AP. Modeling Transmission Dynamics and Control of Vector-Borne Neglected Tropical Diseases. Brooker S, ed. *PLoS Negl Trop Dis*. 2010;4(10):e761. doi:10.1371/journal.pntd.0000761

93. Brauer F, Castillo-Chavez C, Mubayi A, Towers S. Some models for epidemics of vector-transmitted diseases. *Infect Dis Model*. 2016;1(1):79-87. doi:10.1016/j.idm.2016.08.001

Chapter 2: Child, maternal, and community-level characteristics associated with yellow fever vaccination coverage and geographic distribution in the Democratic Republic of Congo

2.1 Abstract

Yellow fever is an acute viral hemorrhagic disease transmitted by infected mosquitos, which is endemic in the Democratic Republic of Congo (DRC). There are well-described disease prevention methods, including mosquito control, avoiding mosquito bites, and the use of an effective vaccine. Children older than 9 months in DRC are vaccinated against yellow fever. However, estimates of vaccination remain lower than necessary to prevent outbreaks of disease. This study aims to explore childhood yellow fever vaccination coverage, identify demographic and behavioral factors associated with vaccination status, and geographic differences in vaccination status to help guide immunization efforts in DRC. Yellow fever vaccination coverage among children 9 to 59 months old was examined using the Demographic and Health Survey (DHS) from 2013-14. Vaccination indicated on a vaccination card was used and vaccination card plus mother's report was assessed as a secondary information source. Survey data analysis methods, including descriptive statistics and a weighted logistic multilevel model, were used to elucidate both individual and community-level fixed factors associated with vaccination. Overall, 16.5% of 13,973 children included in this analysis presented a vaccination card for review and the percentage declined with older age. Yellow fever vaccination coverage was 82.9% when considering documentation on a vaccination card and 69.9% when also considering the mother's report. The odds of yellow fever vaccination were slightly higher

among older children and lower among last-born children than in middle-born children. The odds were higher if mothers utilized antenatal and postnatal care and were considerably lower if the mother gave birth at home compared to delivering at a government or public facility. The association between yellow fever vaccination and geography type differed depending on the source of information. Few studies have previously focused on factors associated with yellow fever vaccination specifically, and none have focused on yellow fever in DRC. Although the vaccination card indicated very favorable vaccination coverage, the percentage of children who presented a vaccination card was low. Interventions to improve vaccination must be multi-faceted as no single factor alone contributes to vaccination coverage for yellow fever. However, these findings demonstrate a continuum of care whereby mothers establish care during pregnancy, with repeated visits to a healthcare facility for antenatal care followed by delivery at an institution, especially government and public facilities, and ultimately vaccination of their child.

2.2 Introduction

Yellow fever is an acute viral hemorrhagic disease caused by the yellow fever virus, a member of the genus *Flavivirus*, a family of positive-strand, single-strand RNA viruses, most of which are transmitted by mosquitoes or ticks and cause viral hemorrhagic fevers.[1] Unprotected exposure of an unvaccinated individual to mosquitoes in an endemic area is the major risk factor for yellow fever infection. New infections and outbreaks of widespread transmission of yellow fever can are preventable through several relatively available methods such as mosquito control efforts (eliminating potential breeding sites using larvicides and insecticide spraying to kill adult mosquitoes[2]) or avoiding mosquito bites by using insect repellant and wearing long sleeve or

insecticide-treated clothing. Early elimination campaigns successfully controlled outbreaks of disease throughout the Americas through mosquito control and eradication alone.[3] Significant progress has been made in eliminating urban yellow fever transmission using the yellow fever vaccine, which was developed in the 1930s. Despite these efforts, yellow fever is still considered a reemerging disease and remains associated with significant morbidity and mortality, especially in parts of Africa. Incomplete vaccination coverage and inadequate vector control allows the virus to persist and outbreaks still occur in urban and rural settings.[3]

The current yellow fever vaccine is especially effective[2] and is part of the childhood vaccination schedule in several countries in Africa. The National Expanded Program on Immunization (EPI) in the Democratic Republic of Congo (DRC), which is responsible for overseeing and monitoring vaccination activities in the country, has incorporated the yellow fever vaccination for all children at nine months of age since 2003.[4] Routine immunization occurs throughout the country, however, the DRC is the largest country in sub-Saharan Africa. Most of the population lives in rural and isolated communities that are extremely difficult to access due to poor road infrastructure and challenging landscape. The EPI experiences significant challenges due to the country size and existence of remote health districts and health centers where immunization activities are conducted and data are collected. Despite efforts by EPI to provide routine vaccination for all children, DRC was among the top 10 countries with the highest number of fully unimmunized children in 2014.[5] Communicable, maternal, neonatal, and nutritional diseases still contribute to the most death and disability combined and cause significantly more premature death compared to similar regions.[6] As a result, DRC has been the focus of efforts to strengthen the quality of surveillance data to facilitate prioritizing and planning for the immunization program and receives regular support from the Global Alliance

for Vaccines and Immunizations (GAVI), a public-private partnership aiming to improve childhood vaccination coverage in poor countries and to accelerate access to new vaccines.[5,7] GAVI has been supporting EPI immunization efforts since 2002 by providing various vaccines, injection safety equipment, and strengthening health systems.[8,9] Funding from GAVI has been abundant, however, successfully implementing immunization programs in the DRC continues to be difficult.[8]

Estimates of yellow fever vaccination in DRC vary by source. The WHO and UNICEF estimate that coverage for yellow fever vaccination was approximately 66% in 2015, 67% in 2016, and 76% in 2017. These estimates are slightly lower than the official estimates (as reported by national authorities reflecting a combination of administrative coverage, survey-based data and other data sources) of 88% in 2015, 78% in 2016, and 87% in 2017.[10] Achieving high vaccination coverage may be especially challenging for the yellow fever vaccine since it is administered later than most other vaccines. Most vaccines in DRC are administered by 14 weeks, however, an additional follow-up is required at nine months for the yellow fever and measles vaccines, increasing the chance of missing the vaccine.[4]

Despite this routine immunization program by EPI, DRC (and neighboring Angola) experienced outbreaks of yellow fever in 2016.[11] Local transmission was quickly observed in three provinces (Kwango, Kinshasa, and Kongo Central) as a result of frequent travel between the two countries, inadequate vaccination coverage, and high vector (mosquito) density in both countries. Between January 1 and August 11, 2016, 2,269 suspected cases were reported and ultimately, 78 (4%) were confirmed.[12] In response to the outbreak, disease control and surveillance measures were implemented, including reactive vaccination campaigns for all ages, in order to avoid further spread of the disease.[13] In combination with the vaccination campaigns

in Angola (30 million vaccines total), this vaccination effort, while exhausting the global stockpile several times, succeeded in stopping the outbreaks in both countries.

Improving routine vaccination coverage is essential for preventing outbreaks of yellow fever and avoiding the need for costly emergency vaccination campaigns. Identifying factors that can be modified or targeted for intervention can provide opportunities to improve baseline vaccination coverage and allow for more efficient vaccination campaigns outside of routine programs. Few studies have assessed predictors of vaccination in DRC and even fewer have focused on yellow fever vaccination.[14–18] Clarifying which factors may be predictors of vaccination, specifically for yellow fever in DRC, can help guide immunization efforts to prevent future outbreaks and improve protection against this vaccine-preventable disease. This study aims to explore the level of childhood yellow fever vaccination in DRC, identify demographic and behavioral factors associated with vaccination status among children (ages 9-59 months), and determine differences in yellow fever vaccination status by geographic area in DRC.

2.3 Methods

The Demographic and Health Survey (DHS) program has implemented more than 300 surveys in over 90 countries on population, health, HIV, and nutrition. Between November 2013 and February 2014, the second DHS survey was administered in the Democratic Republic of Congo (DRC) by the Ministry of Monitoring, Planning, and Implementation of the Modern Revolution in collaboration with the Ministry of Health. Households were selected in a stratified two-stage cluster sampling procedure where enumeration areas (or clusters) were established based on the general census and stratified into urban and rural areas, then randomly selected with

a probability proportional to the size of the population. Households were then randomly sampled within each cluster without replacement from a complete list of all households in the cluster. Ultimately, 18,360 households (5,474 in urban areas in 161 clusters and 12,886 in rural areas in 379 clusters) were selected for the 2013/14 DRC DHS.[19,20]

All women aged 15-49 years old who usually lived in the selected household or who were present the night before the survey and all men aged 15-59 years old in one of every two households were eligible for the individual survey. In total 18,827 women and 8,656 men were interviewed in 536 clusters (four clusters, two in Katanga, one in Orientale province and one in North Kivu, could not be surveyed due to insecurity). The overall household response rate of selected households was 99.9% and the response rate in surveyed households was 99% among women and 97% among men and were similar in urban and rural areas.[20]

The children's dataset was analyzed to assess vaccination coverage of yellow fever. This dataset includes 18,716 children, one record for every biological child of all surveyed women born in the last five years (ages 6 to 59 months). Information related to the pregnancy, pre- and ante-natal care and vaccination history was collected. Infants and children were included in biomarker data collection (height, weight, anemia, malaria, and vaccine-preventable disease serology) if the household had been selected for a men's questionnaire (i.e., half of all households). Children aged 9 to 59 months were included in this analysis because these children would be eligible for the yellow fever vaccine in DRC.

This analysis aims to identify modifiable factors associated with yellow fever vaccination that may be potential targets for interventions. Since predictors of yellow fever vaccination in DRC have not been examined, factors previously identified as being associated with various indicators of complete vaccination in children in DRC as well as other parts of Africa will be

assessed. These include child level characteristics (child's age, sex and birth order),[14,17,21–24] maternal characteristics (maternal age at birth, wealth index/income, maternal education/literacy, use of ante- and postnatal care, place of delivery, and the number of children ever born),[14,16–18,21–35] and community (or contextual) level characteristics (access to health facilities, affordability of health care, and type of geographic location).[15–17,22,25–31,33]

Yellow fever vaccination status was ascertained using the DHS questionnaire. Participants were asked to provide a vaccination card for each child included in the survey and completion of yellow fever including the date, if available, was recorded. If a vaccination card was not available, the mother was asked to provide information about the child's vaccination status. This was recorded and compiled by DHS to provide information about completed vaccination (e.g., "Vaccination date on card", "Reported by mother", "Vaccination marked on card", "Don't know", or "No" vaccination received). Yellow fever vaccination indicated (marked or dated) on a vaccination card was primarily used as the source of vaccination status and vaccination card plus maternal report was assessed as a secondary source of information. Each source of information for yellow fever vaccination status was also mapped along with geographic factors such as province and type of geography to examine the spatial distribution of vaccination coverage.

Survey data analysis methods were used to take into account the staged-sampling design. Sample weights provided by the DHS were incorporated into the analysis to account for sample design and make the sampled data more representative of the entire population. The individual weights were produced using the household sample selection probabilities and the response rates for households and for individuals. The initial weights were standardized by dividing by the average of the initial weights.[36] Stratum and cluster factors were used to allow for accurate

statistical inference as prescribed by the DHS (i.e., the sampling weights affect the calculation of point estimates and the stratification and clustering factors affect the calculation of standard errors).

Variable descriptive statistics (frequencies and percentages or mean and standard deviation) were obtained for categorical and continuous variables, respectively, applying the sampling weight, stratum, and cluster. A weighted logistic multilevel model was used to elucidate both individual and community-level fixed factors associated with vaccination. A two-level model was used to account for children (level 1) nested within mothers (level 2) with common maternal and community-level characteristics with random effects for level 2 (random intercepts) to address variability not explained by the covariates in the model defined at each level. In the case of some variables which were only ascertained from the mother for the most recent pregnancy (youngest child), such as antenatal and postnatal care, weighted logistic regression was used. Bivariate odds ratios (ORs) and 95% confidence intervals (CIs) will be reported for each factor.

All analyses were completed in SAS 9.4 and maps were generated in ESRI GIS ArcMap 10.5. These data are publicly available for download and use by registered participants. The DHS program authorized the use of these data for this investigation. During data collection by the DHS program, verbal informed consent for the questionnaire and specimen collection was obtained from each respondent before the interview. For children, consent was obtained from one of the child's parents or a responsible adult who was at least 18 years of age. The DHS Program maintains strict standards to protect the privacy of respondents and household members.

2.4 Results

Overall, 17,228 children had information recorded regarding yellow fever vaccination (1,488 children were not included due to being deceased, nine children were missing information, and 151 respondents did not know their vaccination status). 14,297 children who were nine months old or older and eligible for the vaccine were included in this analysis and 14,146 had information about vaccination documented (excluding 5 with missing information and 146 who responded "don't now"), resulting in 13,973 children in the analysis after applying survey weights. All subsequently reported frequencies are after applying the survey weights.

Overall, 2,308 (16.5%) children older than nine months old presented a vaccination card for review. 1,914 children had yellow fever vaccination documented on their vaccination card with an estimated vaccination coverage of 82.9% and 9,766 had received the yellow fever vaccination when considering both the vaccination card as well as mother's report with an estimated vaccination coverage of 69.9% (Table 2.1). Although most children are eligible for the vaccine at nine months of age, the proportion of children who were nine months old at the time of the survey who were vaccinated was slightly lower than 30%, and vaccination coverage slowly increased among older aged children until about 51 months old at the time of the survey and plateaued. The number and proportion of children with vaccination cards were generally very low and fewer older children had vaccination cards, indicating that maternal report may be a valuable source of information for the older children (Figure 2.1).

Utilizing only the vaccination card, the average age of vaccinated children (30.2 months) was higher than non-vaccinated children (21.7 months) (Table 2.1). Yellow fever vaccination percentage was similar among both male and female children (82.8% and 83.0%, respectively) and varied depending on birth order with middle children having the highest vaccination

coverage (90.3%) followed by firstborn children with multiple children in the household (83.9%) and only children (83.2%) compared to last born (78.6%). Maternal age at birth and the average total children ever born were similar among mothers of vaccinated and non-vaccinated children. Vaccination coverage varied slightly by maternal education level with the highest coverage among mothers with higher education (Table 2.1). Vaccination was overall lowest among richer families (79.3%), however, there was variation observed dependent on whether the area was characterized as urban or rural. Vaccination coverage among most wealth index categories was higher in rural areas than in urban areas (except in the richest areas, which were equivalent). In urban areas, the percent vaccination coverage increased from poorer wealth index to richest wealth index, and in rural areas, the percentage remained relatively similar among the wealth index categories. (Table 2.1 and Figure 2.2B).

Antenatal and postnatal care was only ascertained for the youngest child, however, yellow fever vaccination coverage was higher among mothers' who had 4 to 7 antenatal care visits (82.8%) and who utilized postnatal care within two months (84.1%) versus among those who did not utilize postnatal care (78.0%). Vaccination coverage was lowest among mothers who delivered at home and highest among mothers who delivered at a government or public facility (64.9% versus 85.4%, respectively) and was higher among mothers who did not perceive a big problem getting medical help. Lastly, vaccination was higher in rural areas (85.3%) than in urban areas (79.4%) overall and within provinces. Even in provinces with higher vaccination coverage, the percentage was higher in rural areas than in urban areas (Figure 2.2A). In general, vaccination was higher in provinces not affected by conflict (84.4%) than in provinces affected by conflict (81.6%), and this was also observed within provinces except in North Kivu where the vaccination coverage is generally high (Table 2.1 and Figure 2.2A).

Yellow fever vaccination percentages were overall lower when considering the vaccination card as well as maternal response. The average age of vaccinated children was 34.7 months compared to 30.6 months among unvaccinated children. Vaccination percentage was similar among both male and female children (69.8% and 69.9%, respectively) and, again, did vary depending on birth order, however, following a different pattern. Only children and last-born children had slightly lower vaccination coverage compared to middle born (73.3%) and firstborn (71.1%). Maternal age at birth was similar among vaccinated and non-vaccinated children and the average total children ever born varied slightly, similar to when utilizing just the vaccination card. Vaccination was lower among mothers with no education (63.3%) and increased up to 94.6% among mothers with higher education (Table 2.1). Similarly, vaccination was overall low among the poorest families (58.1%) and gradually increased to 86.5% among the richest families, however, this trend is more complex when examining the wealth index among the urban areas versus the rural areas. The poorest families in rural areas have the lowest vaccination coverage (57.3%) and the richest families have the highest vaccination coverage (94.7%) based on vaccination card and maternal report and the middle wealth index categories tended to have slightly higher coverage in rural areas compared to urban areas (Figure 2.2D).

Vaccination coverage was also higher among mothers' who had attended 4-7 antenatal care visits (75.2%) and more than eight visits (72.2%) compared to less than three visits (59.0%) and who utilized postnatal care within two months compared to those who did not (78.7% versus 64.3%, respectively). Vaccination coverage was again lowest among mothers who delivered at home and highest among mothers who delivered at a privately-owned facility (40.4% versus 77.3%, respectively) and was higher among mothers perceiving that getting medical help was not a big problem. Lastly, vaccination was overall higher in urban areas (78.4%) than in rural areas

(66.2%) and higher in provinces not affected by conflict (74.9%) than in provinces affected by conflict (65.5%) (Table 2.1). This variation exists overall and within provinces with the exception of North Kivu and South Kivu, which had equal or higher yellow fever vaccination coverage in rural areas and are also affected by conflict (Figure 2.2C).

Utilizing the vaccination card information only, the odds of yellow fever vaccination were slightly higher among older children and were lower for last-born children (OR: 0.169, 95% CI: 0.079, 0.362) compared to middle born children. The odds of yellow fever vaccination of children did not vary by maternal education level or between wealth index groups. Health care system utilization increased the odds of yellow fever vaccination. Utilizing antenatal and postnatal care contributed to increased odds of vaccination where the odds of vaccination were 1.623 times higher among mothers who used 4-7 antenatal care visits during pregnancy and 1.493 times higher among mothers who had a postnatal care visit within two months. The odds of childhood vaccination were also considerably lower if the mother gave birth at home (OR: 0.146, 95% CI: 0.038, 0.562) compared to delivering at a government or public facility. Community characteristics were also important factors in yellow fever vaccination, where children in rural areas had 0.428 times the odds of being vaccinated (95% CI: 0.208, 0.878) compared to rural areas but the odds of vaccination did not differ between children depending on if they lived in conflict-affected provinces or if their family had no problems with the distance to the health center for getting medical help (Table 2.2).

Similar factors were found to be important when utilizing the vaccination card and maternal report as the source for yellow fever vaccination. The odds of yellow fever vaccination were higher among older children and varied by birth order. The odds of vaccination were lower for last-born children (OR: 0.324, 95% CI: 0.257, 0.408) as well as only children (OR: 0.451,

95% CI: 0.293, 0.695) when compared to middle born children. Additionally, the odds of having a vaccinated child decreased with more children ever born (OR: 0.938, 95% CI: 0.89, 0.988). The odds of childhood vaccination varied by maternal education level; the odds among secondary and higher educated mothers were seven times the odds compared to mothers with no education (95% CI: 4.787, 10.495). Furthermore, the odds of childhood vaccination varied greatly between wealth index groups with the richest group having about 18 times the odds than the poorest group (95% CI: 11.078, 30.823) (Table 2.2).

Utilization of health care services was also important when considering the vaccination card and maternal report to determine yellow fever vaccination status. The odds of the child being vaccinated were higher among children whose mothers did not have a problem getting money from medical help, used antenatal, and postnatal care. The odds of childhood vaccination were also considerably lower if the mother gave birth at home (OR: 0.048, 95% CI: 0.034, 0.066) compared to delivering at a government or public facility. In addition, the community characteristics represented higher odds of vaccination in urban areas (OR: 4.429, 95% CI: 3.276, 5.987), for children whose mothers did not perceive a problem with distance to a health center (OR: 2.823, 95% CI: 2.151, 3.705), and children from conflict-affected provinces (OR: 2.943, 95% CI: 2.236, 3.874) (Table 2.2).

2.5 Discussion

This study represents the first assessment of factors associated with yellow fever vaccination among children in DRC. Ensuring high vaccination coverage in the population is one of the most effective ways to prevent yellow fever cases and outbreaks. Using the DHS survey from 2013-14, the estimated vaccination coverage among children is approximately between

69.9% and 82.9%, depending on the source of information used. These estimates are consistent with other estimates of yellow fever vaccination in DRC. Shearer et al. estimated that children in DRC less than four years old was were 60-70% vaccinated in 2016[37] and UNICEF/WHO estimates that overall yellow fever vaccination coverage was approximately 66% in 2015.[10] However, a recent Multiple Indicator Cluster Surveys (MICS) survey in 2017-18 indicated that vaccination coverage among children ages 12 to 23 months and 24 to 35 months might, in fact, be lower (52.6% and 63.0%, respectively).[38] In general, estimates of vaccination coverage are lower than necessary, potentially because yellow fever is administered later in the vaccine schedule than other routine vaccines, requiring additional follow-up, and contact with the healthcare system. This may result in these later vaccines being neglected or forgotten. Previous studies indicate that there are identifiable predictors of immunization, some that can be targets of interventions to improve vaccination coverage in the DRC. The context of these factors is particularly important as some social factors may be similar across countries, but others may differ based on income level and the specific populations.[39] Clarifying these factors specifically for yellow fever in DRC can help guide immunization efforts to improve protection against this vaccine-preventable disease.

The estimate of yellow fever vaccination coverage varied considerably depending on which information source was used (82.9% for vaccination card only versus 69.9% when considering both the vaccination card as well as mother's report), which would change the assumption of protection against yellow fever in DRC. Relying on the presence of vaccination card only seems to be a limitation to estimating vaccination coverage for yellow fever. Although the vaccination card indicated very favorable vaccination coverage, only about 16.5% (2,308 out of 13,973) of children presented a vaccination card and the number of children with a

vaccination card declined with older age, so this may not represent the entire child population of DRC. Those missing a vaccination card may represent an unvaccinated population, therefore, it would be helpful to understand the barriers to retaining vaccination cards in DRC to improve use of this important record keeping mechanism. As a result, maternal information may be a helpful source of information in this type of assessment to augment the information obtained from the vaccination card. Unfortunately, maternal recall is known to be subject to bias[40] and not only requires the mother to remember that the child received a vaccine but also which vaccine was given and when. Maternal recall may also suffer from social desirability bias, not only for vaccination status, but other indicators of health and wellness. However, some studies have found that maternal recall is accurate compared to vaccine card information in a similar setting and that these two information sources can be used together to compile accurate surveillance data.[41,42] The DHS survey only collected one source of information for each child (i.e., either vaccination card if available or mother's report if it was not available), so the two sources could not be directly compared in this analysis. Future assessments of vaccination coverage may further compare these two sources to better understand their accuracy and ascertain a more complete assessment of vaccination coverage.

Previous studies have noted that characteristics of the child such as older age, being male,[14,21–23] and firstborn in the birth order [17,23,24] are important factors in determining vaccination status. Gender disparities in accessing some services, such as health and education, are possible, however, this study, along with others, did not demonstrate a difference in vaccination based on the sex of the child.[24,25] Being a firstborn child was also not as relevant in this study. Using a more discrete categorization for birth order revealed that last-born children had a lower odds of yellow fever vaccination compared to middle born children. Only children

also had lower odds of being vaccinated when compared to middle children, although this depended on whether the information was gathered from the vaccination card or the vaccination card and the mother's report. This may also be influenced by the actual presence of the vaccination card (i.e., last-born children may be more likely to have the vaccination card in their possession) and may need to be further clarified.

It is clear that most mothers play an essential role in their child's vaccination status. Utilizing a multilevel model allowed us to account for correlation in vaccination status between children who have common mothers and communities, however, many maternal characteristics were still associated with their child's vaccination status, especially when using the vaccination card and mother's report as the source of vaccination information. As in other studies about vaccination, maternal education of secondary school and higher was found to be an important factor associated with a higher odds of yellow fever vaccination than no education.[14,16–18,22–31,33,35] Additionally, increasing total number of children ever born or in the family or household[34,35] was associated with lower odds of vaccination when considering information from the vaccination card and mother's report. Of note, the DHS only includes biological children of mothers in the survey, so these data may exclude a high-risk population of children that may not be vaccinated. Obtaining information about these children could help clarify the role of mothers in their child's vaccination status.

Factors related to the healthcare and immunization system have been identified as crucial for improving vaccination efforts. Common limitations to vaccination associated with the immunization systems typically include factors such as "poor access and distance from vaccination services, inadequate vaccine supply, health worker availability and knowledge, missed opportunity to vaccinate (including non-specified missed opportunities, misuse of

contraindications, lacking vaccination card[…], and no screening for vaccination during receipt of curative services), vaccinator absent at the scheduled time for vaccinations, direct and indirect costs associated with vaccination, place of residence (living in rural or certain urban settings such as slums), low political and financial support for health system, and lack of integration with maternal health services."[43] Although many of these elements were not directly ascertained in the DRC DHS survey, elements relating to healthcare system utilization such as money needed to access care, difficulty with the distance to health facilities, antenatal, postnatal care, and delivery location were examined. Specific distance to a health facility was not ascertained, however, mothers were asked if the distance to a health facility to get medical help and getting money for medical care were a "big problem" and identifying that neither was a problem was associated with yellow fever vaccination in children when using the vaccination card and mother's report. Other studies elucidated that having to walk to reach a healthcare center (specifically half an hour to one hour) or the need to travel to get to a health facility in general were barriers to vaccination.[15,30]

Maternal healthcare utilization, including having at least four antenatal care visits and utilizing postnatal care within two months after birth, were associated with increased child vaccination for yellow fever.[16,25,26] Furthermore, giving birth at home was associated with much lower odds of vaccination compared to giving birth in a government or public facility. This was also observed in studies in similar settings, although, vaccination at a privately funded health facility[29] or delivery at any institution (all institutions were grouped)[16,25,26] were associated with complete vaccination when compared to home delivery. These findings demonstrate a continuum of care whereby mothers establish care during pregnancy, with repeated visits to a healthcare facility for antenatal care followed by delivery at an institution, especially government and

public facilities, and ultimately vaccination of their child. These facilities are responsible for and likely prioritizing providing health counseling and vaccination information, which helps facilitate childhood vaccination success after birth.

The effect of poverty and health is significant and complex. Poverty is a major cause of poor health outcomes and is a barrier to accessing health care. More impoverished communities carry a disproportionate burden of poor health, for example, higher than average child and maternal mortality and higher levels of chronic and infectious disease.[44] Not only is the relationship financial but also logistical. The poor may not be able to afford to access health care when needed, experience barriers in transportation to access care, availability and affordability of quality food, and lack of opportunity to maintain a healthy lifestyle. Poorer individuals also experience challenges accessing important health education information and often lack advocates for their health needs. However, poor health is also a determinant of poverty. Healthcare is expensive and often paid through out-of-pocket spending. Furthermore, illness may result in loss of income for the sick and family members who may be providing care, subsequent need to borrow money resulting in immense debt for an individual or household, further perpetuating a spiral of loss of income and high healthcare costs. Ensuring good health is central to overall human development and poverty reduction.[44,45] Poverty specifically contributes to challenges in achieving adequate vaccination coverage in the DRC, where more than 70% of people live below the poverty line,[8,46] and in several other countries and similar settings.[16,18,22,23,28,30,35] In fact, this study demonstrates that a higher percentage of children from higher wealth index categories were vaccinated for yellow fever and this trend was especially true in urban areas. In addition, having big problems with money to pay for medical care was identified as a factor contributing to lower odds of yellow fever vaccination among children in DRC and lack of money to pay for

immunization fees, specifically, have been identified as an obstacle to immunization.[31] Addressing poverty would not only improve vaccination coverage but could also improve the overall health of many communities in DRC.

The size of DRC and the numerous rural communities creates challenges with vaccine supply and availability. Urban settings are typically reported as having higher vaccination levels potentially due to availability and accessibility of vaccines,[17,22,28] although in some settings increased presence of public health officials and vaccination campaigns in rural areas contributes to higher vaccination coverage.[27,33] In this study, the association between yellow fever vaccination status and geography type differed depending on the source of information. Using both the vaccination card and mothers' report, only 30.5% of children in this survey lived in an urban setting, which was associated with four times the odds of being vaccinated for yellow fever. Within each province, urban areas tended to have, on average, 13-14% higher vaccination coverage than rural settings with the exception of South Kivu, where vaccination was higher in rural areas, and North Kivu, where vaccination did not differ greatly by type of geography. A disproportionate percentage of children in South Kivu live in a rural area (90% per this DHS survey) which may account for the higher vaccination observed among rural residents. North Kivu is also an area of DRC with ongoing conflict and humanitarian crisis, so emergency vaccination campaigns have been used in this area to help maintain vaccination levels.[47] Using the vaccination card only, the odds of vaccination were lower in urban areas than in rural areas, overall and within provinces. There may be more focus on vaccination campaigns and retaining vaccination cards in rural areas, although this information was not ascertained in this survey and could not be assessed.

Children who were from provinces not affected by conflict had overall higher odds of vaccination than children who were from conflict-affected provinces. Vaccination activities in DRC are complicated by conflict and unrest, leading to prolonged interruptions in vaccination programs. Additionally, conflict has a deleterious effect on children's nutritional status resulting in stunted growth, emaciation, and weight inadequacy, which has implications on immune status and vaccine immunity uptake. DRC experiences conflict in six of the eleven old provinces: Equateur, Orientale, North Kivu, South Kivu, Maniema, and Katanga, resulting in poverty and displacement of populations.[48] In fact, 81.4% of internally displaced persons (IDPs) in DRC were displaced because of armed conflict and an additional 16.3% because of conflict-related insecurity.[48] These individuals may be missed in vaccination efforts due to their movement. Furthermore, political unrest also creates challenges specifically for yellow fever control. Population movement and migration of non-immune people from non-endemic areas to areas with ongoing sylvatic transmission to escape violence have resulted in yellow fever outbreaks in Sudan and Uganda and could similarly affect DRC where yellow fever is endemic.[49–51]

The findings in this study came from using a large population-based and validated dataset, which can be used to make inferences about the entire country. The DHS program uses trained local surveyors to ensure that the quality of responses is consistent and standardized. Surveys are also repeated every few years in each country, so future trends over time can be assessed using this standardized survey. However, there are some limitations. This study relies on cross-sectional survey data and, therefore, cannot establish temporality or causal relationships between predictors and yellow fever immunization. However, some variables of interest incorporate a temporal relationship such as mother’s age at birth, ante- and postnatal care, number of children in the family, and place of delivery and other variables are unlikely to change

over time in DRC such as type of geography and presence of conflict. Using cross-sectional data also allows for estimates of prevalence, which may help the local Ministry of Health since they are useful from a public health perspective for resource allocation, determining the extent of disease burden, and opportunities to intervene at a population level. Although the DHS is intended to be nationally representative, there may be some influence of non-response bias. However, the response rates reported in the final report of the 2013-14 DRC survey are sufficiently high to negate this concern. There is also the possibility for recall bias among the predictor information due to the retrospective nature of data collection, but recall bias was not observed in DHS surveys by comparing overlapping data from consecutive surveys.[52] Not all participants had a vaccination card and there may be a potential for differential missing data. We are limited by the data that has been collected, however, by comparing the different sources of yellow fever vaccination information (vaccination indicated on card and reported by mother and indicated on card) we were able to assess for differences in prevalence patterns and associated factors. The small proportion of children that had a vaccination card limited the factors that could be clarified, however, certain factors such as birth order, ante- and postnatal care and delivery place were important in both assessments, which reinforces the importance of these findings.

Lastly, some variables were not ascertained as part of the DHS survey that could also influence compliance with vaccination such as quality of health care services, information regarding the content of counseling and education about vaccines, use of reminder communication, or follow-up visits[31]. However, some information was available regarding access to care (e.g., funds availability and travel requirement to health care facility) and were utilized in this study to explore some elements of healthcare accessibility and utilization. Other studies have also indicated that elements of vaccine knowledge and attitudes are important

factors associated with vaccination coverage[26,53] and especially contributed to non-vaccination rather than under-vaccination[43], but this information was also not gathered through the DHS survey.

The health delivery system in DRC faces many challenges due to poor infrastructure and competing priorities for prevention. Despite routine immunization for yellow fever, cases still occur sporadically throughout DRC and as part of an outbreak in 2016. The DRC has also experienced outbreaks of several other diseases recently including cholera, the worst outbreak of measles in DRC's history, vaccine-derived polio, the 11th Ebola outbreak on record, and DRC is now experiencing cases associated with the ongoing coronavirus disease 2019 (COVID-19) pandemic which requires attention and priority.[54,55] Unfortunately, COVID-19 is expected to interrupt many health services even further, including vaccination. In fact, many countries, including DRC, have suspended or reduced routine and supplemental vaccination campaigns in fear of spreading COVID-19. This is expected to exacerbate gaps in vaccination coverage further and leave millions of children at risk of vaccine-preventable infectious diseases.[56,57] Furthermore, if the trend of decreasing yellow fever vaccination coverage indicated in the recent MICS results continues, this will create additional challenges for prevention.[38] Few studies have previously focused on factors associated with yellow fever vaccination specifically, and none have focused on yellow fever in DRC; this is the first study to accomplish these aims. Identifying these factors can provide defined opportunities to target interventions for specific groups or areas to improve vaccination coverage, especially during a time where resources for providing preventative services such as routine vaccination are limited. These goals support local Ministry of Health efforts as well as align with the Eliminate Yellow Fever Epidemics (EYE) Global Strategy for 2017-2026 that has been revised after the 2016 outbreak.[58]

The findings of this study indicate that it is important to address maternal factors that may be barriers when developing public health interventions for promoting childhood vaccinations. Access to the healthcare system and immunization services is essential. Ensuring access to ante- and postnatal care as well as encouraging delivery in a health care setting can improve vaccination efforts. Furthermore, improving accessibility, providing cost-sharing for healthcare, and outreach services, especially in rural and conflict-affected areas, may be beneficial but should also be explored further. Lastly, improving mother's degree of education as well as decreasing poverty may improve the overall health of the community and increase yellow fever vaccination coverage in DRC. These efforts must also be multi-faceted as no single factor alone contributes to vaccination coverage for yellow fever. This study identifies important opportunities to protect at-risk populations, improve vaccination coverage, and prevent future outbreaks and international spread of yellow fever.

2.6 Tables and Figures

Table 2.1 Demographic characteristics by source of vaccination information of children ages 9 – 59 months old in the Democratic Republic of Congo 2013-14 Demographic and Health Survey

	Yellow fever on vaccination card (n= 2,308, unweighted = 1,989)			Yellow fever on card and maternal report (n= 13,973, unweighted = 14,146)		
	Total	Yes (n = 1,914, unweighted = 1,622)	Chi-sq/ t-test p-value	Total	Yes (n = 9,766, unweighted = 9,141)	Chi-sq/ t-test p-value
	n *mean (SE)	n (%) *mean (SE)		n *mean (SE)	n (%) *mean (SE)	
Child Characteristics						
Child's age (months)*	28.8 (0.51)	30.2 (0.54)	<.0001	33.5 (0.14)	34.7 (0.18)	<.0001
Child's Sex			0.9073			0.8648
Male	1122	773 (82.80)		6919	4830 (69.81)	
Female	1186	849 (83.03)		7054	4935 (69.97)	
Birth Order			<.0001			<.0001
Only child	341	284 (83.24)		1428	982 (68.79)	
First born	191	160 (83.94)		1314	968 (73.68)	
Middle born	631	570 (90.32)		5044	3695 (73.26)	
Last born	1146	900 (78.57)		6187	4120 (66.59)	
Maternal Characteristics						
Maternal age at birth (years)*	27.2 (0.24)	27.3 (0.25)	0.3234	27.1 (0.10)	27 (0.13)	0.4611
Total children ever born*	4.1 (0.10)	4.1 (0.11)	0.9906	4.4 (0.04)	4.3 (0.05)	0.0382
Maternal education			0.2757			<.0001
No education	401	344 (85.78)		2677	1694 (63.27)	
Primary	831	687 (82.68)		6113	3958 (64.75)	
Secondary	992	804 (81.12)		4979	3921 (78.76)	
Higher	85	78 (92.72)		204	193 (94.55)	
Wealth index			0.591			<.0001
Poorest	304	254 (83.57)		3055	1774 (58.08)	

Poorer	445	370 (83.15)		3118	2046 (65.62)	
Middle	495	417 (84.37)		2887	1995 (69.09)	
Richer	490	389 (79.27)		2586	1938 (74.93)	
Richest	574	483 (84.24)		2327	2013 (86.52)	
Getting money needed for medical help			0.5611			<.0001
Big problem	1338	1243 (82.37)		9985	6734 (67.44)	
Not a big problem	651	671 (83.95)		3985	3031 (76.06)	
Number of antenatal care visits during pregnancy			0.0653			<.0001
0-3	577	432 (74.75)		3780	2232 (59.03)	
4-7	852	705 (82.77)		3563	2678 (75.15)	
8+	49	39 (80.15)		223	161 (72.17)	
Postnatal care within 2 months			0.0388			<.0001
No	949	848 (77.98)		6097	3918 (64.27)	
Yes	324	327 (84.10)		1479	1164 (78.70)	
Place of delivery			0.0003			<.0001
Home	141	92 (64.88)		2575	1040 (40.39)	
Government or Public Facility	1680	1435 (85.40)		9148	7043 (76.99)	
Private Facility	463	368 (79.48)		2083	1609 (77.28)	
Other	19	15 (78.04)		119	63 (53.01)	
Community Characteristics						
Type of Geography			0.0312			<.0001
Urban	869	740 (79.40)		4257	3336 (78.36)	
Rural	1120	1173 (85.30)		9715	6429 (66.18)	
Distance to health center for getting medical help			0.3495			<.0001
Big problem	845	688 (81.38)		5714	3692 (64.62)	
Not a big problem	1463	1226 (83.80)		8253	6071 (73.56)	
Conflict-affected Province			0.3296			<.0001
Yes	1248	1019 (81.63)		7452	4878 (65.46)	
No	1060	895 (84.43)		6521	4888 (74.95)	

Figure 2.1 Weighted number of children and cumulative percent with yellow fever vaccination by current age of child and source of vaccination information among children ages 9 – 59 months old in the Democratic Republic of Congo 2013-14 Demographic and Health Survey

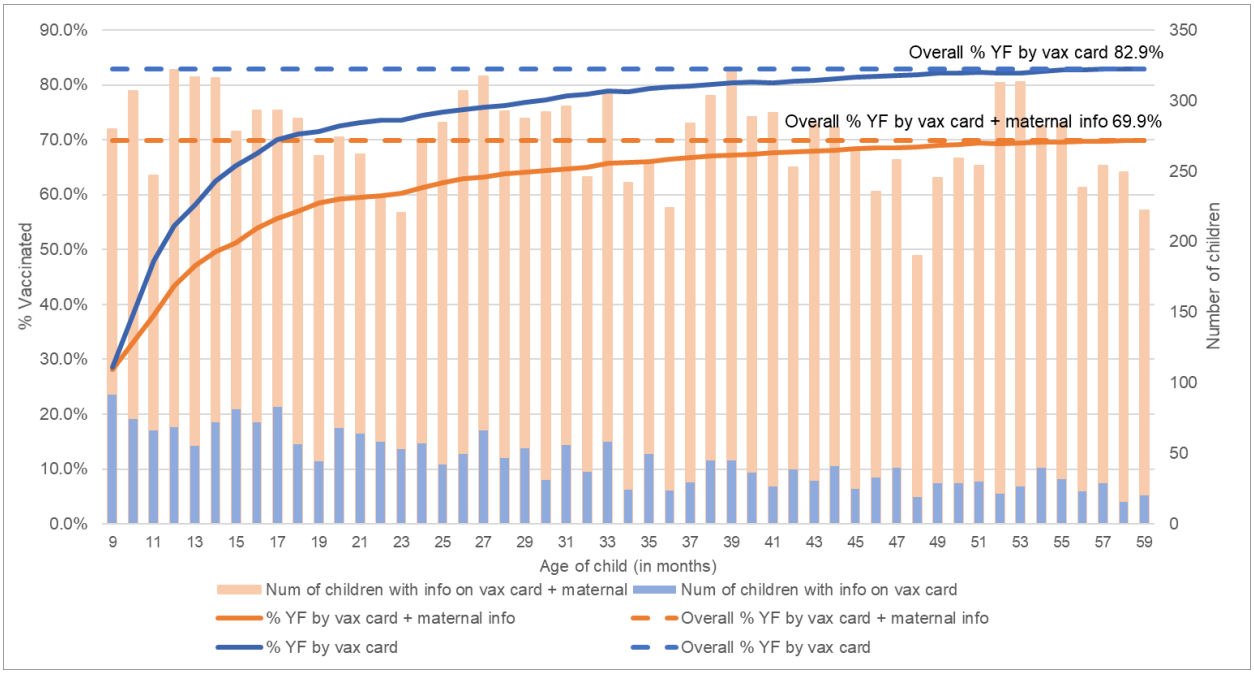
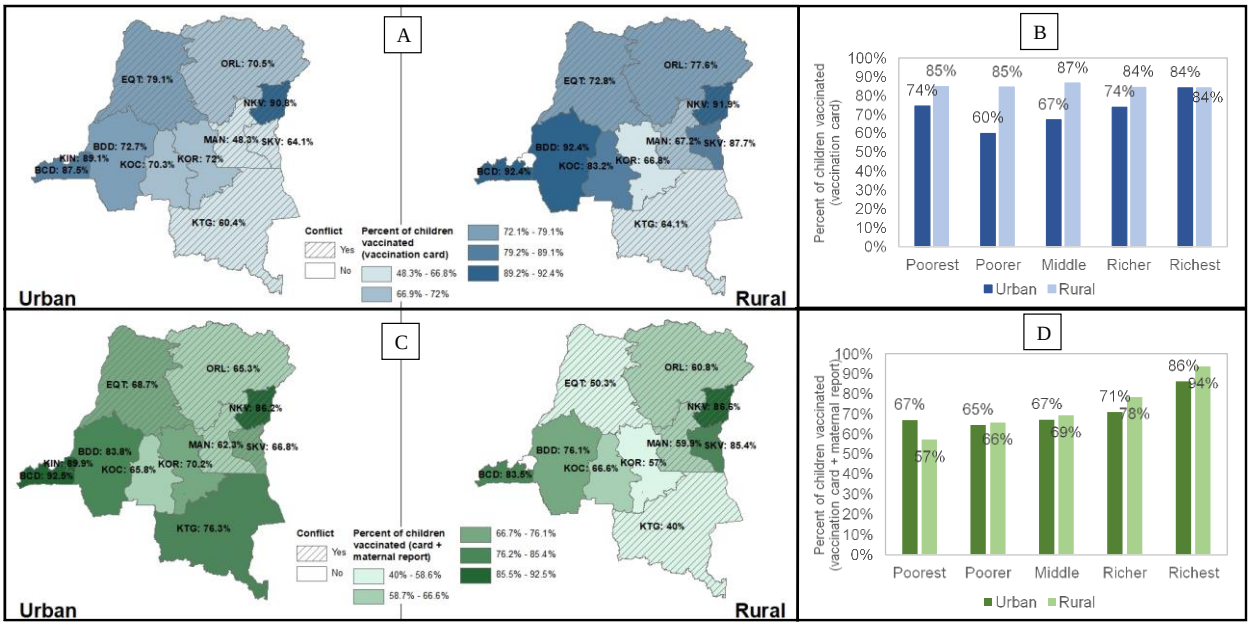


Figure 2.2 Percent of children vaccinated by province, type of geography, wealth index, and source of vaccination information among children ages 9 – 59 months old in the Democratic Republic of Congo 2013-14 Demographic and Health Survey



Provinces: BDD – Bandundu, BCD: Bas Congo, EQT: Equateur, KIN: Kinshasa, KOC: Kasai Occidental, KOR: Kasai Orientale, KTG: Katanga, MAN: Maniema, ORL: Orientale, NKV: North Kivu, SKV: South Kivu

Table 2.2 Bivariate relationship between selected factors and yellow fever vaccination status by source of vaccination information among children ages 9 – 59 months old in the Democratic Republic of Congo 2013-14 Demographic and Health Survey

Fixed effects	Yellow fever on vaccination card (n= 2,308, unweighted = 1,989) OR (95% CI)	Yellow fever on card and maternal report (n= 13,973, unweighted = 14,146) OR (95% CI)
Child Characteristics		
Child's age (months)	1.094 (1.060, 1.129)	1.049 (1.041, 1.056)
Child's Sex		
Male	ref	ref
Female	1.098 (0.595, 2.025)	0.972 (0.792, 1.193)
Birth Order		
Only child	0.381 (0.135, 1.073)	0.451 (0.293, 0.695)
First born	0.524 (0.169, 1.627)	0.938 (0.636, 1.384)
Middle born	ref	ref
Last born	0.169 (0.079, 0.362)	0.324 (0.257, 0.408)
Maternal Characteristics		
Maternal age at birth (years)	1.011 (0.964, 1.060)	0.981 (0.962, 1.000)
Total children ever born	0.972 (0.853, 1.107)	0.938 (0.89, 0.988)
Maternal education		
No education	ref	ref
Primary	0.644 (0.212, 1.951)	1.236 (0.875, 1.746)
Secondary and Higher	0.69 (0.238, 1.996)	7.088 (4.787, 10.495)
Wealth index		
Poorest	1.033 (0.325, 3.289)	0.452 (0.308, 0.663)
Poorer	ref	ref
Middle	1.363 (0.487, 3.817)	1.611 (1.069, 2.428)
Richer	0.582 (0.199, 1.698)	3.114 (2.001, 4.847)
Richest	1.286 (0.482, 3.431)	18.479 (11.078, 30.823)
Getting money needed for medical help		
Big problem	ref	ref
Not a big problem	1.26 (0.611, 2.598)	2.942 (2.128, 4.065)
Number of antenatal care visits during pregnancy*		
0-3	ref	ref
4-7	1.623 (1.121, 2.35)	2.098 (1.776, 2.479)
8+	1.364 (0.397, 4.686)	1.8 (0.928, 3.491)
Postnatal care within 2 months*		
No	ref	ref
Yes	1.493 (1.021, 2.183)	2.054 (1.673, 2.520)
Place of delivery		
Home	0.146 (0.038, 0.562)	0.048 (0.034, 0.066)
Government or Public Facility	ref	ref
Private Facility	0.463 (0.207, 1.038)	1.034 (0.732, 1.460)
Other	0.114 (0.002, 7.450)	0.116 (0.043, 0.309)

Community Characteristics		
Type of Geography		
Rural	ref	ref
Urban	0.428 (0.208, 0.878)	4.429 (3.276, 5.987)
Distance to health center for getting medical help		
Big problem	ref	ref
Not a big problem	1.561 (0.767, 3.178)	2.823 (2.151, 3.705)
Conflict-affected Province		
Yes	ref	ref
No	1.562 (0.800, 3.048)	2.943 (2.236, 3.874)

OR = odds ratio, CI = confidence interval.
Results based on weighted generalized (logistic) multilevel model except for variables indicated with * are based on weighted logistic regression (as described in the Methods section)

2.7 References

1. Monath TP, Vasconcelos PFC. Yellow fever. *J Clin Virol*. 2015;64:160-173. doi:10.1016/j.jcv.2014.08.030
2. World Health Organization. Yellow fever Fact Sheet. http://www.who.int/mediacentre/factsheets/fs100/en/. Published 2016.
3. Rogers DJ, Wilson AJ, Hay SI, Graham AJ. The global distribution of yellow fever and dengue. *Adv Parasitol*. 2006;62:181-220. doi:10.1016/S0065-308X(05)62006-4
4. World Health Organization. Emergencies preparedness, response - Yellow fever in the Democratic Republic of the Congo. *WHO*. 2015. https://www.who.int/csr/don/2010_07_19a/en/. Accessed November 13, 2018.
5. Centers for Disease Control and Prevention. Fostering Ownership of Childhood Immunization Data in Democratic Republic of Congo. https://www.cdc.gov/globalhealth/immunization/stories/child-immunization-drc.htm. Published 2014. Accessed January 20, 2019.
6. Institute for Health Metrics and Evaluation. Democratic Republic of the Congo. http://www.healthdata.org/democratic-republic-congo. Accessed January 20, 2019.
7. Global Alliance for Vaccines and Immunization. Gavi country factsheet : The Democratic Republic of the Congo. https://www.gavi.org/country/drc/. Accessed October 13, 2018.
8. Ferrinho P, Mohammed M. Barriers to immunization coverage in DRC: An analysis of the GAVI-Alliance cash-based support. *Ann Trop Med Public Heal*. 2013;6(4):401. doi:10.4103/1755-6783.127773
9. PATH. *Immunization in the Democratic Republic of the Congo: Landscape Analysis and Policy Recommendations*. Seattle; 2016. https://path.azureedge.net/media/documents/APP_drc_landscape_rpt.pdf. Accessed January 19, 2019.

10. WHO and UNICEF. *Democratic Republic of the Congo: WHO and UNICEF Estimates of Immunization Coverage: 2017 Revision*.; 2018. https://www.who.int/immunization/monitoring_surveillance/data/cod.pdf. Accessed March 10, 2019.

11. World Health Organization. Emergencies preparedness, response, Yellow Fever – Democratic Republic of the Congo, 11 April 2016. WHO. http://www.who.int/csr/don/11-april-2016-yellow-fever-drc/en/. Published 2016. Accessed May 19, 2017.

12. Ingelbeen B, Weregemere NA, Noel H, et al. Urban yellow fever outbreak—Democratic Republic of the Congo, 2016: Towards more rapid case detection. Beasley DWC, ed. *PLoS Negl Trop Dis*. 2018;12(12):e0007029. doi:10.1371/journal.pntd.0007029

13. World Health Organization. Emergencies preparedness, response, Yellow fever – Democratic Republic of the Congo, 2 June 2016. WHO. http://www.who.int/csr/don/02-june-2016-yellow-fever-drc/en/. Published 2016. Accessed May 19, 2017.

14. Kabudi AM, Mukobelwa P, Kazadi JM, Bardella IJ. Prevalence and associated factors of partially/non-immunization of under-five in Goma city, Democratic Republic of Congo: a community-based cross-sectional survey. *Pan Afr Med J*. 2015;20(38). doi:10.11604/pamj.2015.20.38.4483

15. Mwamba GN, Yoloyolo N, Masembe Y, et al. Democratic Cite this: The Pan African Medical Journal. 2017;27:7. doi:10.11604/pamj.supp.2017.27.3.11930

16. Acharya P, Kismul H, Mapatano MA, Hatløy A. Individual- and community-level determinants of child immunization in the Democratic Republic of Congo: A multilevel analysis. Ali M, ed. *PLoS One*. 2018;13(8):e0202742. doi:10.1371/journal.pone.0202742

17. Ashbaugh HR, Hoff NA, Doshi RH, et al. Predictors of measles vaccination coverage among children 6–59 months of age in the Democratic Republic of the Congo. *Vaccine*. 2018;36(4):587-593. doi:10.1016/j.vaccine.2017.11.049

18. Zivich PN, Kiketa L, Kawende B, Lapika B, Yotebieng M. Vaccination Coverage and Timelines Among Children 0–6 Months in Kinshasa, the Democratic Republic of Congo: A Prospective Cohort Study. *Matern Child Health J*. 2017;21(5):1055-1064. doi:10.1007/s10995-016-2201-z

19. Demographic and Health Survey. *Sampling and Household Listing Manual*. Calverton; 2012. https://dhsprogram.com/pubs/pdf/DHSM4/DHS6_Sampling_Manual_Sept2012_DHSM4.pdf. Accessed March 11, 2019.

20. Demographic and Health Survey. *Democratic Republic Congo DHS, 2013-14 - Final Report (French)*. Rockville; 2014. www.DHSprogram.com. Accessed March 11, 2019.

21. Adokiya MN, Baguune B, Ndago JA. Evaluation of immunization coverage and its associated factors among children 12–23 months of age in Techiman Municipality, Ghana, 2016. *Arch Public Heal*. 2017;75(1):28. doi:10.1186/s13690-017-0196-6

22. Wiysonge CS, Uthman OA, Ndumbe PM, Hussey GD. Individual and Contextual Factors Associated with Low Childhood Immunisation Coverage in Sub-Saharan Africa: A Multilevel Analysis. Moormann AM, ed. *PLoS One*. 2012;7(5):e37905.

doi:10.1371/journal.pone.0037905

23. Oleribe O, Kumar V, Awosika-Olumo A, Taylor-Robinson SD. Individual and socioeconomic factors associated with childhood immunization coverage in Nigeria. *Pan Afr Med J*. 2017;26. doi:10.11604/pamj.2017.26.220.11453

24. Munthali AC. Determinants of vaccination coverage in Malawi: Evidence from the demographic and health surveys. *Malawi Med J*. 2007;19(2):79-82. doi:10.4314/mmj.v19i2.10934

25. Sunguti JL, Neave PE, Taylor S. Family factors associated with immunization uptake in children aged between twelve and fifty-nine months: a household survey in Kakamega Central district, Western Kenya. *Healthc Low-resource Settings*. 2016;4(1). doi:10.4081/hls.2016.5447

26. Meleko A, Geremew M, Birhanu F. Assessment of Child Immunization Coverage and Associated Factors with Full Vaccination among Children Aged 12-23 Months at Mizan Aman Town, Bench Maji Zone, Southwest Ethiopia. 2017. doi:10.1155/2017/7976587

27. Kagoné M, Yé M, Nébié E, et al. Vaccination coverage and factors associated with adherence to the vaccination schedule in young children of a rural area in Burkina Faso. *Glob Health Action*. 2017;10(1):1399749. doi:10.1080/16549716.2017.1399749

28. Gram L, Soremekun S, ten Asbroek A, et al. Socio-economic determinants and inequities in coverage and timeliness of early childhood immunisation in rural Ghana. *Trop Med Int Heal*. 2014;19(7):802-811. doi:10.1111/tmi.12324

29. Odusanya OO, Alufohai EF, Meurice FP, Ahonkhai VI. Determinants of vaccination coverage in rural Nigeria. *BMC Public Health*. 2008;8(1):381. doi:10.1186/1471-2458-8-381

30. Ekouevi DK, Gbeasor-Komlanvi FA, Yaya I, et al. Incomplete immunization among children aged 12–23 months in Togo: a multilevel analysis of individual and contextual factors. *BMC Public Health*. 2018;18(1):952. doi:10.1186/s12889-018-5881-z

31. Zida-Compaore WIC, Ekouevi DK, Gbeasor-Komlanvi FA, et al. Immunization coverage and factors associated with incomplete vaccination in children aged 12 to 59 months in health structures in Lomé. *BMC Res Notes*. 2019;12(1):84. doi:10.1186/s13104-019-4115-5

32. Mthiyane TN. Factors associated with vaccination status in children under 5 years of age in two communities in South Africa. 2016. http://wiredspace.wits.ac.za/handle/10539/22309. Accessed August 20, 2018.

33. Schoeps A, Ouédraogo N, Kagoné M, Sié A, Müller O, Becher H. Socio-demographic determinants of timely adherence to BCG, Penta3, measles, and complete vaccination schedule in Burkina Faso. *Vaccine*. 2013;32(1):96-102. doi:10.1016/J.VACCINE.2013.10.063

34. Abadura SA, Lerebo WT, Kulkarni U, Mekonnen ZA. Individual and community level determinants of childhood full immunization in Ethiopia: a multilevel analysis. *BMC Public Health*. 2015;15(1):972. doi:10.1186/s12889-015-2315-z

35. Mthiyane TN, Cohen C, Norris SA, et al. Factors associated with missed and delayed

DTP3 vaccination in children aged 12-59 months in two communities in South Africa, 2012-2013. *South African Med J*. 2019;109(8):562-569. doi:10.7196/SAMJ.2019.v109i8.13244

36. Rutstein SO, Rojas G. *Demographic and Health Survey Guide to DHS Statistics*. Calverton; 2006. https://dhsprogram.com/pubs/pdf/DHSG1/Guide_to_DHS_Statistics_29Oct2012_DHSG1.pdf. Accessed March 11, 2019.

37. Shearer FM, Moyes CL, Pigott DM, et al. Global yellow fever vaccination coverage from 1970 to 2016: an adjusted retrospective analysis. *Lancet Infect Dis*. 2017;17(11):1209-1217. doi:10.1016/S1473-3099(17)30419-X

38. INS. *Multiple Indicator Cluster Survey (MICS), 2017-2018, Survey Results Report. Kinshasa, Democratic Republic of the Congo*. Kinshasa; 2019. https://mics-surveys-prod.s3.amazonaws.com/MICS6/West and Central Africa/Congo%2C Democratic Republic of the/2017-2018/Survey findings/Congo%2C Democratic Republic of the%2C 2017-18 MICS SFR_French.pdf. Accessed July 8, 2020.

39. Tauil M de C, Sato APS, Waldman EA. Factors associated with incomplete or delayed vaccination across countries: A systematic review. *Vaccine*. 2016;34(24):2635-2643. doi:10.1016/j.vaccine.2016.04.016

40. Valadez JJ, Weld LH. Maternal recall error of child vaccination status in a developing nation. *Am J Public Health*. 1992;82(1):120-122. doi:10.2105/AJPH.82.1.120

41. Ndirangu J, Bland R, Bärnighausen T, Newell M-L. Validating child vaccination status in a demographic surveillance system using data from a clinical cohort study: evidence from rural South Africa. *BMC Public Health*. 2011;11(1):372. doi:10.1186/1471-2458-11-372

42. Binyaruka P, Borghi J. Validity of parental recalls to estimate vaccination coverage: evidence from Tanzania. *BMC Health Serv Res*. 2018;18(1):440. doi:10.1186/s12913-018-3270-z

43. Rainey JJ, Watkins M, Ryman TK, Sandhu P, Bo A, Banerjee K. Reasons related to non-vaccination and under-vaccination of children in low and middle income countries: Findings from a systematic review of the published literature, 1999-2009. *Vaccine*. 2011;29(46):8215-8221. doi:10.1016/j.vaccine.2011.08.096

44. World Health Organization. *Poverty and Health DAC Guidelines and Reference Series* .; 2003. https://www.who.int/tobacco/research/economics/publications/oecd_dac_pov_health.pdf. Accessed May 10, 2020.

45. The World Bank. Poverty and Health. https://www.worldbank.org/en/topic/health/brief/poverty-health. Published August 25, 2014. Accessed May 10, 2020.

46. Demographic and Health Survey. *Democratic Republic of the Congo Demographic and Health Survey (DRC-DHS II 2013-2014) Supplemental Vaccine-Preventable Diseases Report*.; 2015. https://dhsprogram.com/pubs/pdf/FR300/FR300.vpd.pdf. Accessed October 27, 2018.

47. UN Office for the Coordination of Humanitarian Affairs. *Democratic Republic of Congo • North Kivu Situation Report No. 17*.; 2012.

48. Conflicts in the Democratic Republic of Congo: Causes, impact and implications for the Great Lakes region | United Nations Economic Commission for Africa. https://www.uneca.org/publications/conflicts-democratic-republic-congo-causes-impact-and-implications-great-lakes-region. Published 2015. Accessed May 3, 2020.

49. Baba MM, Ikusemoran M. Is the absence or intermittent YF vaccination the major contributor to its persistent outbreaks in eastern Africa? *Biochem Biophys Res Commun*. 2017;492(4):548-557. doi:10.1016/j.bbrc.2017.01.079

50. Onyango CO, Ofula VO, Sang RC, et al. Yellow fever outbreak, Imatong, Southern Sudan. *Emerg Infect Dis*. 2004;10(6):1064-1068. doi:10.3201/eid1006.030738

51. Wamala JF, Malimbo M, Okot CL, et al. Epidemiological and laboratory characterization of a yellow fever outbreak in northern Uganda, October 2010-January 2011. *Int J Infect Dis*. 2012;16(7):e536-e542. doi:10.1016/j.ijid.2012.03.004

52. Murray CJL, Shengelia B, Gupta N, Moussavi S, Tandon A, Thieren M. Validity of reported vaccination coverage in 45 countries. *Lancet (London, England)*. 2003;362(9389):1022-1027. doi:10.1016/S0140-6736(03)14411-X

53. Wemakor A, Kofi Helegbe G, Abdul-Mumin A, Amedoe S, Zoku JA, Dufie AI. Prevalence and factors associated with incomplete immunization of children (12-23 months) in Kwabre East District, Ashanti Region, Ghana. doi:10.1186/s13690-018-0315-z

54. WHO | Democratic Republic of the Congo. https://www.who.int/csr/don/archive/country/cod/en/. Accessed June 19, 2020.

55. DRC Ebola outbreak crisis update | MSF. https://www.msf.org/drc-ebola-outbreak-crisis-update. Accessed June 19, 2020.

56. Infectious Disease Vulnerability in DR Congo | UNICEF USA. https://www.unicefusa.org/stories/ebola-measles-and-now-covid-19-dr-congo-crisis/37185. Accessed June 19, 2020.

57. At least 80 million children under one at risk of diseases such as diphtheria, measles and polio as COVID-19 disrupts routine vaccination efforts, warn Gavi, WHO and UNICEF. https://www.who.int/news-room/detail/22-05-2020-at-least-80-million-children-under-one-at-risk-of-diseases-such-as-diphtheria-measles-and-polio-as-covid-19-disrupts-routine-vaccination-efforts-warn-gavi-who-and-unicef. Accessed June 19, 2020.

58. World Health Organization. Eliminate Yellow fever Epidemics (EYE): a global strategy, 2017-2016. *Wkly Epidemiol Rec*. 2017;92(16):193-204. https://www.who.int/wer/2017/wer9216/en/. Accessed August 13, 2018.

Chapter 3: Exploring spatial patterns and identifying sociodemographic, environmental, and organizational risk factors associated with yellow fever in the Democratic Republic of Congo

3.1 Abstract

Yellow fever is transmitted by infected mosquitoes in three transmission cycles. Although environmental factors such as rainfall and high temperatures generally play a role in increased mosquito-borne disease transmission, vaccine-induced or natural immunity to yellow fever in these areas is likely lower than necessary to prevent outbreaks. This study aims to identify spatial patterns in reported yellow fever cases and analyze the spatial relationship between important sociodemographic, environmental, and organizational risk factors with the distribution of yellow fever cases in DRC to help identify targets for enhanced surveillance and intervention. This population-based ecological study uses data from the Demographic and Health Survey (DHS) 2013-14 survey, the DHS Service Provision Assessment (SPA) 2017-18 survey, and the DRC Integrated Disease Surveillance and Response (IDSR) system aggregated and summarized within DRC health zones. Non-spatial descriptive statistics and Poisson log-linear regression were used to assess relationships between risk factors and reported yellow fever standardized morbidity ratio (SMR). Spatial analyses included assessing spatial autocorrelation, spatial clustering, and a spatial generalized linear mixed model for areal data to extend the regression analysis and model spatial autocorrelation using risk factor information and a set of random effects represented by a conditional autoregressive (CAR) prior distribution. Yellow fever cases were reported in 273 health zones, information was available for 331 health zones from the DHS 2013-14 survey, and 442 health zones from the DHS 2017-18 SPA survey.

Moderate positive and statistically significant global spatial autocorrelation (Moran's I statistic = 0.1764, p-value = 0.001) and significant High-High clusters located in the Central and Northern areas of DRC. Using methods that account for this clustering as well as Bayesian inference strategies and data augmentation, the relative risk of reported yellow fever was lower with increased mean wealth index, increased (log) mean population density, presence of proper vaccine transport, and higher with increasing mean vegetation index. This is the first study to identify geographic patterns in reported yellow fever cases and provides a comprehensive geographic assessment of yellow fever risk. In DRC, yellow fever cases are not reported at random but are clustered among certain health zones. This study highlights areas of high yellow fever reporting and improves the understanding of geographical risk, which is essential to future efforts for preventing and controlling yellow fever in DRC. These results are specific to health zones in the DRC and provide actionable areas for improvement to the Ministry of Health.

3.2 Introduction

Yellow fever is an acute viral hemorrhagic disease caused by the yellow fever virus, the prototype member of the genus *Flavivirus*, a family of positive-strand, single-strand RNA viruses, the majority of which are transmitted by mosquitoes or ticks and cause viral hemorrhagic fevers.[1] Yellow fever is transmitted by infected mosquitoes, primarily the *Aedes* or *Haemoagogus* species,[2] in three transmission cycles: jungle/sylvatic (transmission of the virus between non-human primates, mosquitos, and humans visiting the jungle), intermediate/savannah in Africa (transmission between mosquitos and non-human primates and humans living or working in jungle border areas), and the urban cycle (transmission only

between humans and urban mosquitos once the virus is brought to urban areas by an infected human).[3]

Mosquito eradication campaigns have been successful at reducing vector populations and the yellow fever vaccine, developed in 1930, has almost eliminated urban yellow fever transmission in parts of the world.[4] Despite these efforts, yellow fever is still considered a reemerging disease and is endemic in all or parts of 34 countries in Africa where 90% of cases are reported, including in the Democratic Republic of Congo (DRC), and tropical parts of South America with over 50 countries worldwide at risk for reemergence.[5] Forty-four countries in Africa, South and Central America are considered part of the modern yellow fever endemic zone and almost 900 million people are at risk of infection.[6] Estimates of the burden of yellow fever vary by source; anywhere from 5,000 to 200,000 cases annually have been reported in the tropical regions of Africa, South America, and Central America.[2,6–8] Reported cases collected through passive surveillance likely greatly underestimate true incidence since early symptoms of yellow fever are mild and non-specific and cases often occur in rural, under-resourced areas resulting in misdiagnosis and misreporting.[1] WHO reported 1,111 reported cases in 2016, which represents a substantial increase over previous years, but a modeling study based on African data sources estimated 84,000–170,000 severe cases and 29,000–60,000 deaths in 2013.[2]

Since the 1980s, several outbreaks of yellow fever have occurred throughout Africa and South America, including in Nigeria, which had numerous cases in several outbreaks from 1986-1994, and more recently in Uganda, Sudan, Ethiopia, DRC, Angola, and currently in Brazil.[1,8,9] In 2016, 78 cases of yellow fever were confirmed in an outbreak in 3 provinces in DRC. Most cases were among adult males who traveled or worked in Angola, but 19% of cases were locally transmitted. There were 18 deaths among confirmed cases (23% case fatality).[10] The

intermediate and urban transmission cycle are most responsible for recent outbreaks of yellow fever.[4–6,11]

Unprotected exposure of an unvaccinated individual to mosquitoes in an endemic area is the major risk factor for yellow fever infection. Large mosquito and human population sizes and increased density increase exposure rates contributing to urban outbreaks and rapid transmission.[12,13] The rate of urban growth in Africa is the most rapid in the world and the proportion of urban populations is estimated to reach 63% by 2020.[11] Increasingly dense urban populations and lower than desired immunization rates result in an increased chance of virus transmission.

Mosquito burden is mediated by environmental and geographic factors, such as climate.[14] Severe or prolonged rainy seasons are associated with increased numbers of vectors and may be implicated in increased transmission.[1] The Aedes mosquito is capable of breeding in small amounts of water that accumulates in artificial containers inside or close to dwellings or in natural reservoirs such as tree holes. This is especially exacerbated in urban areas where overcrowding is possible and low-income housing, inadequate water supply, poor sanitation, and waste removal practices result in open containers becoming inadvertently filled with rainwater (or intentionally used to store drinking water).11 These environmental conditions help support disease transmission in urban settings and increase the risk for outbreaks of yellow fever.[1,14] Certain ecosystems also support vector abundance such as the low-lying rain forests and forest-savanna ecotones in both South America and Africa.[1] Although environmental factors such as rainfall and high temperatures generally play a role in increased mosquito-borne disease transmission, it is likely that vaccine-induced or natural immunity to yellow fever in these areas is also lower than expected.[1]

Studies that have estimated yellow fever risk and burden of disease have considered factors such as rainfall, surface or air temperature, vegetation index, land cover classification, longitude, latitude, altitude (typically based on satellite imagery), and existing disease patterns to create global risk maps.[4,12,13,15,16] A recent assessment of global yellow fever risk included factors about the vector and reservoir including, *Aedes aegypti* temperature and habitat suitability and distribution of suspected non-human primate reservoirs, to identify areas outside of common risk areas that may also be at high risk for yellow fever transmission.[16]

Yellow fever is preventable through vaccination. The current yellow fever vaccine is especially effective[2] and is part of the childhood vaccination schedule in several countries in Africa, including the DRC which began vaccinating all children at nine months of age in 2003.[17] However, low and middle-income countries tend to have a limited health infrastructure (limited health facilities, shortage of medical personnel, and poor sanitation) making them especially susceptible to vector-borne disease outbreaks.[14] Furthermore, limited immunization systems such as poor access, long distances, inadequate vaccine supply, and place of residence (i.e., living in a rural area or urban slums) have been one of the leading factors associated with under-vaccination as well as non-vaccination in low and middle-income countries.[18]

Problems with the cold chain (the system that ensures these proper temperatures are maintained during transport and storage of equipment, personnel are trained, and efficient management procedures are in place[19]) have also been implicated in outbreaks of vaccine-preventable disease, but few studies have examined this issue, especially not in the DRC. Temperature variations related to exposure to light and repeated freezing and thawing can have adverse effects on vaccine stability. Exposure to temperatures outside the recommended ranges can reduce vaccine potency and increase the risk that the recipient will not be protected from the

disease.[20] Problems with vaccine storage have been identified in health facilities throughout Africa[21–23] and vaccines have been found to be less potent than expected despite being far from the expiration date.[24] The yellow fever vaccine is especially susceptible to temperature variations since it is required to be stored between 35ºF to 46ºF and never frozen and the half-life is reduced from approximately 14 days to 3 to 4.5 days when stored at a slightly higher temperature of 45ºF to 47ºF.[25] A malfunctioning cold chain can result in vaccine waste and unnecessary costs as well as unintentional human harm and cold chain deficiencies may be ubiquitous in Africa and a major barrier to effective vaccination campaigns.

Although DRC has implemented an Integrated Disease Surveillance and Response (IDSR) system for disease reporting, there are several burdens on the system including the logistics of transferring information, accessibility between health centers, and varying priorities of health care workers that may result in delays in reporting or in some cases, no reporting. Indeed throughout West Africa, surveillance for yellow fever likely suffers from under-recognition, underreporting, and underestimation secondary to limitations with diagnostic capabilities and health infrastructure.[14] Therefore, there are still challenges with detecting and controlling disease outbreaks throughout DRC. It would be advantageous to develop alternative ways to identify targets for enhanced surveillance and potential intervention to prevent yellow fever transmission. Analyzing patterns in the spatial distribution of yellow fever may assist with these efforts.

Yellow fever is endemic in the DRC with suspected cases sporadically reported throughout the country despite having an active routine immunization program. The recent yellow fever outbreak highlights the need to understand yellow fever risk and susceptibility in DRC. This study aims to identify spatial patterns in reported yellow fever cases and analyze the

spatial relationship between important sociodemographic, environmental, and organizational risk factors with the distribution of yellow fever cases in DRC. This will be the first study to incorporate a comprehensive assessment of yellow fever risk, specifically focused on DRC, a high-risk area, that can help inform local public health programs and interventions.

3.3 Methods

Study Design and Data Sources

This is a population-based ecological study examining sociodemographic, environmental, and organizational risk factors gathered from several spatially referenced datasets. A complete data set was compiled by aggregating and summarizing data within each health zone and matching with a geographic shapefile of DRC health zones obtained by the UCLA-DRC Research Program, which included 519 health zones. DRC is currently made up of 26 provinces (previously 11 provinces before 2015), each of which is broken into health zones (the number has changed over time but approximately 519 in total). On average, 10 to 15 health zones make up a province. Most programs regarding disease prevention and surveillance are coordinated at this level then carried out throughout the health zones. Within each health zone, smaller defined health areas have health centers or posts that support local populations.

Datasets

The Demographic and Health Survey (DHS) program has implemented more than 300 surveys in over 90 countries on population, health, HIV, and nutrition. Between November 2013 and February 2014, the second DHS survey was administered in the Democratic Republic of Congo (DRC) by the Ministry of Monitoring, Planning, and Implementation of the Modern

Revolution in collaboration with the Ministry of Health. A detailed description of participant sampling and data collection have been previously described and are available directly through the DHS program.[26,27] The children's dataset, including children aged 9 to 59 months, is used in this analysis. The DHS Program collects geographic information that can be linked with health data, health facility locations, and other local infrastructure information. Each sampling cluster is geocoded in the field using GPS receivers. The GPS latitude and longitude positions for all surveys are randomly displaced to ensure confidentiality but still reflect the location of the cluster. GPS coordinates are generally accurate to less than 15 meters.[28] The DHS program has also created datafiles with commonly used geospatial covariates that can be easily linked to the DHS survey data by cluster.

The DHS program also conducted a Service Provision Assessment (SPA) survey in DRC in 2017-18. The SPA survey is a health facility assessment focused on a country's health service delivery. Several key topics are assessed, including infrastructure, resources, and systems. This includes an assessment of water sources, electricity, latrines, storage and stock monitoring for vaccines, contraceptives, and medicines, and infection control.[29,30] The exact geocoded location of the health facility was recorded by the DHS program without displacement.

The DRC has implemented an Integrated Disease Surveillance and Response (IDSR) system, a comprehensive regional framework for strengthening national public health surveillance and response systems in Africa.[31] Data from the IDSR system is available from 2006 for a combination of 24 diseases that have varied over the years (Supplemental Table 3.1). Data from 2010-2015 were used to provide a background level of yellow fever in DRC.

Yellow fever cases and expected counts

The total number of suspected yellow fever cases reported per health zone between 2010-2015 in the IDSR system was obtained from the Direction for Disease Control (DGLM) within the Ministry of Health and summarized over the time period. Suspected cases were obtained from the IDSR already aggregated by health zone, but health zone names were cross-matched and standardized between years and matched with the DRC health zone shapefile. Age or sex-stratified case counts and population estimates were not available, therefore, the expected count of cases in each area was determined by standardizing the reported cases using the DRC population.[32,33] The health zone population estimates were based on extrapolation from the 2013 Expanded Program for Immunization (EPI) microplan estimates obtained from the DRC Ministry of Health. A population growth rate of 1.03 was assumed to extrapolate forward and backward for each year and the average of 2010-2015 was used to represent the health zone. The standardized morbidity ratio (SMR) was calculated as the observed number of reported cases divided by the expected count. A small constant (10^{-5}) was added to both the observed and expected count to ensure the SMR could be determined.[33] The SMR is commonly used in disease mapping as a simple estimate of elevated levels of disease risk (relative risk) in an area (e.g., health zone).[32,34]

Risk factor variables

The risk factors of interest in this study were informed by the known disease process and literature describing yellow fever. The variables were grouped into three categories: sociodemographic, environmental, and organizational, which included variables to assess health facility capacity to offer yellow fever vaccination such as access, quality (cold chain capacity,

vaccine transportation, and storage) and availability. Sociodemographic and environmental data were obtained from the DHS 2013-14 health survey and the organizational factors were obtained from the DHS 2017-18 SPA survey. The geocoded locations for clusters for the DHS 2013-14 survey and geocoded locations of health facilities from the DHS 2017-18 SPA survey were geographically matched with the health zone shapefile and assigned a corresponding health zone. The variables were summarized within each health zone (mean value, percentage, or majority value category) while incorporating the survey weights provided by the DHS program to account for sample design and provide estimates representative of the entire population and region (see Table 3.2 for a description of variables).

After health zone matching and summarization, the IDSR, DHS 2013-14 and DHS 2017-18 SPA surveys were merged by health zone and compiled for analysis.

Statistical Analysis

Non-spatial analysis

Non-spatial exploratory analyses included reviewing the distributions of each variable as well as pairwise relationships in the data. Descriptive statistics by health zone were examined, including means and standard deviations or frequencies and percentages, and missing data were reviewed. The total number of cases and the reported yellow fever SMR were visualized by mapping all available data by quantile.

Poisson log-linear regression was used to assess relationships between sociodemographic, environmental, and organizational risk factors and reported yellow fever SMR. Risk ratios and 95% confidence intervals were reported for all risk factors. Count data often demonstrates high overdispersion, a violation of one of the assumptions of the Poisson model that the mean and

variance are equal, which could potentially underestimate the standard errors and overstate the significance of variables.[35] A quasi-Poisson regression model was used to adjust the standard errors by a scale (dispersion) parameter and address overdispersion in the data. However, non-spatial analysis of the SMR or count data does not account for similarities of disease risk in neighboring areas (spatial autocorrelation), which can be an additional cause of overdispersion in geographically correlated count data.[36,37] Spatial autocorrelation is correlation between values based on their close location to each other, potentially resulting from a similar pattern of exposure, level of disease risk, or infectious potential. This introduces a violation of the assumption of most statistical tests that observations are independent and identically distributed which needs to be accounted for in the analysis.[32,38]

Spatial analysis

Assessing spatial autocorrelation was used to reveal patterns in disease risk and indicate the potential need for different statistical techniques. To accurately assess spatial autocorrelation, neighboring areas must be defined and represented by a neighbor weight matrix structure. There are several methods available for this process, included adjacent neighbors who share only common boundaries ("Rook" method), any common points ("Queen" method), and distance-based methods, such as inverse distance, number (k) of nearest neighbors, nearest neighbors based on distance, among other classifications.[33] The underlying spatial processes of yellow fever are unknown, however, previous studies have found that distance-based approaches generally perform better than adjacency based approaches especially for irregular shapes and sizes of areas and that a simple nearest neighbors approach is reasonable for spatial processes that assume the nearest neighboring spatial units have the most influence.[33,39] In this study, k=6

nearest neighbors were used, which was found to fit the data better than other distance-based methods based on the Deviance Information Criterion (DIC)[40] from regression results in sensitivity analyses (Supplemental Table 3.3). The six nearest neighbors of each health zone were determined by Euclidean distance and assigned a binary classification weight (1 = neighbor, 0 = not a neighbor).

The Moran's *I* is a standard measure of spatial autocorrelation in the data. A Monte Carlo simulation with 1,000 simulations of the Moran's *I* statistic was used to explain the geographic pattern of yellow fever SMR. The null hypothesis for the global test is that no clustering exists (i.e., random distribution). The value of Moran's *I* is similar to a correlation coefficient, which quantifies the similarity between areas that are spatially related.[41] Positive spatial autocorrelation indicates patterns where neighboring areas are similar and negative spatial autocorrelation indicates that neighboring areas are dissimilar. Applying Moran's *I* to the SMR accounts for the spatial distributions of the observed cases and the underlying population.[32] Local Indicator of Spatial Autocorrelation (LISA) analysis using Local Moran's *I* was used to decompose the global Moran's *I* findings by clarifying the contribution of each observation to the magnitude of the global Moran's *I* statistic and identify clusters of similarly high-high or low-low SMR values or outlier values that are surrounded by opposite values (i.e., high-low or low-high).[42] LISA analysis was used to identify influential observations (or hot spots of influence) and the location of these observations or clusters were mapped by High-High, High-Low, Low-High, and Low-Low classification. Clustering and influential observations were considered significant if the p-value was lower than 0.05.

As mentioned, analysis of count data using Poisson log-linear regression is limited by the presence of overdispersion and, in the case of geographically referenced data, spatial

autocorrelation even after adjusting for known risk factors in the model. To assess the Poisson model fit, model residuals were also tested for spatial autocorrelation using Moran's *I*. In the presence of residual spatial autocorrelation, a spatial generalized linear mixed model for areal data was used to extend the regression analysis and model spatial autocorrelation using risk factor information and a set of random effects represented by a conditional autoregressive (CAR) prior distribution. Modeling the random effects is used to account for any overdispersion or spatial autocorrelation that persists after adjusting for risk factors in the model. This model is a preferred framework for spatially structured models because it uses information from nearby neighboring areas to create smoothed risk ratios over the observed data.[34,41,43] Parameter estimates and smoothed estimates of the SMR were estimated in a hierarchical Bayesian spatial modeling framework using Markov chain Monte Carlo (MCMC) simulation with a combination of Gibbs sampling and Metropolis-Hastings steps.[34,41] Several CAR prior models for the random effects have been proposed in disease mapping. The Leroux prior model was used because it is based on a single set of random effects and can represent a range of weak and strong spatial correlation structures. A prior investigation determined that this model is both theoretically and practically appealing and produces consistently good results regardless of whether the data are independent or contain strong spatial correlation.[34]

The CAR hierarchical modeling structure was implemented in R with the package "CARBayes" using the Leroux prior distribution of spatial random effects with the default parameter hyperprior distributions.[44] Parameters were estimated in a Bayesian framework using MCMC and three chains of 300,000 iterations each, with 100,000 steps discarded as burn-in, and then thinned by 100 (resulting in 2,000 samples in each chain). Model convergence was assessed by reviewing trace plots for convergence and Geweke's criterion (a score test based on

comparing the means of the first and last part of the Markov chain).[44] Risk ratios and 95% credible intervals for each risk factor were computed based on the posterior medians of the parameter estimates after combining results from all three chains. The posterior median and 95% credible interval for the spatial variance parameter (τ^2) and spatial correlation parameter (ρ) are reported. Implementing the CAR prior model MCMC allows for missing values in the outcome variable. The missing values are treated as additional values to estimate and are updated in the MCMC algorithm using data augmentation.[44] The regression models were rerun using this functionality to represent more health zones in the analysis. Lastly, model residuals were tested for any remaining spatial autocorrelation using a Monte Carlo simulation with 1,000 simulations of the Moran's *I* statistic.

To create a yellow fever risk map of DRC based on available data, smoothed risk ratio estimates of the reported yellow fever SMR was calculated by extracting the fitted values based on the posterior mean divided by the expected number.

All dataset cleaning and summarization were completed in SAS version 9.4. Health zone mapping and matching were completed in ESRI ArcMap version 10.7, and statistical analyses and map creation were done in R version 3.6.1. The DHS datasets are publicly available for download and use by registered participants. The DHS program authorized the use of these data for this investigation. The deidentified IDSR surveillance data was obtained for use by the UCLA-DRC Research Program from the DGLM, Ministry of Health in DRC.

3.4 Results

The process of merging and matching the three datasets is depicted in Figure 3.1. Overall, yellow fever cases were reported in 273 health zones (1 reporting "health zone" could not be

mapped, however, this was determined to be a prison camp and not a geographic health zone). A total of 2,135 suspected cases of yellow fever were reported during the 2010-2015 period, with a mean of 7.82 per health zone. Additionally, information was available for 331 health zones from the DHS 2013-14 survey, 442 health zones from the DHS 2017-18 SPA survey, and information was available for all variables considered for 169 health zones in DRC. The average health zone urban geography was 31.4% and average yellow fever vaccination coverage was 62.6%. The average population density was skewed and varied greatly across health zones, so this variable was log-transformed in regression analyses. Additionally, vaccinations were available very few days out of the month in most health zones (average 2.6 days at the facilities and average 1.7 days through outreach), but most facilities had a proper means of transporting vaccines (84.02%) and few reported stock-outs of yellow fever vaccine in the last three months (9.47%). Vaccine storage quality (proper storage with current, accurate temperature and long-term cold chain monitoring) was low (average 20.71%) (Table 3.4). Initial review of pairwise correlations among these variables indicated potential correlation between mean population density, mean wealth index, and urban geography type. However, the variance inflation factor (VIF) was reviewed in regression analysis and multicollinearity was not present in regression.

The SMR value could be determined for all health zones that reported yellow fever cases (n=273). SMRs ranged from 0.00 to 56.31, with a mean of 2.30 and a median of 0.60. The map of SMR quantiles showed higher SMRs in the center and north of the country (Figure 3.2). Moran's *I* testing indicated moderate positive and statistically significant global spatial autocorrelation (statistic = 0.1764, p-value = 0.001), indicating clustering in nearby areas with similar values. LISA analysis showed that there were significant High-High clusters based on local Moran's *I* estimates and they are located in the Central and Northern areas of DRC (Figure

3.3). The Central cluster includes Monkoto, Wema, Boende, Mompono, Bafale, and Yalifafo health zones, the North Central cluster includes Bili, Titule, Buta, and Basali health zones, and the North Western cluster includes Bili (Equateur), Bwamanda, Bominenge, and Businga health zones.

The relative risk of reporting yellow fever by a health zone from the Poisson log-linear regression was lower with increasing mean wealth index, lower with increasing (log) mean population density, lower with presence of proper vaccine transport equipment, lower with highest vaccine storage quality, and lower in the presence of yellow fever vaccine stock outs in the past three months. The relative risk of reporting yellow fever by a health zone was also higher with increased mean vegetation index and rainfall and only very moderately higher with a higher percentage of urban geography and increased vaccination coverage. However, the non-spatial Poisson log-linear regression showed significant overdispersion, so the model was adjusted using the quasi-Poisson distribution to adjust the standard errors (and confidence intervals) for the estimates. After this adjustment, only increased mean vegetation index remained an influential risk factor where the relative risk of reporting yellow fever increased with increasing mean vegetation index. Both non-spatial models (even after adjusting for overdispersion) showed significant residual spatial autocorrelation (Moran's I statistic = 0.0864, $p = 0.014$) indicating the need to account for spatial autocorrelation in regression by using a CAR prior model for spatial random effects (Table 3.5).

The spatial neighbor structure between health zones (k=6 nearest neighbors) used to define adjacency in the CAR model is depicted in Figure 3.4a where neighbor health zones are connected with a green line. The estimated (smoothed) risk ratio map of 169 health zones was created, which still demonstrates the increased risk in the Central and Northern areas of DRC

(Figure 3.4b) and the residuals indicated good fit in most areas. There appears to be some clustering of model overprediction in some of the higher risk health zones, but there was no significant autocorrelation noted in the residuals (Figure 3.4c). The spatial model accounted for the spatial dependence in the model, eliminating the residual spatial autocorrelation (Moran's *I* statistic = 0.1807, p = 0.22) and accounted for moderate spatial correlation (ρ = 0.33) and spatial variance (τ^2 = 4.20). However, the risk factors considered were no longer significantly associated with reported yellow fever SMR (Table 3.5).

Lastly, to better represent yellow fever risk in the DRC, the CAR prior model was re-fit with 285 health zones with complete data for the risk factors using the data augmentation approach in a Bayesian framework using MCMC. In this case, the relative risk of reported yellow fever was lower with increased mean wealth index, increased (log) mean population density, presence of proper vaccine transport, and was moderately lower with increasing days per month that the yellow fever vaccine was offered at the facility. The relative risk was also higher with increasing mean vegetation index and very moderately higher with a higher percentage of urban geography and increased vaccination coverage (Table 3.5).

3.5 Discussion

Yellow fever remains associated with significant morbidity and mortality, especially in parts of Africa. The DRC is the largest country in sub-Saharan Africa, where yellow fever is endemic. Previous studies have examined the geographic distribution of yellow fever and associated risk factors in other countries or on the global scale but have not focused on the DRC. Understanding the geographic distribution of environmental factors and the complexity of

ecological interactions is important for prediction, prevention, and implementing proactive and cost-effective vaccination campaigns to minimize outbreaks of disease.

This is the first study to identify geographic patterns in reported yellow fever cases in DRC and provides a comprehensive geographic assessment of yellow fever risk. In DRC, yellow fever cases are not reported at random but are clustered among health zones, especially in the Central, North, and North West. Using a nearest neighbor approach to define neighbors, these clusters did not happen at random and exhibited spatial autocorrelation.

Using methods that account for this clustering as well as Bayesian inference strategies and data augmentation, several risk factors that may be associated with increased reporting of yellow fever were identified. Although elements directly describing the vector (mosquitos) were not available in the datasets, environmental factors that impact the mosquito population were examined since mosquito abundance is directly related to human exposure and infection with yellow fever. Like previous studies, average vegetation index and population density were associated with reported yellow fever cases.[4,12,16] Overcrowding contributes to disease transmission and outbreaks of yellow fever.[1,14] In fact, the urban transmission cycle is responsible for most recent outbreaks of yellow fever in Africa.[4,5] In this analysis, population density (presumably in a more urban setting) was associated with a lower risk of reported yellow fever. The study period (2010-2015) did not include any known outbreaks of disease and was intended to assess the usual prevalence of yellow fever. Furthermore, urban geography type was only moderately associated with increased yellow fever reports, which could indicate that transmission in less dense, non-urban areas is more significant outside of an outbreak setting. However, the health zone may have been too large to represent the heterogeneity of urban and rural areas.

Rainfall has also been associated with yellow fever risk, however, it was not significant in this analysis.[15] Although the rainy season in DRC covers nine out of the 12 months of the year and previous evidence indicates that mosquito breeding opportunities, and therefore yellow fever transmission, can persist through the dry season in countries with high vector burden, rainfall is still seasonal.[1,45] Seasonality was not considered in any of the risk factor variables in this study, but future studies may be needed to investigate seasonal variation and time patterns, especially in the context of climate change. Changes in climate, abnormal rainfall that deviates from normal patterns, and human factors, such as migration and air travel, can change yellow fever risk dynamics over time.[13]

The yellow fever vaccine is considered very effective, and in 2015 the CDC Advisory Committee on Immunization Practices and the World Health Organization issued new recommendations that a single dose of the vaccine provides long-lasting protection.[46] However, estimates of yellow fever vaccination in DRC vary by source.[47] Recent models estimated that children in DRC (less than age 14) were 50-70% vaccinated (depending on specific age group), however after age 15 the vaccination coverage is estimated at approximately 10-20% with overall vaccination between 30-40%.[48] Yellow fever vaccination coverage has been a central component of mapping yellow fever globally, not only to identify high-risk areas but also to guide recommendations for tailored vaccination campaigns.[12,16] In this analysis, increased yellow fever vaccination was moderately associated with increased risk of reported yellow fever, however, coverage was based on childhood estimates that were available through DHS and were based on both maternal report and information from the vaccination card. This may not be the best estimate of yellow fever vaccination coverage for the health zone because it may not be accurate (for example, records could be wrong or maternal recall may be biased[49]) and may not

reflect adult vaccination coverage since it would not capture supplemental vaccination campaigns or other vaccination mechanisms that target adults. Furthermore, problems with the cold chain may indicate that vaccination coverage does not actually correspond with immunity if vaccines routinely lose potency after exposure to temperatures outside of the recommended range.[20]

Organizational factors, including health facility capacity to provide access to vaccines and quality vaccines, were influential in this study. The relative risk of reported yellow fever was lower with presence of proper vaccine transport mechanisms, however, only 22.1% of facilities had highest quality vaccination storage practices (stored vaccines with current accurate temperature and long-term cold chain monitoring). Vaccine storage and temperature recording have been found to be deficient in other African countries, such as in Nigeria, the setting of large yellow fever outbreaks in the 1970s and 80s,[50–52] where access to electricity and a refrigerator were barriers to vaccine handling,[23] in Ethiopia, where facilities were found to be lacking temperature recordings and vaccine storage was not proper,[21] and in Cameroon, where 20% and 24% of surveyed health facilities with functioning thermometers had abnormal temperature readings at the time of the survey and within 2 months, respectively.[22] In general, limitations of the immunization system have been implicated in lower vaccination and increased susceptibility to infection but can be addressed through improving outreach services, vaccine supply, and health worker training.[18] Although this study could not completely elucidate the relationship between health care capacity and cold chain quality, vaccination coverage, and yellow fever cases, it indicates the need for additional research to investigate this important factor in DRC further.

Using geographic data and spatial analysis are increasingly popular tools in public health and epidemiology, especially for addressing questions about environmental risk, however, high-quality spatial data is not readily available, especially for yellow fever. The health system infrastructure in many yellow fever affected countries are especially limited, however, the public health systems to collect, manage, and disseminate spatial data have not been established in many countries. Spatial analysis and modeling efforts could be improved by improving the volume and quality of geographic data. This could increase the capacity to answer more research questions rather than being restricted to existing data collected for other purposes.[16,53] In the absence of robust geographic data, this study utilizes the country's IDSR surveillance data in a new and unique way by linking it with other sources of geographic information for environmental factors, the locations of health resources, and the sociodemographic characteristics of the population representing an innovative and more comprehensive analysis to evaluate this important public health concern.[54]

Although using the surveillance data to investigate patterns of yellow fever and potential predictors is a primary strength of this study, the surveillance data has its limitations. As discussed, there are burdens on the IDSR system that may result in variations in surveillance completeness and accuracy. The system is also based on passive surveillance. Since yellow fever is difficult to diagnose and the distinctive severe symptoms are delayed from initial infection, the cases reported may underestimate the actual yellow fever cases. Currently, the surveillance data only contains suspected cases, but the link to the confirmed cases was not available, so it may also overestimate the number of confirmed cases. The cases may also be misdiagnosed or combined with cases of other acute febrile illnesses, such as malaria. Other studies have noted that surveillance and case finding for yellow fever in Africa may be incomplete due to limited

diagnostic capabilities, poor health infrastructure resulting in under-recognition, underreporting, and underestimation.[14] These limitations must be considered when interpreting any results based on these surveillance data.

Another limitation of this study is the use of aggregated ecological data at the health zone level. Although the health zone is the smallest official health system organizational level in DRC with available surveillance data, it is still a large land area to aggregate and use in the analysis. Ecological studies are also limited because they are often associated with biases such as the ecological fallacy, where associations at the aggregated level do not always translate or represent the associations at the individual level. However, ecological data provides a means to use existing data from public and open access sources and the country's surveillance system to inform countrywide interventions. Furthermore, this study may be impacted by the modified aerial unit problem (MAUP), where the inferences made from data may change when the spatial scale is changed. The results of spatial analyses are highly dependent on the chosen scale with the potential of too many clusters identified with too broad of scale or too few or no clusters identified with too local scale.[41] Unfortunately, the yellow fever surveillance data was only available at the health zone level so other data had to be aggregated to that level, which could change the relationships between the variables. For example, one study found that high levels of full vaccination coverage measured at national and regional levels did not seem to represent individual heterogeneities in vaccination coverage and risk of outbreaks.[55]

The methodologies used in this study were specifically designed for spatial areal data and provide an opportunity to make inference based on an ecological level of data in the presence of overdispersion and residual autocorrelation. CAR prior models extend regression models to allow for spatial autocorrelation and use Bayesian based estimation to help strengthen even

uncertain data using prior information.[41,43] This method can be used to create predicted counts that smooth over observed data and estimate disease risk using both risk factor information and random effects that borrow strength from neighboring areas.[34,43] However, Bayesian techniques can tend to produce less stable estimates in areas with higher sampling variation, such as those with a low number of cases.[41] These spatial methodologies and disease mapping techniques are also highly dependent on the neighbor definition since different definitions could produce different results, especially with regard to spatial autocorrelation.[32] Tests for spatial autocorrelation are also sensitive to spatial patterning from any source and residual spatial autocorrelation could actually be a result of unmeasured confounding or neighbor related effects.[34,37,44] The spatial neighbor structure of yellow fever has not been studied, but a brief sensitivity analysis was completed in this study to arrive at the nearest neighbors definition.

Lastly, this study combined three datasets to complete a novel analysis of yellow fever risk and disease patterns in DRC. However, this data generation process also resulted in missing data for a complete case analysis. Regression analyses were based on only 169 health zones, which may not represent the entire country. However, capitalizing on the data augmentation abilities of the Bayesian estimation process used allowed for expanding to make inference about more health zones. These results indicate that more complete data would assist with making inferences about risk factors of yellow fever. Additionally, sensitivity analyses using global and local Moran's *I* revealed a similar disease clustering trend and similar High-High yellow fever clusters were found in the Central, Northern, and North Western parts of DRC when using only the 169 health zones with complete data indicating that these health zones may represent much of the spatial clustering of yellow fever in DRC (data not shown). However, the missing data

could also affect the validity of the neighbor structure and influence the overall results of all spatial analyses.

The global strategy for yellow fever elimination framework, Eliminate Yellow Fever Epidemics (EYE) Global Strategy, was revised after the outbreaks in Angola and DRC and has three major objectives: 1) To protect at-risk populations, 2) To prevent international spread of the disease, and 3) To contain outbreaks rapidly.[56] These goals can be assisted by using geographically referenced data collection and methods to use this data to produce small area estimates and trends. This study fits this framework by utilizing spatial analysis and disease mapping techniques to combine various data sources and examine patterns in yellow fever epidemiology and associations with sociodemographic, environmental, and organizational risk factors within the DRC. These geospatial modeling tools are especially useful for public health to detect and locate areas that may need targeted intervention, public health messaging, and health system enhancement.[53,57] As more data specifically collected for geographic analysis that represents all of DRC becomes available these modeling and spatial disease mapping efforts could be expanded improved. Furthermore, the availability of diagnostic tests to indicate immunity and confirmed cases of yellow fever would make the results more consistent and specific.

This study highlights areas of high yellow fever reporting and improves the understanding of geographical risk, which is essential to future efforts for preventing and controlling yellow fever in DRC. This study also includes organizational risk factors such as healthcare facility characteristics that may influence the accessibility and quality of vaccines. Furthermore, by focusing specifically on the DRC, this study provides more meaningful information to protect at-risk populations and detect and contain outbreaks more rapidly than

previous studies that have examined the global risk of yellow fever. These results are specific to health zones in the DRC and provide actionable areas for intervention to the Ministry of Health. The recent outbreak in Angola and DRC demonstrated the challenges in the current yellow fever vaccination and prevention efforts so understanding patterns of yellow fever and contributions of sociodemographic, environmental, and organizational risk factors can assist with DRC's public health planning as well as global efforts to prevent and contain yellow fever.

3.6 Tables and Figures

Table 3.1 (Supplemental) Diseases reported to the Integrated Disease Surveillance and Response (IDSR) system, DRC 2010-2015

Reported Disease	2010	2011	2012	2013	2014	2015
AFP	Y	Y	Y	Y	Y	Y
Avian Influenza						
Bacillary dysentery/Shigellosis	Y	Y				
Bloody Diarrhea			Y	Y	Y	Y
Cholera	Y	Y	Y	Y	Y	Y
Dracunculiasis						Y
Gastroenteritis	Y	Y				
Influenza	Y	Y				
Influenza H1N1						
Malaria	Y	Y	Y	Y	Y	Y
Maternal Death						Y
Measles	Y	Y	Y	Y	Y	Y
Meningitis	Y	Y	Y	Y	Y	Y
Monkey Pox	Y	Y	Y	Y	Y	Y
Neonatal Tetanus	Y	Y	Y	Y	Y	Y
Pertussis	Y	Y	Y	Y	Y	Y
Plague	Y	Y	Y	Y	Y	Y
Rabies			Y	Y	Y	Y
Simple Diarrhea						
Typhoid Fever	Y	Y	Y	Y	Y	Y
Typhus						
URI	Y	Y	Y	Y	Y	Y
Viral hemorrhagic fever (VHF)	Y	Y	Y	Y	Y	Y
Yellow fever	Y	Y	Y	Y	Y	Y
Number of diseases reported	16	16	15	15	15	17

Table 3.2 Description of risk factor variables

Variable	Description	Data source*
Sociodemographic		
Urban geography	% of children residing in an urban survey cluster (representing % urban geography in health zone)	DHS 2013-14
Yellow fever (YF) vaccination	% of children vaccinated for yellow fever (using information gathered from vaccination card and maternal report)	DHS 2013-14
Mean wealth index	Average value of cluster average wealth index (wealth index: 1= Poorest, 2= Poorer, 3= Middle, 4= Richer, 5= Richest)	DHS 2013-14
Environmental		
Mean population density	Average cluster population density (log-transformed) - number of people per square kilometer within a radius of 10 km (for rural clusters) or 2 km (for urban clusters), 2015	DHS 2013-14
Mean vegetation index	Average cluster enhanced vegetation index value (density of green leaves in the near-infrared and visible bands). Value between 0 (least vegetation) and 100 (most vegetation) within a radius of 10 km (for rural clusters) or 2 km (for urban clusters), 2015	DHS 2013-14
Mean rainfall	Average cluster rainfall - meters per year within a radius of 10 km (for rural clusters) or 2 km (for urban clusters), 2015	DHS 2013-14
Organizational/Health facility capacity		
Access:		
YF vaccine at facility	Average number of days per month yellow fever vaccine available at facilities located within health zone boundary	DHS SPA 2017-18
YF vaccine through outreach	Average number of days per month yellow fever vaccine available through outreach by facilities located within health zone boundary	DHS SPA 2017-18
Quality:		
Vaccine storage quality index	% facilities located within health zone boundary that store vaccines appropriately (categorized as >=50% (majority) with current accurate temperature and long term cold chain monitoring = High, with 1 or more deficiencies = Moderate, or with multiple deficiencies/do not store vaccine = Poor)	DHS SPA 2017-18
Vaccine transport index	% facilities with both vaccine carrier and ice packs (categorized as >=50% (majority) = Yes, <50% = No)	DHS SPA 2017-18
Availability:		

YF vaccine stockout	% facilities located within health zone boundary with stockouts of yellow fever vaccines in the last 3 months (categorized as >=50% (majority) = Yes, <50% = No)	DHS SPA 2017-18

*DHS - Demographic and Health Survey, SPA – Service Provision Assessment

Table 3.3 (Supplemental) Sensitivity analysis of neighbor definitions

Neighborhood weight matrix structure	DIC
Inverse distance < 500 km	791.1283
Inverse euclidean distance	791.0262
Inverse euclidean distance squared	795.9339
Binary indicator of distance <500 km	789.9525
Binary indicator of 6 nearest neighbors	784.8979
Binary indicator of 6 nearest neighbors no spatial autocorrelation (ρ set to 0)	788.7835
Inverse distance of 6 nearest neighbors	788.5793

Deviance Information Criterion (DIC) is a measure of the relative fit of Bayesian hierarchical models based on the posterior mean which incorporates goodness of fit and complexity. Models with smaller DIC are better supported by the data.

Figure 3.1 Combined dataset creation process

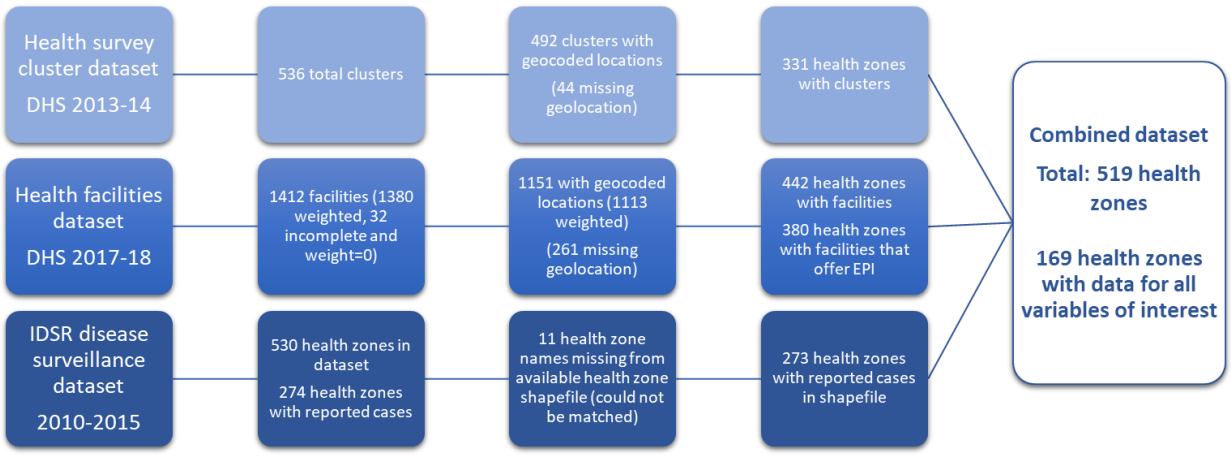


Table 3.4 Summary of variables at the health zone level (n=169)

	mean (standard deviation)/ frequency (%)
Yellow fever cases reported	9.0 (22.33)
Sociodemographic	
Urban geography	31.4 (42.92)
Yellow fever (YF) vaccination	62.6 (27.43)
Mean wealth index	2.6 (1.23)
Environmental	
Mean population density	3571.8 (9223.5)
Mean vegetation index	38.7 (10.11)
Mean rainfall	1.5 (0.21)
Organizational/Health facility capacity	
YF vaccine at facility	2.6 (2.95)
YF vaccine through outreach	1.7 (2.52)
Vaccine transport index (Yes)	142 (84.02%)
Vaccine storage quality index (Moderate)	43 (25.44%)
Vaccine storage quality index (High)	35 (20.71%)
YF vaccine stockout (Yes)	16 (9.47%)

Figure 3.2 Standardized morbidity ratios (SMRs) of reported yellow fever cases by health zone cumulative 2010-2015, Democratic Republic of Congo

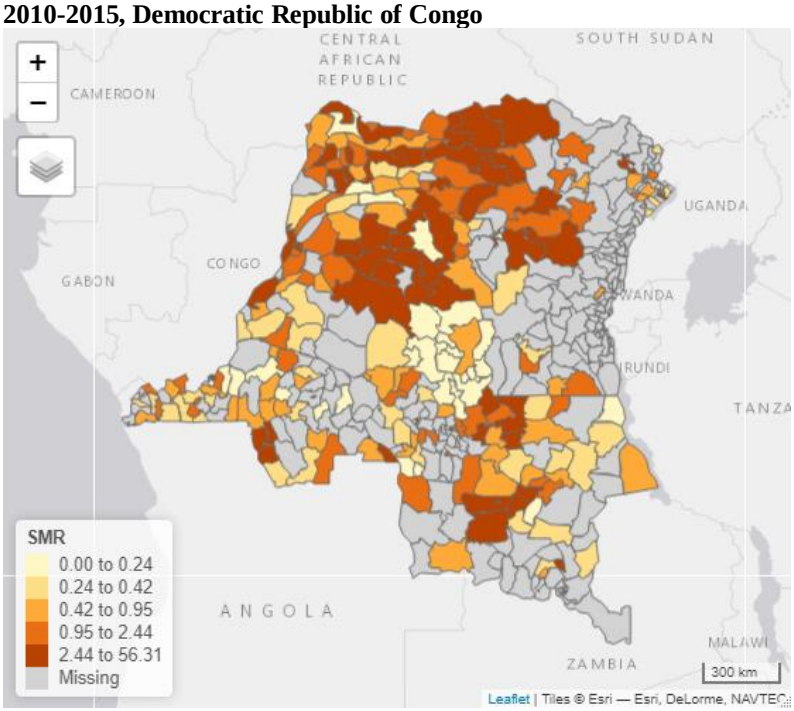
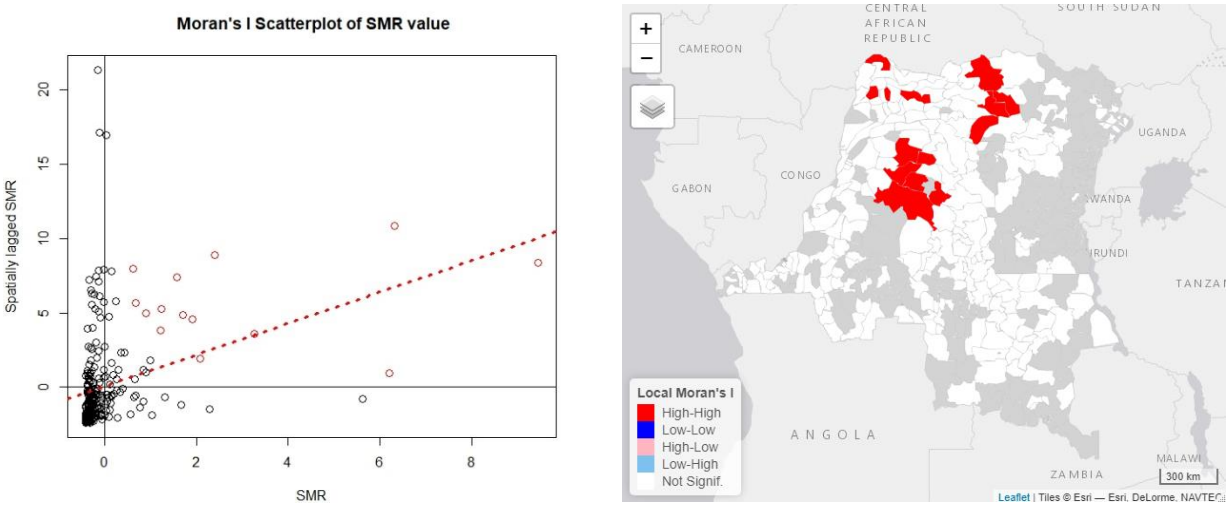


Figure 3.3 Local Moran's I of yellow fever standardized morbidity ration (SMR) by health zone scatterplot and map, Democratic Republic of Congo, 2010-2015

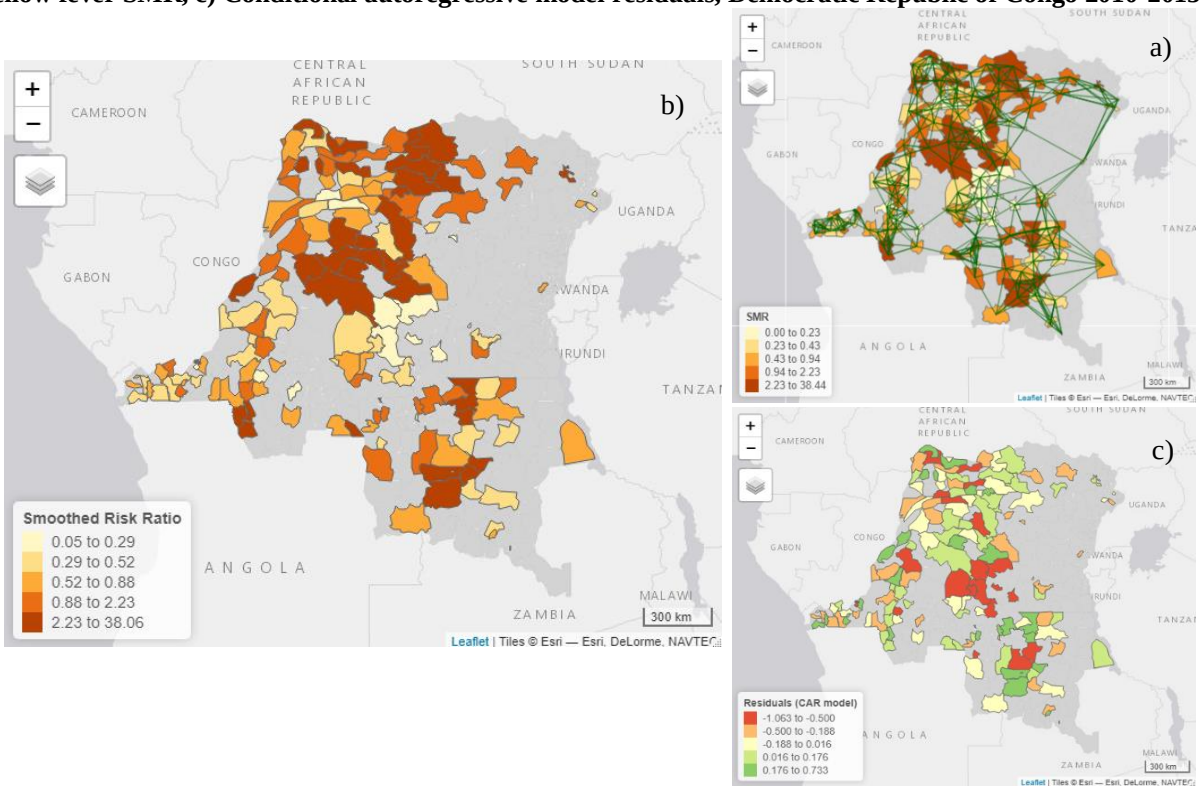


The Moran's *I* scatter plot compares the (scaled) SMR and the spatially lagged (weighted sum of neighboring values) SMR. The global Moran's *I* is the slope of the linear relationship between these: Moran's *I* Global statistic = 0.17641 (dotted red line). The plot is divided into four quadrants by the means of the SMR and the lagged value signifying: Low-Low (dark blue), Low-High (light blue), High-High (dark red), High-Low (light red) (clockwise from bottom left) and health zones with significantly high influence are indicated on the plot and map in similar colors.

Table 3.5 Relative risks of reported yellow fever cases (SMR) for risk factor variables in non-spatial and spatial regression models (Relative risk (RR) and 95% confidence interval (95% CI) for non-spatial and 95% credible interval for spatial analysis (95% CrI))

	Non-spatial		**Spatial**	
	No adjustment for overdispersion (n=169)	**Adjustment for overdispersion (quasi-Poisson) (n=169)**	**CAR model with Leroux prior distribution (n=169)**	**With MCMC data augmentation for missing outcome (n=285)**
	RR (95% CI)	**RR (95% CI)**	**RR (95% CrI)**	**RR (95% CrI)**
Sociodemographic				
Urban geography	1.02 (1.01, 1.02)	1.02 (1.00, 1.03)	1.01 (1.00, 1.03)	1.02 (1.02, 1.03)
Yellow fever (YF) vaccination	1.01 (1.01, 1.01)	1.01 (1.00, 1.03)	1.01 (1.00, 1.02)	1.01 (1.01, 1.02)
Mean wealth index	0.61 (0.55, 0.68)	0.61 (0.33, 1.12)	0.68 (0.43, 1.29)	0.48 (0.40, 0.80)
Environmental				
Mean population density (log)	0.88 (0.84, 0.93)	0.88 (0.68, 1.15)	0.80 (0.62, 1.05)	0.87 (0.81, 0.90)
Mean vegetation index	1.08 (1.06, 1.09)	1.08 (1.02, 1.14)	1.04 (0.99, 1.10)	1.06 (1.04, 1.10)
Mean rainfall	1.52 (1.08, 2.13)	1.52 (0.24, 10.15)	1.96 (0.28, 14.11)	0.68 (0.15, 1.35)
Organizational/Health facility capacity				
YF vaccine at facility	0.99 (0.97, 1.01)	0.99 (0.87, 1.10)	1.02 (0.90, 1.14)	0.95 (0.93, 0.99)
YF vaccine through outreach	1.02 (1.00, 1.05)	1.02 (0.90, 1.18)	0.98 (0.87, 1.11)	0.97 (0.96, 1.03)
Vaccine transport index (Yes vs. No)	0.74 (0.64, 0.86)	0.74 (0.35, 1.72)	0.72 (0.27, 1.31)	0.53 (0.51, 0.77)
Vaccine storage quality index (Moderate vs. Poor)	1.00 (0.88, 1.13)	1.00 (0.49, 1.99)	1.12 (0.51, 1.62)	1.27 (0.89, 1.45)
Vaccine storage quality index (High vs. Poor)	0.76 (0.64, 0.90)	0.76 (0.29, 1.82)	1.47 (0.96, 3.05)	0.65 (0.48, 1.02)
YF vaccine stockout (Yes vs. No)	0.81 (0.67, 0.98)	0.81 (0.24, 2.06)	1.06 (0.75, 1.65)	1.28 (0.34, 1.42)
	Statistic, p-value		**Statistic, p-value**	**Statistic, p-value**
Moran's I test of model residuals	0.086471, p = 0.01399		0.18073, p = 0.2198	0.035204, p = 0.1748
			Posterior median (95% CrI)	**Posterior median (95% CrI)**
Spatial correlation (ρ)			0.33 (0.08, 0.74)	0.74 (0.40, 0.94)
Spatial variance (τ^2)			4.20 (2.21, 7.60)	20.30 (10.78, 32.60)

Figure 3.4 a) Map of nearest neighbor (k=6) structure for health zones with complete information available (neighbor health zones connected with green lines), b) Estimated (smoothed) risk ratio map of reported yellow fever SMR, c) Conditional autoregressive model residuals, Democratic Republic of Congo 2010-2015



3.7 References

1. Monath TP, Vasconcelos PFC. Yellow fever. *J Clin Virol*. 2015;64:160-173. doi:10.1016/j.jcv.2014.08.030
2. World Health Organization. Yellow fever Fact Sheet. http://www.who.int/mediacentre/factsheets/fs100/en/. Published 2016.
3. Centers for Disease Control and Prevention. Transmission | Yellow Fever | CDC. http://www.cdc.gov/yellowfever/transmission/. Published 2015. Accessed June 11, 2017.
4. Rogers DJ, Wilson AJ, Hay SI, Graham AJ. The global distribution of yellow fever and dengue. *Adv Parasitol*. 2006;62:181-220. doi:10.1016/S0065-308X(05)62006-4
5. Barrett ADT. Yellow fever live attenuated vaccine: A very successful live attenuated vaccine but still we have problems controlling the disease. *Vaccine*. 2017;35(44):5951-5955. doi:10.1016/J.VACCINE.2017.03.032
6. Gardner CL, Ryman KD. Yellow fever: a reemerging threat. *Clin Lab Med*. 2010;30(1):237-260. doi:10.1016/j.cll.2010.01.001
7. Barnett ED. Yellow Fever: Epidemiology and Prevention. *Clin Infect Dis*. 2007;44(6):850-856. doi:10.1086/511869
8. Monath TP. Yellow fever: an update. *Lancet Infect Dis*. 2001;1(1):11-20. doi:10.1016/S1473-3099(01)00016-0

9. World Health Organization. Emergencies preparedness, response - Yellow fever – Brazil. *WHO*. 2019. https://www.who.int/csr/don/11-february-2019-yellow-fever-brazil/en/. Accessed March 11, 2019.

10. Ingelbeen B, Weregemere NA, Noel H, et al. Urban yellow fever outbreak—Democratic Republic of the Congo, 2016: Towards more rapid case detection. Beasley DWC, ed. *PLoS Negl Trop Dis*. 2018;12(12):e0007029. doi:10.1371/journal.pntd.0007029

11. World Health Organization. Emergencies preparedness, response - Increased risk of urban yellow fever outbreaks in Africa. *WHO*. 2015. https://www.who.int/csr/disease/yellowfev/urbanoutbreaks/en/. Accessed January 20, 2019.

12. Garske T, Van Kerkhove MD, Yactayo S, et al. Yellow Fever in Africa: Estimating the Burden of Disease and Impact of Mass Vaccination from Outbreak and Serological Data. Hay SI, ed. *PLoS Med*. 2014;11(5):e1001638. doi:10.1371/journal.pmed.1001638

13. Jentes ES, Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. *Lancet Infect Dis*. 2011;11(8):622-632. doi:10.1016/S1473-3099(11)70147-5

14. Baba MM, Ikusemoran M. Is the absence or intermittent YF vaccination the major contributor to its persistent outbreaks in eastern Africa? *Biochem Biophys Res Commun*. 2017;492(4):548-557. doi:10.1016/j.bbrc.2017.01.079

15. Hamrick PN, Aldighieri S, Machado G, et al. Geographic patterns and environmental factors associated with human yellow fever presence in the Americas. Barker CM, ed. *PLoS Negl Trop Dis*. 2017;11(9):e0005897. doi:10.1371/journal.pntd.0005897

16. Shearer FM, Longbottom J, Browne AJ, et al. Existing and potential infection risk zones of yellow fever worldwide: a modelling analysis. *Lancet Glob Heal*. 2018;6(3):e270-e278. doi:10.1016/S2214-109X(18)30024-X

17. World Health Organization. Emergencies preparedness, response - Yellow fever in the Democratic Republic of the Congo. *WHO*. 2015. https://www.who.int/csr/don/2010_07_19a/en/. Accessed November 13, 2018.

18. Rainey JJ, Watkins M, Ryman TK, Sandhu P, Bo A, Banerjee K. Reasons related to non-vaccination and under-vaccination of children in low and middle income countries: Findings from a systematic review of the published literature, 1999-2009. *Vaccine*. 2011;29(46):8215-8221. doi:10.1016/j.vaccine.2011.08.096

19. Rogers B, Dennison K, Adepoju N, Dowd S, Uedoi K. Vaccine Cold Chain Part 1. Proper Handling and Storage of Vaccine. *AAOHN J*. 2010;58(8). doi:10.3928/08910162-20100716-02

20. Peetermans J. Factors affecting the stability of viral vaccines. *Dev Biol Stand*. 1996;87:97-101. http://www.ncbi.nlm.nih.gov/pubmed/8854006. Accessed August 14, 2018.

21. Berhane Y, Demissie M. Cold chain status at immunisation centres in Ethiopia. *East Afr Med J*. 2000;77(9):476-479. doi:10.4314/eamj.v77i9.46692

22. Yakum MN, Ateudjieu J, Pélagie FR, Walter EA, Watcho P. Factors associated with the

exposure of vaccines to adverse temperature conditions: the case of North West region, Cameroon. *BMC Res Notes*. 2015;8:277. doi:10.1186/s13104-015-1257-y

23. Dairo DM, Osizimete OE. Factors affecting vaccine handling and storage practices among immunization service providers in Ibadan, Oyo State, Nigeria. *Afr Health Sci*. 2016;16(2):576-583. doi:10.4314/ahs.v16i2.27

24. Oyefolu AO, Nwaeke AC, Audu RA, et al. Evaluation of measles vaccine cold chain in Lagos State, Nigeria. *African J Clin Exp Microbiol*. 2007;8(1). doi:10.4314/ajcem.v8i1.7457

25. Sanofi Pasteur. *YF-VAX ® LE6103-LE6104 Yellow Fever Vaccine YF-VAX ®*.; 2016. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm142831.pdf. Accessed October 8, 2018.

26. Demographic and Health Survey. *Sampling and Household Listing Manual*. Calverton; 2012. https://dhsprogram.com/pubs/pdf/DHSM4/DHS6_Sampling_Manual_Sept2012_DHSM4.pdf. Accessed March 11, 2019.

27. Demographic and Health Survey. *Democratic Republic Congo DHS, 2013-14 - Final Report (French)*. Rockville; 2014. www.DHSprogram.com. Accessed March 11, 2019.

28. Demographic and Health Survey. GPS Data Collection - Methodology - Collecting Geographic Data. https://dhsprogram.com/What-We-Do/GPS-Data-Collection.cfm. Accessed January 20, 2019.

29. Demographic and Health Survey. Service Provision Assessments (SPA). https://dhsprogram.com/What-We-Do/Survey-Types/SPA.cfm. Accessed May 13, 2019.

30. Ecole de Santé Publique de Kishasa ESPK/Kinshasa RD du C. Republique Democratique du Congo Évaluation des Presentations des Services de souns de Santé EPSS 2017-2018. January 2019. https://dhsprogram.com/publications/publication-SPA30-SPA-Final-Reports.cfm. Accessed May 13, 2019.

31. Centers for Disease Control and Prevention. Integrated Disease Surveillance and Response: About Us | Division of Global Health Protection | Global Health | CDC. https://www.cdc.gov/globalhealth/healthprotection/idsr/about.html. Published 2017. Accessed October 15, 2018.

32. Bivand RS, Pebesma E, Gómez-Rubio V. *Applied Spatial Data Analysis with R: Second Edition*. Springer New York; 2013. doi:10.1007/978-1-4614-7618-4

33. Earnest A, Morgan G, Mengersen K, Ryan L, Summerhayes R, Beard J. Evaluating the effect of neighbourhood weight matrices on smoothing properties of Conditional Autoregressive (CAR) models. *Int J Health Geogr*. 2007;6(1):54. doi:10.1186/1476-072X-6-54

34. Lee D. A comparison of conditional autoregressive models used in Bayesian disease mapping. *Spat Spatiotemporal Epidemiol*. 2011;2(2):79-89. doi:10.1016/j.sste.2011.03.001

35. Lee JH, Han G, Fulp WJ, Giuliano AR. Analysis of overdispersed count data: Application to the Human Papillomavirus Infection in Men (HIM) Study. *Epidemiol Infect*.

2012;140(6):1087-1094. doi:10.1017/S095026881100166X

36. Mohebbi M, Wolfe R, Forbes A. Disease mapping and regression with count data in the presence of overdispersion and spatial autocorrelation: A Bayesian model averaging approach. *Int J Environ Res Public Health*. 2014;11(1):883-902. doi:10.3390/ijerph110100883

37. Oué Draogo Id AM, Crighton EJ, Sawada M, To T, Brand K, Lavigne E. Exploration of the spatial patterns and determinants of asthma prevalence and health services use in Ontario using a Bayesian approach. 2018. doi:10.1371/journal.pone.0208205

38. Griffith DA, Arbia G. Detecting negative spatial autocorrelation in georeferenced random variables. *Int J Geogr Inf Sci*. 2010;24(3):417-437. doi:10.1080/13658810902832591

39. Getis A. Spatial Weights Matrices. *Geogr Anal*. 2009;41(4):404-410. doi:10.1111/j.1538-4632.2009.00768.x

40. Meyer R. Deviance Information Criterion (DIC). In: *Wiley StatsRef: Statistics Reference Online*. Chichester, UK: John Wiley & Sons, Ltd; 2016:1-6. doi:10.1002/9781118445112.stat07878

41. Marek L, Paszto V, Tucek P, Dvorsky J. *Spatial Clustering of Disease Events Using Bayesian Methods*. Prague; 2014. http://www.cs.vsb.cz/dateso/2014/http://www.ceur-ws.org/Vol-1139/. Accessed June 7, 2020.

42. Anselin L. Local Indicators of Spatial Association-LISA. *Geogr Anal*. 1995;27(2):93-115. doi:10.1111/j.1538-4632.1995.tb00338.x

43. Ver Hoef JM, Peterson EE, Hooten MB, Hanks EM, Fortin MJ. Spatial autoregressive models for statistical inference from ecological data. *Ecol Monogr*. 2018;88(1):36-59. doi:10.1002/ecm.1283

44. Lee D. *CARBayes Version 5.2: An R Package for Spatial Areal Unit Modelling with Conditional Autoregressive Priors*. http://www.r-inla.org/. Accessed June 17, 2020.

45. Southern African Development Community. Democratic Republic of Congo Country Profile. https://www.sadc.int/member-states/dr-congo. Accessed February 17, 2019.

46. Centers for Disease Control and Prevention. Vaccine Information | Yellow Fever | CDC. https://www.cdc.gov/yellowfever/healthcareproviders/vaccine-info.html. Accessed October 8, 2018.

47. WHO and UNICEF. *Democratic Republic of the Congo: WHO and UNICEF Estimates of Immunization Coverage: 2017 Revision*.; 2018. https://www.who.int/immunization/monitoring_surveillance/data/cod.pdf. Accessed March 10, 2019.

48. Shearer FM, Moyes CL, Pigott DM, et al. Global yellow fever vaccination coverage from 1970 to 2016: an adjusted retrospective analysis. *Lancet Infect Dis*. 2017;17(11):1209-1217. doi:10.1016/S1473-3099(17)30419-X

49. Valadez JJ, Weld LH. Maternal recall error of child vaccination status in a developing nation. *Am J Public Health*. 1992;82(1):120-122. doi:10.2105/AJPH.82.1.120

50. Monath TP, Wilson DC, Lee VH, Stroh G, Kuteyi K, Smith EA. The 1970 yellow fever

epidemic in Okwoga District, Benue Plateau State, Nigeria. I. Epidemiological observations. *Bull World Health Organ*. 1973;49(2):113-121. http://www.ncbi.nlm.nih.gov/pubmed/4545318. Accessed August 15, 2018.

51. De Cock KM, Nasidi A, Enriquez J, et al. EPIDEMIC YELLOW FEVER IN EASTERN NIGERIA, 1986. *Lancet*. 1988;331(8586):630-633. doi:10.1016/S0140-6736(88)91425-0

52. Nasidi A, Monath TP, DeCock K, et al. Urban yellow fever epidemic in western Nigeria, 1987. *Trans R Soc Trop Med Hyg*. 1989;83(3):401-406. doi:10.1016/0035-9203(89)90518-X

53. Jerrett M, Gale S, Kontgis C. Spatial modeling in environmental and public health research. *Int J Environ Res Public Health*. 2010;7(4):1302-1329. doi:10.3390/ijerph7041302

54. Rushton G. Public Health, GIS, and Spatial Analytic Tools. *Annu Rev Public Health*. 2003;24(1):43-56. doi:10.1146/annurev.publhealth.24.012902.140843

55. Utazi CE, Thorley J, Alegana VA, et al. High resolution age-structured mapping of childhood vaccination coverage in low and middle income countries. *Vaccine*. 2018;36(12):1583-1591. doi:10.1016/j.vaccine.2018.02.020

56. World Health Organization. Eliminate Yellow fever Epidemics (EYE): a global strategy, 2017-2016. *Wkly Epidemiol Rec*. 2017;92(16):193-204. https://www.who.int/wer/2017/wer9216/en/. Accessed August 13, 2018.

57. Kanaroglou P, Delmelle E, Paez A, eds. *Spatial Analysis in Health Geography*. Surrey, England: Ashgate Publishing Limited; 2015.

Chapter 4: Modeling the yellow fever outbreak in the Democratic Republic of Congo and the effect of outbreak interventions

4.1 Abstract

Yellow fever is endemic in all or parts of 34 countries in Africa, including the Democratic Republic of Congo (DRC), and has been responsible for sporadic outbreaks. New infections and outbreaks of yellow fever can be prevented using vaccination, mosquito control, and bite prevention. After a recent yellow fever outbreak in DRC, reactive vaccination campaigns included 30 million vaccines between DRC and Angola and exhausted the global stockpile several times. Given the logistical of outbreak response, the purpose of this study is to examine the outbreak of yellow fever in DRC using a mathematical model of disease transmission and estimate the impact of outbreak interventions on the number of yellow fever infections in DRC. Optimization methods and approximate fit criteria were used to propose parameters for the outbreak using a deterministic formulation of an S-E-A-I-R compartmental model in conjunction with an SM-EM-IM model for the mosquito population in continuous and the reproductive number of the outbreak is estimated. Outbreak preparedness and intervention scenarios were explored using a tau-leaping Gillespie stochastic simulation algorithm (SSA), including varying initial immunity, vaccination campaign scenarios, mosquito control, and human protective behaviors for bite prevention. In simulations, the vaccination campaign implemented at 94 days into the outbreak succeeded in preventing at least 19% to as many as 28% of cases in DRC and R_0 was estimated as 5.10 to 5.25. Initial population immunity impacted the total number of cases and earlier detection and intervention would prevent yellow fever cases in this outbreak. However, the levels of vaccination coverage achieved through the

vaccination campaigns did not appear to change the number of cases prevented in this simulation. A widespread mosquito elimination strategy would reduce almost all the cases, even if only 10% of mosquitoes could be eliminated and bite prevention is also effective. Methods to prevent yellow fever are available. Establishing methods for efficient outbreak preparedness and response is essential to prevent an additional burden on strained health systems like in the DRC. Most interventions considered in this study contributed to outbreak mitigation, however, some may be more efficient and effective than others. While early detection is paramount, it may be most useful to strengthen the health delivery system and implement widespread interventions before an outbreak to establish capacity to detect and respond to all outbreaks.

4.2 Introduction

Yellow fever is an acute viral hemorrhagic disease transmitted by infected mosquitoes, primarily the *Aedes* or *Haemoagogus* species in three transmission cycles: jungle/sylvatic (transmission of the virus between non-human primates, mosquitoes, and humans visiting the jungle), intermediate/savannah (transmission from mosquitoes to humans living or working in jungle border areas), and urban (transmission between humans and urban mosquitoes once the virus is brought to urban areas by an infected human).[1,2] The sylvatic transmission cycle facilitates ongoing transmission between non-human primates and mosquitoes and places humans at continuous risk of infection in the absence of vaccination and other protective behavior.[3] However, the urban transmission cycle is responsible for most recent outbreaks of yellow fever in Africa and is therefore the most concerning from a public health perspective.[4,5] The *Aedes* mosquito is capable of breeding in small amounts of water that accumulates in artificial containers inside or near dwellings.[6] This is exacerbated in urban areas where

overcrowding is also possible, which helps support disease transmission and resulting outbreaks.[7,8]

The transmissibility of yellow fever has not been extensively studied, especially since the disease often occurs in rural parts of the world. However, the clinical course of the disease has been described. The incubation period after an initial bite is typically 3-6 days.[9] Most infected individuals develop only mild symptoms in the initial phase of the disease when the virus is present in the blood, such as fever, muscle pain, loss of appetite, nausea or vomiting, or remain asymptomatic. This early viremic stage lasts from 3-6 days and an individual may serve as a source of infection for mosquitoes during this time.[9] Initial symptoms, if any, usually subside after approximately 2-6 days. After a brief period of symptom improvement, a proportion of individuals then progress to a more severe form of the disease, which includes high fever, liver and kidney failure leading to jaundice, and bleeding that can occur from the mouth, nose, eyes, or stomach. During this severe phase, antibodies appear in the blood and virus disappears.[7,10] Approximately 20-50% of patients who have severe symptoms die within 7-10 days.[7]
New infections and outbreaks of widespread transmission of yellow fever can be prevented. The yellow fever vaccine is especially effective[1] and is part of the childhood vaccination schedule in several countries in Africa. Other yellow fever prevention methods include mosquito control efforts such as eliminating potential breeding sites using larvicides and insecticide spraying to kill adult mosquitoes.[1] Lastly, individuals can use methods to avoid mosquito bites such as using insect repellant and wearing long sleeve or insecticide-treated clothing. The *Aedes aegypti* mosquito feeds during the daytime, therefore caution from early daytime hours until the evening is essential for bite prevention.[11]

Yellow fever is endemic in all or parts of 34 countries in Africa, including the Democratic Republic of Congo (DRC), and has been responsible for sporadic outbreaks.[1] There is potential for outbreaks of yellow fever in the DRC due to the abundance of mosquitoes and gaps in vaccination coverage. Furthermore, deficiencies in the national surveillance system may be responsible for delayed detection and notification of potential outbreaks of yellow fever. The Integrated Disease Surveillance and Response (IDSR) system is a nation-wide surveillance network intended to monitor infectious diseases throughout the country. The DRC is a vast country with many rural communities. Surveillance information must travel from individual health posts to the central health zone monitoring centers and ultimately reach the national level for the disease to be recognized. Due to several logistical and infrastructural constraints, this surveillance system may not be effective in detecting disease outbreaks throughout the country in a timely manner or even at all.

Additionally, when an outbreak is detected, current interventions typically only consist of reactive vaccination campaigns and sporadic vector control. Vaccination campaigns can be costly and logistically challenging to implement and are often implemented after an outbreak has already begun to decline. The campaigns typically seek to vaccinate as many people as possible and may not pause to distinguish individuals that may already be vaccinated or maybe have gotten the disease and either do not have symptoms or have already recovered contributing to vaccine waste. Outbreak response puts an immense burden on already strained health delivery systems which further hinders response efforts.[12]

In March 2016, the DRC began reporting yellow fever cases in connection with an outbreak occurring in neighboring Angola[13] and the outbreak was officially declared in April 2016. Cases associated with the outbreak are recorded as early as February 2016. Local

transmission was quickly observed in three border provinces (Kwango, Kinshasa, and Kongo Central) due to frequent travel between the two countries, inadequate vaccination coverage, and high vector (mosquito) density in both countries. In response to the outbreak, disease control and surveillance measures were implemented, including reactive vaccination campaigns, to avoid further spread of the disease.[14] In DRC, the first vaccination campaign ultimately began three months after the outbreak began due to limited vaccine supply. The CDC estimates that approximately 1.5 million doses were administered during two mass vaccination campaigns in the Kongo Central province alone and the campaigns were estimated to have reached 99% administrative vaccination coverage.[15] In total, the WHO reports that approximately 9.4 million doses were approved and sent to DRC for four vaccination campaigns. All were seemingly administered, including using a fractional dose scheme in Kinshasa to maximize vaccination coverage.[16] This vaccination effort combined with the vaccination campaigns in Angola (30 million vaccines total), while exhausting the global stockpile several times, succeeded in stopping the outbreak in both countries. It was ultimately determined that significant delays occurred in detecting cases due to delays in reporting and the use of a case definition with low accuracy. The median time to hospitalization for severe cases was 17 days, too late for effective supportive care or to allow for other prevention strategies such as the use of vector control measures around confirmed cases homes.[17]

There is a paucity of literature regarding modeling the dynamics of yellow fever in general and few published articles regarding any aspect of the recent outbreak in the DRC and Angola. One study that investigated the outbreak used a statistical logistic model to estimate the geographic expansion of yellow fever in the DRC and Angola. It highlighted the need to incorporate factors related to vector ecology and demographic factors when modeling the spread

of yellow fever. They suggested that their findings needed to account for constraints such as vaccine supply and delivery to translate any findings into policy.[18] Another study used a mathematical model and likelihood-based statistics techniques to analyze the epidemiological processes of the outbreak in Angola. They used a more complex vector-host model to account for transmission dynamics, including separating stages of the yellow fever disease, and studied the impact of the vaccination campaigns. The vaccination campaigns were timely and saved approximately five times the number of deaths and 5.6 times the number of observed cases.[19] More generally, Yusuf and Daniel used a deterministic mathematical model to investigate transmission dynamics of yellow fever and various control measures. They concluded that measures to reduce the mosquito biting rate, the human to vector and vector to human transmission rates, and increase the vaccination success rate would be most effective for preventing the spread of disease.[20] Lastly, another study which used a mathematical model to explore transmission of yellow fever by modeling the human, adult mosquito, and egg populations similarly found that if the mortality rate of mosquitoes is high enough, yellow fever is naturally eradicated from the population, further emphasizing the need for vector control.[21] Several studies have modeled the dynamics of dengue virus, another vector-borne disease,[22,23] and have recommended incorporating interventions related to vector control and vaccination in vector-transmitted disease prevention,[22–24] especially strategies to decrease the actual number of mosquitoes rather than just bite protection.[25] Dengue has a very similar transmission mode, including the same mosquito species, so these studies can be used to inform modeling efforts for yellow fever.

The health delivery system in DRC is continuously burdened by the large country size, where most of the population resides in remote and rural areas, and ongoing instability and

conflict. Addressing recurring outbreaks of several diseases, including cholera, measles, Ebola, and novel diseases such as the ongoing coronavirus disease 2019 (COVID-19) pandemic, contributes to additional strain on the system.[26,27] Given the logistical considerations involved in outbreak response, the purpose of this study is to examine the outbreak of yellow fever in DRC using a mathematical model of disease transmission and estimate the impact of outbreak interventions on the number of yellow fever infections in the DRC.

4.3 Methods

Outbreak description

This study focuses on the DRC outbreak, which displayed slightly different dynamics than the Angola outbreak (e.g., the duration of the outbreak was somewhat similar, however far fewer cases were ultimately infected).[16] The outbreak has been previously described in detail.[17] Briefly, the first confirmed case had symptom onset on February 22, 2016. The suspected case definition proposed by WHO guidelines for routine surveillance in DRC was used, including acute onset of fever followed by jaundice within 14 days after onset of the first symptoms. Blood samples were collected from all suspect cases and the Ministry of Health was notified. Samples were tested at the Institut National de Recherche Biomedicale (INRB) in Kinshasa and cases were confirmed if anti-yellow fever IgM antibodies or yellow fever viral RNA was detected in serum and if the patient was not immunized against yellow fever. Most cases were among adult males who traveled or worked in Angola but 19% of cases were locally transmitted. Among a subset of 14 confirmed cases, the most commonly reported symptoms were considered mild including myalgia (88.9%), vomiting (77.8%), and headaches (66.7%), 92.9% reported fever and 71.4% had jaundice, and only 1 case had hemorrhagic signs (severe symptoms). The median

time from symptom onset to jaundice was eight days and 23% of confirmed cases died after a median of 15 days following the onset of symptoms. Of 2,269 suspect cases, 2,025 underwent confirmatory testing and 78 were confirmed.[17]

The published WHO Situation Reports and a line list of the outbreak obtained from the published literature[17] were used to gather information regarding outbreak duration and the epidemic curve of the outbreak. The epidemic curve stratified by case classification (autochthonous, imported, not classified, and probable) was constructed (Figure 4.1). There was a total of 79 confirmed or probable cases included in the line list, however, the case identified from Lualaba was not officially considered to be part of the outbreak. Most cases were imported and identified in Kongo Central province (Table 4.1). Several vaccination campaigns were implemented in response to the outbreak in various parts of the affected provinces, the first of which took place in May 2016, approximately 94 days from the documented start of the outbreak. The timeline of major events considered in this analysis, including outbreak detection, declaration, and vaccination campaigns, is described in Supplemental Table 4.2.

Yellow fever model

Yellow fever transmission occurs only via the vector-borne route so the basic S-I-R compartmental epidemic model of direct disease transmission may not fully account for the whole disease dynamics. An S-E-A-I-R model in conjunction with an S_M-E_M-I_M model for the mosquito population was utilized for this study. The human state variables include an exposed ("E") population as well as two infected states to account for the disease stages of yellow fever ("A" = asymptomatic/mildly infected and "I" = severely infected). Based on previous literature and modeling studies, there are differences in transmission dynamics and surveillance robustness

among the two infected groups which necessitates distinguishing them in the model. Asymptomatic/mild cases may make up a larger proportion of infected cases but are likely more inconsistently detected or reported due to the non-specific signs of mild yellow fever infection. Severe cases may be reported but also no longer have the virus in their blood, so they are assumed to not contribute to transmission.[7,9,10] Asymptomatic/mild cases are assumed to transmit when bitten by a mosquito and severe cases do not. The recovered ("R") group represents individuals who have recovered from the disease or who have been vaccinated (in vaccination scenarios).

The mosquito state variables include susceptible and infected but also include an exposed ("E_M") population to incorporate the latent period in the mosquito. The two state variable systems interact to infected susceptible humans or mosquitoes after interaction with their infected counterparts. Demography is included (e.g., birth and death rates) in the model and the model assumes homogenous mixing of humans and mosquitoes where both mosquitoes and humans can infect each other upon contact. Lastly, an infected mosquito remains infected until death, however, humans can recover from the disease from both the asymptomatic/mild state or the severely infected state. Beyond the basic model and the typical parameters included in vector-borne disease transmission models, elements reflecting personal protective behavior (proportion of bites prevented), vector control (mosquito mortality), and vaccination are included to use in intervention response scenarios and assess how these factors influence yellow fever transmission and the magnitude of the outbreak.

This model was first formulated as a deterministic model in continuous time to explore the model dynamics and possible parameter values. This transmission model of yellow fever is approximately represented by the diagram (Figure 4.2) and ordinary differential equations:

$$\frac{dS_H}{dt} = b_H(N_H) - m\beta_H S_H \frac{I_M}{N_H}(1-p) - \mu_H S_H - \nu S_H$$

$$\frac{dE_H}{dt} = m\beta_H S_H \frac{I_M}{N_H}(1-p) - \sigma_A E_H - \mu_H E_H$$

$$\frac{dA_H}{dt} = \sigma_A E_H - (1-a)\gamma_A A_H - a\gamma_A A_H - \mu_H A_H$$

$$\frac{dI_H}{dt} = (1-a)\gamma_A A_H - (1-d)\gamma I_H - d\gamma I_H - \mu_H I_H$$

$$\frac{dR_H}{dt} = a\gamma_A A_H + (1-d)\gamma I_H - \mu_H R_H + \nu S_H$$

$$\frac{dS_M}{dt} = b_M - m\beta_M S_M \frac{A_H}{N_H}(1-p) - \mu_M S_M - \mu_C S_M$$

$$\frac{dE_M}{dt} = m\beta_M S_M \frac{A_H}{N_H}(1-p) - \sigma_M E_M - \mu_M E_M - \mu_C E_M$$

$$\frac{dI_M}{dt} = \sigma_M E_M - \mu_M I_M - \mu_C I_M$$

$$N_H = S_H + E_H + A_H + I_H + R_H$$

Using population estimates from 2016 in DRC, approximately 6 million people were at risk in the affected health zones. This population estimate was used as the initial N_H condition in deterministic model exploration and the average population size of affected health zones (215,000 people) was used in stochastic simulations of outbreaks. A ratio of mosquitoes to humans of 8 to 1 (estimated from 3.62-11.66 mosquitoes per human from other studies)[19] and an influx of 1,000 mosquitoes per day (estimated from 400-5000 per day)[22] were assumed. Furthermore, the initial immune population was assumed to be 40% based on a recent estimate of the overall yellow fever vaccination coverage in DRC.[28]

Model Parameters: Estimating the DRC outbreak

Table 4.3 outlines the parameter values that have been identified in the literature from yellow fever and dengue models. Several parameters in the model could be informed from the literature about the DRC and the yellow fever outbreak and a recent paper that modeled the Angola outbreak. The human birth (b_H) and death rate (μ_H) were estimated from available DRC demographic information[29] and the infectious period for asymptomatic/mild cases (γ_A^{-1}) and severe cases (γ^{-1}) and the proportion of deaths among severe cases (d) was obtained from an analysis of the outbreak.[17] The proportion of exposed cases recovering from asymptomatic/mild infection (a) and the mosquito natural mortality rate (μ_M). However, since the DRC outbreak ultimately affected less people than the Angola outbreak, this may indicate that the transmission parameters (mainly β_H: transmission probability from vector to human, β_M: transmission probability from human to vector, and m: mosquito biting rate), could differ from those used in Angola models and the exact incubation periods (σ_A^{-1}: incubation period for asymptomatic cases and σ_M^{-1}: incubation period for mosquitoes) are unknown but potentially range from 3 to 7.14 days and 7 to 12 days, respectively (Table 4.3).

Several approximate fit criteria were used to determine optimized parameters for the DRC outbreak using the deterministic formulation of the model and the full at risk population in the affected health zones. The first framework for optimization ("no intervention framework") aimed to reach parameters for an outbreak without any intervention (e.g., in the case the vaccination campaigns did not change the trajectory of the outbreak) and with similar total number of cases (78) and time to peak of outbreak (approximately 81 days) that was estimated for the DRC outbreak (i.e., minimal difference in these criteria between the simulation and the outbreak). The second framework ("intervention framework") included the first vaccination

campaign intervention at 94 days and an assumed vaccination coverage of 99% and the same fit criteria. Only this vaccination campaign was included since the remaining vaccination campaigns took place after the last confirmed case was reported (see Timeline in Supplemental Table 4.2). The optimization package "optimx" in R 3.6.1 was applied.

Model Parameters: Case detection

An alternative explanation for the smaller than expected outbreak observed in DRC in comparison to Angola is poor case detection. The early symptoms of yellow fever are not very specific. However, the suspected case definition used in the 2016 DRC outbreak required cases to have fever and jaundice, which should have been indicative of more severe yellow fever infection, but did not accurately capture the yellow fever cases.[17] Most yellow fever cases are asymptomatic and mild which may go undetected or misdiagnosed and may have been missed in case detection. In fact, 81.1% of 90 discarded cases tested were malaria positive indicating case detection may not have been focused enough on yellow fever.[17] This possibility and the implications for the model parameters were explored by considering the parameter values if the number of reported cases was, in fact, a representation of only severely infected cases (i.e., those with more severe symptoms such as jaundice). This was also approached as an investigation of the optimized parameters using the optimization package "optimx" in R 3.6.1.

Estimating R_0 using the next generation method

The reproductive number (R_0) is a common measure of the infectiousness of a disease and represents the average number of secondary cases resulting from one infected individual. The next generation matrix method is a systematic procedure to calculate R_0 for a compartmental

model of disease spread.[34] The next generation matrix $G = F \cdot V^{-1}$, where F is the Jacobian matrix of the new infection (or transmission) rates vector and V is the Jacobian matrix of the transition (or transfer) rates vector. The vector of transmission rates (f) is given by:

$$f = \begin{bmatrix} m\beta_H I_M \frac{S_H}{N_H}(1-p) \\ 0 \\ 0 \\ m\beta_M S_M \frac{A_H}{N_H}(1-p) \\ 0 \end{bmatrix}$$

And the transition rates (v) are given by:

$$v = \begin{bmatrix} (\sigma_A + \mu_H)E_H \\ (\gamma_A + \mu_H)A_H - \sigma_A E_H \\ (\gamma + \mu_H)I_H + (a-1)\gamma_A A_H \\ (\sigma_M + \mu_M + \mu_C)E_M \\ (\mu_M + \mu_C)I_M - \sigma_M E_M \end{bmatrix}$$

The Jacobian matrices were obtained by taking the partial derivative with respect to the infected states under the disease-free equilibrium (DFE = susceptible classes are 100% of the population).

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & m\beta_H(1-p) \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & m\beta_M(1-p)r & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \sigma_A + \mu_H & 0 & 0 & 0 & 0 \\ -\sigma_A & \gamma_A + \mu_H & 0 & 0 & 0 \\ 0 & (a-1)\gamma_A & \gamma + \mu_H & 0 & 0 \\ 0 & 0 & 0 & \sigma_M + \mu_M + \mu_C & 0 \\ 0 & 0 & 0 & -\sigma_M & \mu_M + \mu_C \end{bmatrix}$$

R_0 is the dominant eigenvalue of the next generation matrix, where r is the mosquito-to-human population ratio. The next generation matrix for this model is given by:

$$G = F \cdot V^{-1}$$

$$= \begin{bmatrix} 0 & 0 & 0 & \frac{m\beta_H(1-p)(\sigma_M-\mu_M-\mu_C)}{(\sigma_M+\mu_M+\mu_C)(\mu_M+\mu_C)} & \frac{m\beta_H(1-p)}{(\mu_M+\mu_C)} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\sigma_A m\beta_M(1-p)r}{(\sigma_A+\mu_H)(\gamma_A+\mu_H)} & \frac{m\beta_M(1-p)r}{(\gamma_A+\mu_H)} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

The effective reproductive number (R_{eff}) is the reproductive number when there is some immunity or intervention in place during an outbreak, which is relevant in the case of yellow fever since in areas with routine vaccination against yellow fever, such as the DRC, the population is not entirely susceptible. Zhao et. al. defined $R_{eff} = R_0\sqrt{\frac{S_H}{N_H} \cdot \frac{S_M}{N_M}}$ for vector-transmitted diseases which incorporates potential changes to the transmissibility of the virus, characteristics of the mosquito vector, and availability of susceptible individuals to become infected.[19,35]

Stochastic implementation

The Gillespie stochastic simulation algorithm (SSA) was used to implement a stochastic simulation of this model and explore the system dynamics while incorporating the potentially random nature of transmission events at the individual level. The Gillespie SSA procedure can generate statistically correct trajectories of finite well-mixed populations in continuous time. The exact method assumes all possible transitions are independent and simulates each transition between compartments at each time step with constant probability per unit of time depending on the current state of the system.[36,37] To improve the computational efficiency, the explicit tau-leaping algorithm has been developed as an approximation and is utilized here. In this approximation, the algorithm "leaps" over time steps and the number of transitions that occur

together during each step are determined by sampling independently from a Poisson distribution.[38] A predefined time step size (τ) must be established and in this case τ =0.1, which is considered small enough that any changes in the transition rates during each leap will be limited, satisfying the leap condition.[38]

Outbreak and intervention scenarios

Baseline simulations of the outbreak were implemented with and without a vaccination intervention at 94 days with the average population size of affected health zones (215,000 people) as the initial human population size (N_H), 40% baseline yellow fever immunity for each optimization framework, and a 200 day duration of simulations. Simulations included 1,000 iterations of the Gillespie SSA tau-leaping algorithm and the median number and interquartile range (IQR) of the total number of infections, number of asymptomatic/mild, and number of severe infections were used to summarize the resulting outbreaks along with the median peak time of the outbreak. These simulations were used to compare intervention scenarios.

Several intervention scenarios were explored with the goal of limiting the extent of the outbreak size. The existing level of yellow fever immunity in DRC varies by source and may be anywhere from 30% to 87%.[28,39] The impact of this initial immunity was considered first and the total size and peak of the outbreak with various initial immunity values (30% to 90% in increments of 10%) were compared to explore if higher baseline immunity could have prevented the outbreak in DRC from the onset. Simulations similarly included 1,000 iterations of the Gillespie SSA tau-leaping algorithm and the median number and interquartile range (IQR) of the total number of infections, number of asymptomatic/mild, and number of severe infections were used to summarize the resulting outbreaks along with the median peak time of the outbreak.

As mentioned, several vaccination campaigns were pursued during the outbreak in DRC, however, only one took place before the official end of the outbreak. There were delays in outbreak detection, time to diagnosis, and implementation of vaccination campaigns during this outbreak. In DRC, approximately 61 days had elapsed from the first confirmed case when the outbreak was declared and another 33 days elapsed before the first vaccination campaign had been implemented in 8 health zones. Various vaccination campaign scenarios were explored to assess the effectiveness of the vaccination campaign intervention and provide recommendations for future planning. The number of days to detection and number of days to intervention were varied to determine if the times of the actual vaccine campaign contributed to containing the outbreak of yellow fever in DRC. The time of detection was varied at weekly intervals from day 1 of the outbreak to day 56 (8 weeks) and time to intervention was varied at weekly intervals from day 7 to 35 (assuming at least one week was needed to arrange a vaccination campaign). Three levels of vaccination coverage were explored: 50%, 75%, and 99% and each vaccination intervention was modeled as a 10-day campaign. Simulations included 1,000 iterations of the Gillespie SSA tau-leaping algorithm and the median number of the total number of infections was compared to the median number of infected individuals from the baseline scenario with intervention (DRC outbreak simulation) and the percent change (percent of infections prevented) was reported.

Finally, mosquito control was explored as an intervention to limit the number of infected individuals. In Angola and DRC, mosquito control measures aimed to target the areas around confirmed cases' homes or around the homes of reported deaths associated with the outbreak in the case of limited resources. These two scenarios were explored by evaluating the strength of mosquito control, represented by the percentage of mosquitoes eliminated (in 10% increments

from 10% to 100%) proportional to the number of confirmed cases and deaths. Additionally, a more widespread mosquito control scenario was evaluated (not targeted). Lastly, human protective behaviors such as using mosquito repellant or wearing long sleeve clothing can be utilized to prevent mosquito bites. This was explored by varying the percentage of bites prevented in 10% increments from 10% to 100% and reviewing the resulting median number of the total number of infections from 1,000 iterations of the Gillespie SSA tau-leaping algorithm. All modeling, analyses, and simulations were performed in R version 3.6.1.

4.4 Results

Estimating the DRC outbreak

The optimization frameworks aimed to replicate the dynamics of the DRC outbreak to estimate the transmission parameters and incubation periods which had not been described in the literature. The results from both frameworks (assuming no intervention during the outbreak and assuming an intervention) for optimization are summarized in Table 4.4, along with the values used to model the Angola outbreak for comparison. The results from the two frameworks for optimization were similar with the exception of slight variation in the transmission probability from vector to human (β_H), the incubation period for asymptomatic cases (σ_A^{-1}), and the incubation period for mosquitoes (σ_M^{-1}). The intervention framework was designed to replicate the DRC outbreak and associated vaccination campaigns. Using these parameters showed appropriate fit after optimization with 78 total cases in a simulation with vaccination (similar to the total cases in DRC) with a slightly earlier peak of the outbreak (around 70 days) in deterministic simulation (data not shown). As a result, the parameters from this framework were used to represent the DRC outbreak in subsequent intervention scenarios.

The baseline stochastic simulations for each optimization framework, with and without a vaccination campaign, and an initial population of 215,000 people are summarized in Table 4.5. The median number of total infections varied slightly between each framework and whether the vaccination campaign was introduced. Based on these simulations, the vaccination campaign implemented at 94 days into the outbreak succeeded in preventing at least 19% to as many as 28% of cases in DRC when comparing the simulations with and without vaccination under the intervention framework. The Angola parameter values resulted in much larger outbreaks than what happened in DRC even when vaccination was considered in the simulation, so these parameters likely do not represent the DRC outbreak.

Using this yellow fever transmission model, R_0 was estimated as 5.10 to 5.25 and R_{eff} was 3.98 to 4.07 depending on the parameter values (Table 4.5). The simulation using the intervention framework values without a vaccination campaign (median infections: 85.5 infections, IQR: 14.75 to 165.25 infections) will be used to compare intervention scenarios.

Inaccurate case detection may also be a possible explanation for the smaller size of the outbreak. The case definition included fever and jaundice symptoms, so reported cases might be a reflection of only the severe cases in the outbreak and not the asymptomatic/mild cases. Using the optimization method while assuming the severe cases count was 78, the transmission parameters reveal a very different projection. These parameters now approach the values for Angola (Table 4.4) and the median total number of cases in the outbreak could reach 489 total cases and approximately 74 (IQR: 19.75 to 135) severe cases with a peak of the outbreak around 92 days even with a vaccination campaign. Figure 4.3 shows the possible outbreak size from simulations with this set of possible parameters overlaid with the cumulative number of infections from DRC. Although the trajectory is not similar, the total number of cases closely

approaches the total number of severe cases. In this case, for every severe yellow fever case, there were approximately 5 to 6 potential asymptomatic/mild cases that may not have been detected.

Outbreak and intervention scenarios

Initial population immunity impacted the total number of cases in this model of yellow fever in DRC. However, even with 99% of the population being immune, a few cases would still occur (median: 3 infections, IQR: 1 to 6 infections) and with worse population immunity than assumed in the parameter frameworks (e.g., 30%) the outbreak would have been much larger than observed (median: 100 infections, IQR: 29 to 192 infections) (Figure 4.4).

Vaccination scenarios

Earlier outbreak detection and earlier intervention would prevent cases of yellow fever in this outbreak. The baseline simulation, which included the vaccination campaign as was observed in the outbreak (approximately 61 days to detection and 33 days to intervention), prevented approximately 28% of infections (reduction of median 85.5 infections to 61.5 infections (Table 4.5). Even if detection time was at least one week earlier and intervention another week earlier, additional reductions in cases could occur, regardless of the level of vaccination coverage achieved. In this scenario, a vaccination campaign at 49 days to detection and 28 days to intervention would prevent 33.3%, 33.9%, and 38% of infections if the campaign achieved 50%, 75%, and 99% vaccination coverage, respectively. Clearly, the earliest detection and intervention times simulated prevented the highest number of cases: 93%, 96.5%, and 97.7% of cases if the campaign achieved 50%, 75%, and 99% vaccination coverage, respectively

(Figure 4.5). Both factors appear to be important, but more reduction was seen across days to detection if days to intervention were held constant rather than across days to intervention. Furthermore, the level of vaccination coverage achieved through the vaccination campaigns did not appear to change the number of cases prevented in this simulation.

Mosquito control (elimination) targeted at confirmed cases and even confirmed deaths would not have had enough impact on limiting the outbreak of yellow fever. Even if 100% of mosquitoes could be eliminated, targeting this intervention only at confirmed cases and deaths would not contribute to a change in the median number of infections of 85.5 from the baseline scenario without intervention (Figure 4.6). However, a more widespread universal mosquito elimination strategy would reduce almost all the cases, even if only 10% of mosquitoes could be eliminated. In fact, 10% mosquito reduction produced a median of two infections in stochastic simulations (Figure 4.6) and R_0 would be reduced to 1.79 in this scenario (data not shown). Bite prevention is also an effective means of limiting the number of infections. Even with 10% of bites prevented the median number of infections is reduced from the baseline scenario and continues to progressively decline with increasing prevention coverage (Figure 4.7).

4.5 Discussion

Using a stochastic simulation of yellow fever transmission, we quantified how types of interventions influence the magnitude and severity of an outbreak. Previous modeling studies have identified that control measures aimed at reducing the mosquito biting rate, reducing the mosquito population, decreasing transmission rates, and vaccination success help reduce disease transmission.[19–21] Similarly, interventions considered in this study, including vaccination,

mosquito control, and human behavior such as bite prevention, can contribute to outbreak prevention, however, some interventions may be more efficient and effective than others.

Early detection of cases is often mentioned in recommendations for effective outbreak response and is an important strategy to explore. Disease surveillance systems usually utilize passive surveillance methods, which may not capture all cases. However, many countries have made improvements in disease detection capacity through strengthening surveillance and laboratory capacity.[40,41] Although, DRC has implemented the IDSR system, there was still a delay in case reporting during the yellow fever outbreak. The simulations indicated that cases were prevented with the observed time to detection and intervention. However, even if the outbreak was detected one to two weeks earlier, as many as 50% of infections could have been prevented. In our simulations, we distinguished between time to detection and time to intervention. Although both factors appeared to be important for reducing the number of infections, more reduction was seen with reduced days to detection, quantifying that earlier detection of outbreaks is necessary. Earlier detection could also prevent delays in accessing healthcare and delivery of necessary treatment.

The vaccination campaigns in DRC were reported to achieve anywhere from 99% to 103% of the target population, which required incredible human resources and 30 million doses of vaccines total, creating a worldwide shortage of vaccines for months. Additionally, most campaigns took place after the outbreak appeared to have ended. Through simulations, this level of vaccination coverage may not have been necessary. In the case of this outbreak in DRC, targeting fewer people (either 50% or 75% of the population) would not have resulted in meaningful differences in the total number of cases. These findings are vital to consider for future outbreaks, especially when human resources and vaccine supply may be limited.

Fortunately, even if the vaccination campaigns were very delayed and may not have influenced the 2016 outbreak, they could likely help prevent future outbreaks by boosting the immunity in selected health zones in these three provinces. These campaigns can be seen more as supplemental vaccination campaigns rather than reactive outbreak-response related campaigns. From the simulations, higher initial population immunity to yellow fever would help reduce cases during outbreaks of yellow fever by as much as 90% if at least 70% to 80% yellow fever immunity could be achieved. While early detection is paramount, outbreak response also relies on having an existing stable health infrastructure and the availability of significant human resources, financing, and the ability to manage emergency logistics, however, many low-income countries still need additional support to strengthen these systems.[12,40] Systematically improving the population immunity through routine immunization would be a more efficient use of the health systems resources and would be effective for reducing outbreaks.

The case definition used in this outbreak was consistent with the WHO recommended surveillance standard for yellow fever: "a case that is characterized by acute onset of fever followed by jaundice within two weeks of the onset of the first symptoms" followed by laboratory confirmation in the absence of yellow fever vaccination.[17,42] However, this definition more closely describes severe infection with yellow fever and could exclude individuals with asymptomatic or mild infections. Also, depending on how vaccination status was ascertained, individuals who did not have accurate vaccination records could be excluded. An assessment of the outbreak found that a better definition would have been "a combination of fever or jaundice and myalgia or a negative malaria test," which could have allowed for more mild cases to be detected but not asymptomatic cases.[17] In a simulation where the detected case in DRC represented only the severe cases, the projected outbreak would have been more extensive than

observed. This simulation highlights the potential for an "iceberg effect" scenario of undetected asymptomatic/mild cases in yellow fever outbreaks, which has been a note for concern when assessing other outbreaks of yellow fever.[33] However, approximately 2,000 suspect cases underwent confirmatory testing in this outbreak in DRC, so case detection could have been robust enough to capture asymptomatic and mild cases, but they still may have been omitted using the case definition.

Vector control strategies are often targeted around confirmed cases' homes to prevent further transmission, although this strategy could not be effectively implemented in DRC due to delays in diagnosis and access to care.[17] However, based on the simulations in this study, this strategy may not have been the most effective. The simulations that included mosquito elimination that was proportional to the number of confirmed cases and diagnosed deaths did not seem to have enough impact in the yellow fever outbreak simulation. It was only in the presence of widespread mosquito elimination that a significant effect was observed. Mosquito fogging and habitat elimination should be more widespread in outbreak areas to see the benefits. Routine mosquito control could be implemented to aid preparedness efforts and help prevent outbreaks from occurring. Targeting mosquito control as soon as a case is suspected would be beneficial to interrupt transmission rather than waiting for confirmation.[19] Several studies have emphasized that vector elimination would have the most effect on the reproductive number. High enough mosquito mortality would naturally eliminate yellow fever from the population.[21,25] However, bite prevention also seems like a very effective intervention to prevent yellow fever. This may also be cost-effective since it distributes the effort and responsibility across many individuals rather than few that are responsible for eliminating all the mosquitoes. However, it may also require a cost to implement since individuals or governments would need to provide insect

repellent or clothing that would be conducive to preventing mosquito bites. Many programs exist for distribution of insecticide-treated or other bed nets for malaria prevention in endemic countries, so programs could be augmented by adding protection for daytime biting mosquitoes as well.

The S-E-A-I-R-S_M-E_M-I_M model in this study builds upon the existing limited models of yellow fever and incorporates several components that are often neglected in recent models of vector-borne diseases including explicitly modelling the vector population, the latent period in the mosquito, and representing clinical outcomes and stages of disease.[43] This model uses more thorough knowledge of the disease process and does not include the severe stage of disease in disease transmission, which has only recently been incorporated into yellow fever models.[20] By leveraging optimization methods, possible values for unknown parameters that approximately fit characteristics of this outbreak were estimated and compared to other models of yellow fever and the Angola yellow fever outbreak.

Using the next generation method, R_0 was estimated at around 5.10 to 5.25. Other studies have estimated R_0 of yellow fever in the Angola outbreak to be between 2.6 and 3.4, which is a bit lower than the estimates in this study.[19] However, based on the methods, this may represent the effective reproductive number estimated in this study (between 3.98 to 4.07). Furthermore, the R_0 estimates are consistent with other studies that estimated R_0 to be 4.8 and, in another study, 5.2 (95% CI 4.3–6.1) if the mosquito lifespan was 7 days and 7.1 (5.5–8.7) if the mean mosquito lifespan was 14 days early in the Angola outbreak.[18,44] Since interventions were very late in DRC, it is reasonable that the reproductive number would be comparable to that of the early stages of the Angola outbreak.

There are several limitations of this study. The fit criteria used were approximations of the available outbreak data. The data suggests that the outbreak occurred in two small waves, which was not explicitly modeled in this study. Zhao, et. al. also noted a similar phenomenon in the Angola data. They hypothesized that these waves could be due to changes in individual protective behavior as a reaction to reported cases that could have waned over time and this interaction is not included in the simulations in this study. Furthermore, environmental factors such as climate could have played a role in propagating the second wave.[19] An important finding from this analysis was the effectiveness of bite prevention for mitigating the yellow fever outbreak. Extra consideration may be need when modeling changes in biting behavior since protecting some individuals from biting may simply redistribute biting to other humans, which could require two classes of humans with different biting rates to be modeled fully.[25] Vector-borne disease models have often excluded heterogenity of biting rates, so future models may incorporate variation in biting behavior into the model to improve simulations of this intervention.[43]

Only one vaccination campaign is simulated in this study, mainly because the initial vaccination campaign in DRC was considerably delayed, so subsequent campaigns probably had little effect on the outbreak. However, other factors could also contribute to the outbreak ending, such as closer monitoring of travel or the effects of the vaccination campaigns that had already started in Angola. Furthermore, estimates stated that they reached 99% or greater vaccination coverage in each campaign, so by this definition, only one campaign may be necessary. Additionally, the model used also incorporates several assumptions, such as accounting for the urban transmission cycle and not others, which implies transmission only among humans. However, this seems to be the more problematic transmission cycle in Africa based on previous

outbreaks. No seasonality was included in the model. Indeed, dependence on climate and heterogeneity in population mixing are noted to be lacking from vector-borne disease models.43 Previous descriptions of yellow fever in this area indicate that transmission may persist even through the dry season where *A. aegypti* becomes the dominant vector and water accumulation in domestic containers provides excessive breeding sites.[7] The probability of yellow fever reporting is relatively high throughout the year secondary to an interaction between temperature and rainfall that can facilitate transmission for most of the year apart from January to March when it is slightly lower.[45] Furthermore, equal mixing of humans and mosquitoes may be reasonable in a densely populated urban setting. Lastly, age-specific risks of infection are not modeled, however they are negligible since mosquitoes will not typically differentially bite humans. Age-specific risks of death and disease severity exist [10] but were not incorporated.

The literature regarding this outbreak and modeling yellow fever, in general, is limited. Using optimization methods and approximate fit criteria, parameter values are proposed to approximate the recent outbreak in DRC, the reproductive number of the outbreak is estimated, and outbreak preparedness and response scenarios were explored. Outbreaks of endemic diseases such as yellow fever, as well as novel diseases, will continue to occur in the absence of population immunity. Methods to prevent yellow fever are available. Establishing methods for efficient outbreak preparedness and response is essential to prevent additional burden on strained health systems like in the DRC. Although large scale vaccination campaigns are typically the first mode of prevention employed in yellow fever outbreaks, more limited campaigns may be more efficient in an outbreak setting. Additionally, it may be most useful to strengthen the health delivery system and implement interventions before an outbreak occurs so that capacity to detect and respond to all outbreaks is established. Population immunity to yellow fever can be

improved by continuing existing routine immunization and the addition of supplemental immunization activity campaigns in DRC. Widespread mosquito elimination campaigns and programs to prevent mosquito bites can also be utilized to reduce the transmission potential. This modeling study adds new information about yellow fever transmission in DRC that can be the basis of future investigations and recommendations to prevent subsequent outbreaks of yellow fever in this region.

4.6 Tables and Figures

Figure 4.1 Yellow fever outbreak epidemic curve, Kongo Central, Kinshasa, Kwango, Democratic Republic of Congo, 2016 (data obtained from Ingelbeen, et al.[17])

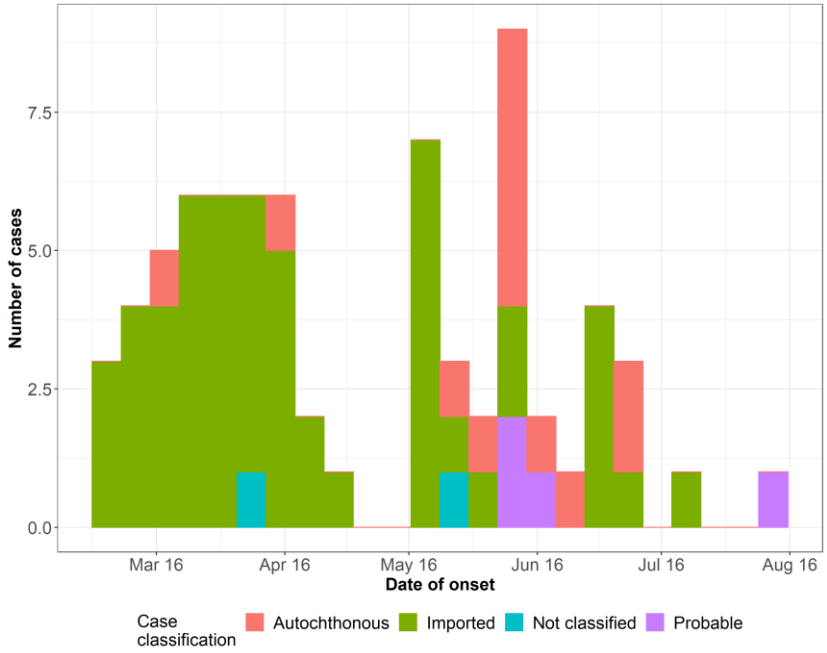


Table 4.1 Case counts and locations of yellow fever outbreak, Kongo Central, Kinshasa, Kwango, Lualaba, Democratic Republic of Congo, 2016 (data obtained from Ingelbeen, et al.[17])

	Total	Autochthonous	Imported	Not classified	Probable
Kongo Central	40	3	36	1	0
Kinshasa	23	8	10	1	4
Kwango	15	4	10	0	1
Lualaba	1	0	1	0	0
Total	79	15	57	2	6

Table 4.2 (Supplemental) Yellow fever outbreak timeline of major events, Democratic Republic of Congo, 2016 (data obtained from WHO situation reports and Ingelbeen, et al.[17])

Date	Event	Days	Vaccination coverage details
2/22/2016	First confirmed case symptom onset		
3/22/2016	First notification of a potential outbreak	29 days	
4/23/2016	Outbreak declared	61 days	
	Approximate peak of imported cases	81 days	
5/26/2016 – 6/4/2016	*Vaccination campaign seven health zones in Kongo central province and Ndjili health zone in Kinshasa province*	*94 days*	*2.1 million people were vaccinated (99% coverage)*
	Approximate peak of autochthonous cases	98 days	
7/12/2016	Last confirmed case	141 days	
7/20-7/29	*Vaccination campaign Kisenso health zone in Kinshasa province and in Kahemba, Kajiji, and Kisandji health zones in Kwango province*	*149 days*	*Kisenso 104%* *Kahemba, Kajiji and Kisandji Health Zones in Kwango province ranging from 70 to 107%*
8/11/2016	Last suspected case	171 days	
8/17-9/5	*Large scale fractional dose campaign 47 health zones (32 in Kinshasa, 15 along the border with Angola). All children over 9 months of age and all adults in urban Kinshasa (a target population of 7,586,400)*	*177 days*	*Preliminary results indicate that immunization coverage reached 103.1% in Kinshasa, 101% in Kasai Central, 98.3% in Kongo Central, 101% in Kasai, 101% in Kwango, and 100.8% in Lualaba.*
10/2-10/19	*Vaccination campaign Feshi (Kwango)*	*223 days*	*152,492 people were vaccinated*
10/20/2016	*Vaccination campaign Mushenge (Kasai province*	*241 days*	

Figure 4.2 Model structure of yellow fever transmission

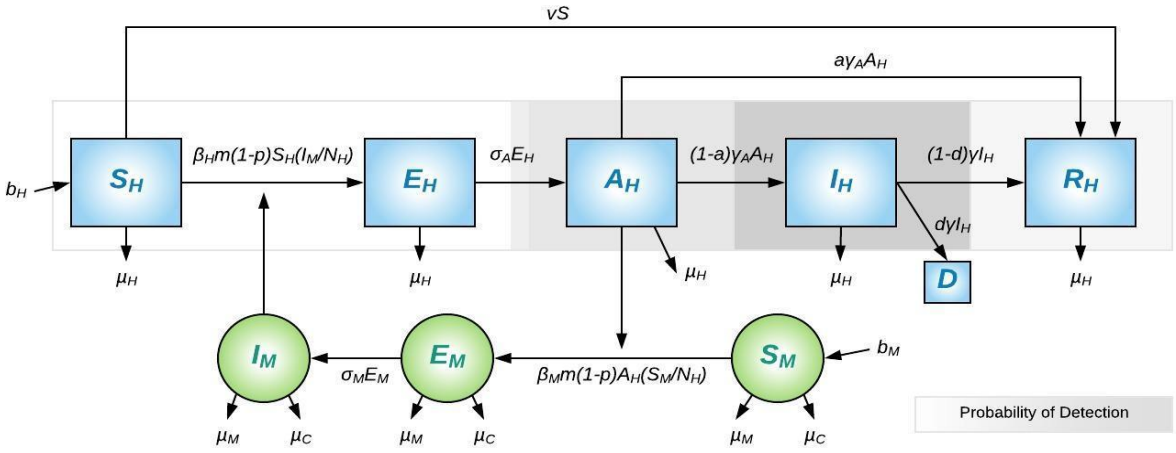


Table 4.3 Summary of potential model parameters and values from the literature

Parameters	Values
Humans	
b_H = human birth rate	0.0001158/day (DRC)[29]
β_H = transmission probability from vector to human	0.1-0.75,[22] 0.4,[19] 0.6,[20,21] 1.0[30,31]
σ_A^{-1} = incubation period for asymptomatic cases	3-6 days,[9] 3.2,[20] 4 days, [19] 4.3 days, [32] 7.14 days[31]
a = proportion of exposed cases recovering from asymptomatic/mild infection	0.85,[19,20] 0.88 [33]
γ_A^{-1}= infectious period, asymptomatic/mild	3-6 days,[9] 3-14 days,[22] 4 days,[19] 7 days,[21] 8 days (DRC)[17]
γ^{-1} = infectious period, severe cases	3-8 days,[9] 7-10 days to death,[9] 7 days (DRC),[17] 8 days,[19] 10 days[30,31]
μ_H = human natural mortality rate	0.0000272/day (DRC)[29]
d = proportion of death among severe cases	0.06,[19] 0.23 (DRC),[17] 0.47,[33] 0.00035/day[20,21]
p = proportion of mosquito bites prevented by human behavior	Varied
v = proportion vaccinated for yellow fever through campaign	Varied
Mosquitoes	
m = mosquito biting rate	0.3-1/day,[22] 0.5/day,[19] 0.78/day,[31] 1.2/day,[30] 3/day[20,21]
b_M = mosquito birth rate/influx/recruitment	0.051/day,[20] 400-5000 mosquitoes[22]
β_M = transmission probability from human to vector	0.5-1,[22] 0.5,[19,20] 0.8,[21] 1.0,[30,31]
σ_M^{-1}= incubation period for mosquitoes	7 days,[21,31] 8-12 days,[22] 10 days,[19,32] 12 days[30]

μ_M = mosquito natural mortality rate	0.051/day (19.6 days),[20] 0.09/day (11 days),[21] 0.15/day (6.67 days),[30,31] 1/(4 -50) days,[22] 1/20 days[19]
μ_C = mosquito mortality rate due to control measures	Varied

Table 4.4 Parameters values based on optimization for each framework for estimation

Parameter	Angola Outbreak values	Optimized values		
		No Intervention Framework values	Intervention Framework values	Severely infected Framework values
β_H = transmission probability from vector to human	0.4	0.36	0.37	0.48
σ_A^{-1} = incubation period for asymptomatic cases	4 days	5.38 days	5.29 days	4 days
m = mosquito biting rate	0.5/day	0.42/day	0.42/day	0.49/day
β_M = transmission probability from human to vector	0.5	0.5	0.5	0.5
σ_M^{-1}= incubation period for mosquitoes	10 days	11.18 days	11.28 days	10.04 days
R_0	6.53	5.10	5.25	7.07
R_{eff} with 40% initial immunity	5.06	3.98	4.07	5.48

Table 4.5 Baseline stochastic simulations with and without a vaccination campaign, median and interquartile range (IQR) of the number of infections by infection type and median day of outbreak peak

Parameters	Simulation	Total Infections	Asymptomatic/ Mild Infections	Severe Infections	Day of outbreak peak
Angola Outbreak values	No Vaccination	469 (148.75, 850.25)	390 (127.75, 717.25)	71 (21, 126)	80
	Vaccination	275.5 (94.5, 526.5)	234.5 (79.75, 448)	41.5 (14.75, 79.25)	76.25
No Intervention Framework values	No Vaccination	72 (13.75, 155.25)	62 (12.75, 133)	10 (2, 23)	57.5
	Vaccination	54 (15, 115)	46 (13, 99)	8 (2, 17.25)	57.25
Intervention Framework values	No Vaccination	85.5 (14.75, 165.25)	74 (13, 143)	12 (2, 24)	58
	Vaccination	61.5 (12, 124.25)	54 (11, 107)	9 (2, 18)	63
Severely infected	No Vaccination	809.5 (224, 1494)	681 (191, 1263.5)	118.5 (30.75, 219.5)	89

Framework values	Vaccination	488.5 (129.75, 885.5)	416.5 (110.75, 748.25)	74 (19.75, 135)	91.75

Figure 4.3 Stochastic simulation using parameters from severely infected framework, with and without vaccination campaign at 94 days and cumulative cases in DRC outbreak

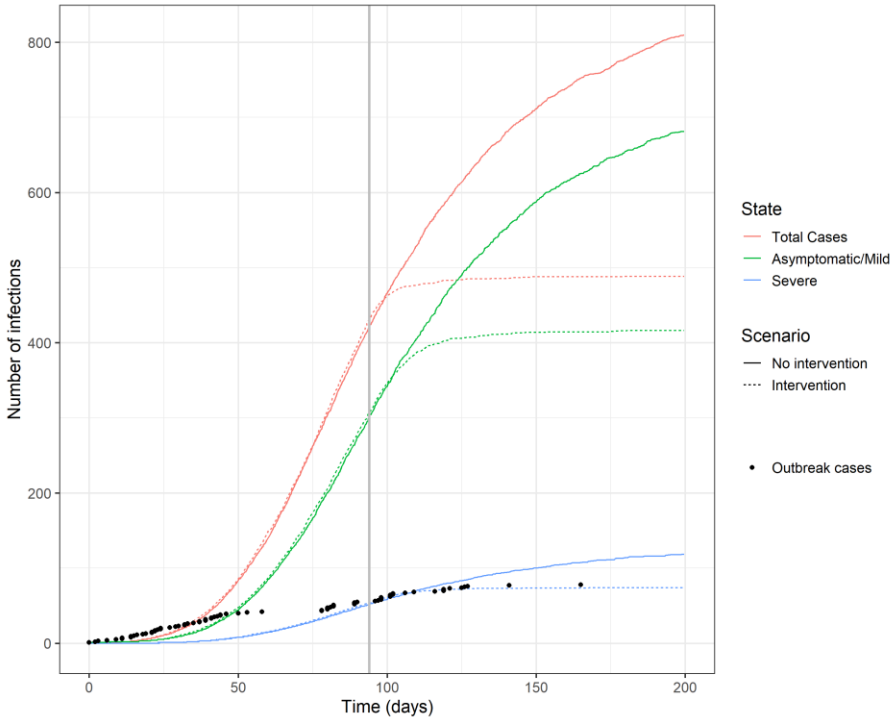


Figure 4.4 Stochastic simulations with various initial population immunity values from 30% to 90% in increments of 10%, outbreak trajectory, median and interquartile range (IQR) of total number of infections and median day of outbreak peak

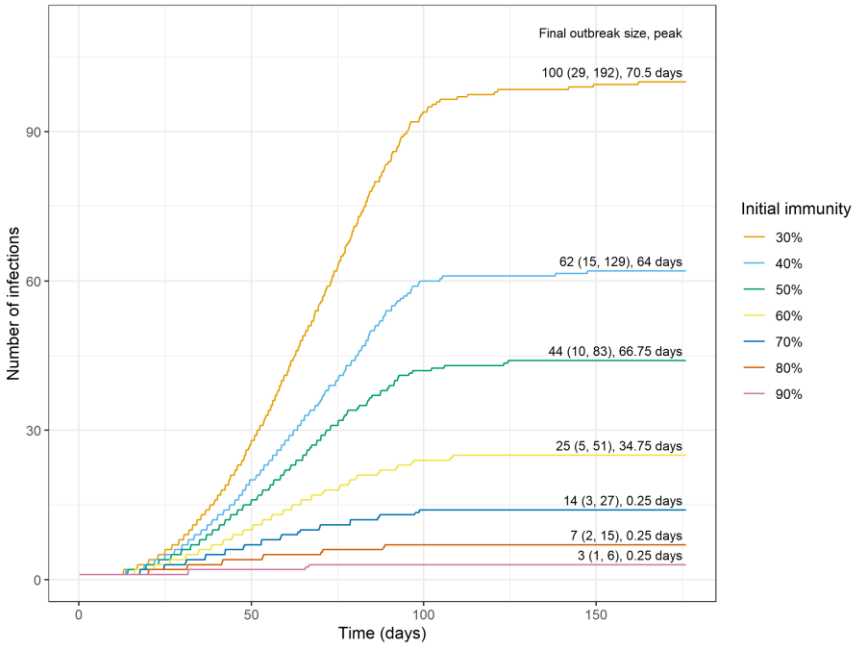


Figure 4.5 Stochastic simulation of vaccination campaign scenarios by level of vaccination coverage achieved in the campaign and time to detection versus time to intervention of campaign, median number of total infections (left) and percent change in cases (right)

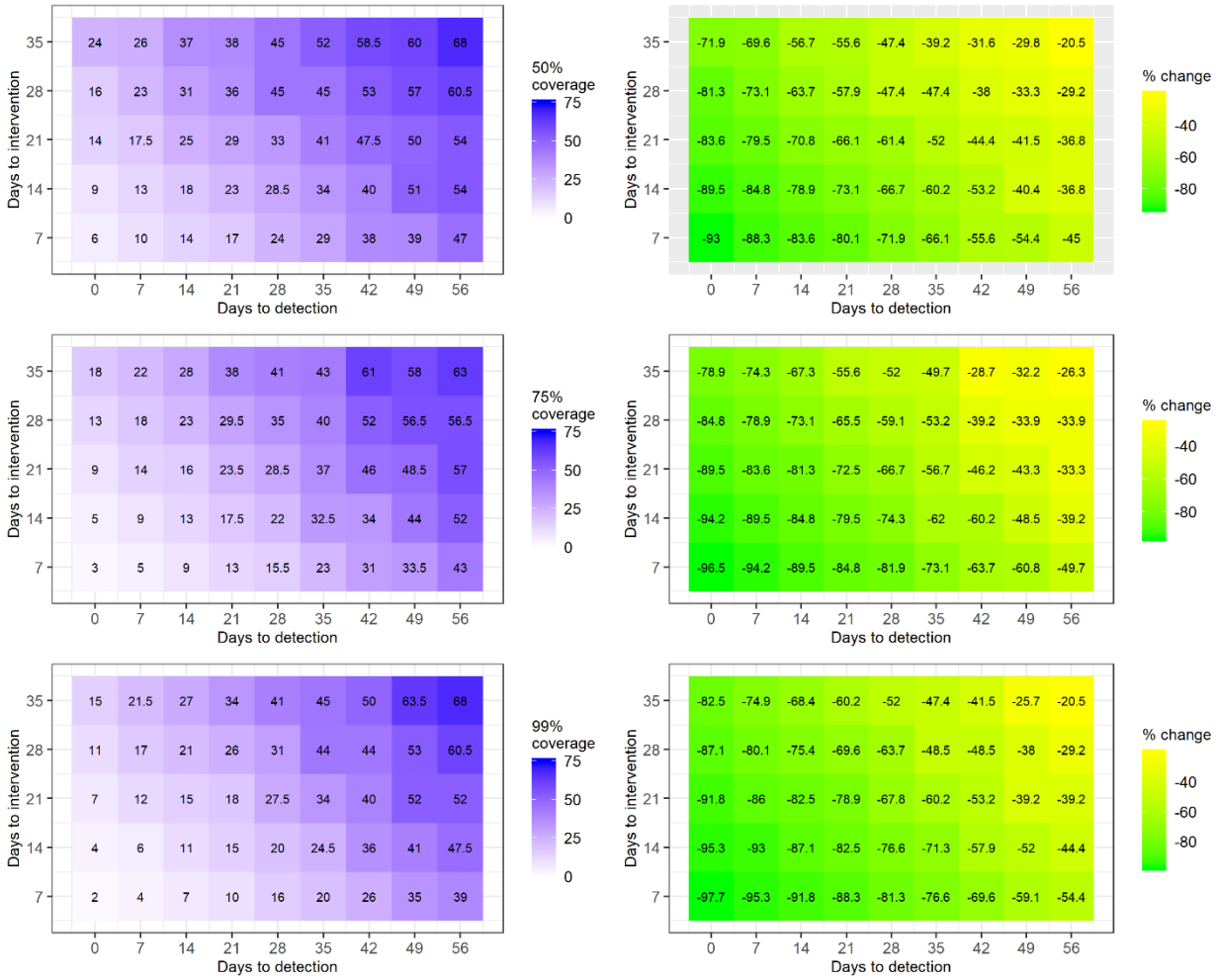


Figure 4.6 Stochastic simulation of mosquito control scenarios by percentage of mosquitoes controlled and elimination strategy, median number of total infections

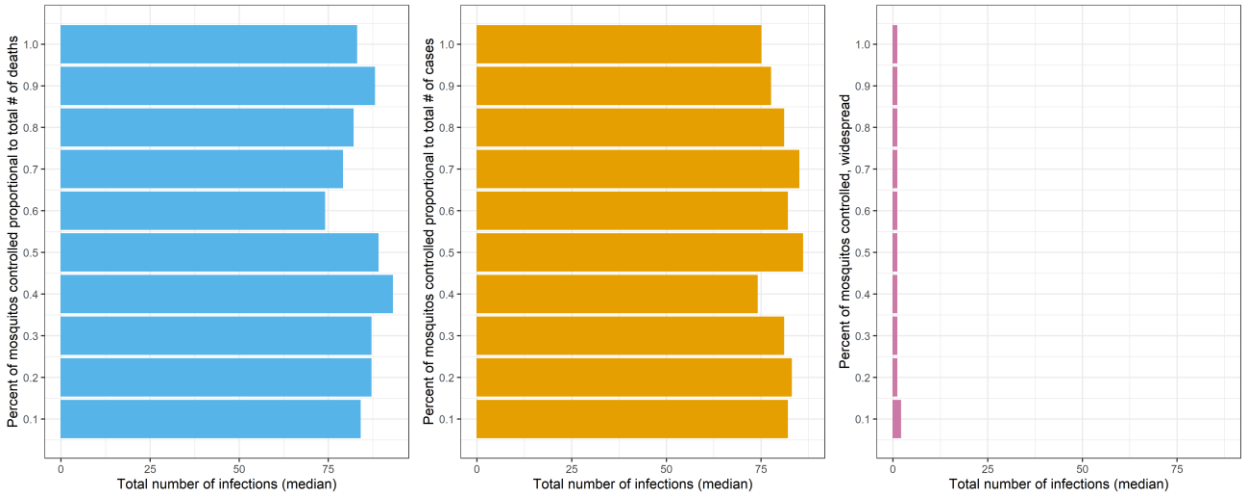
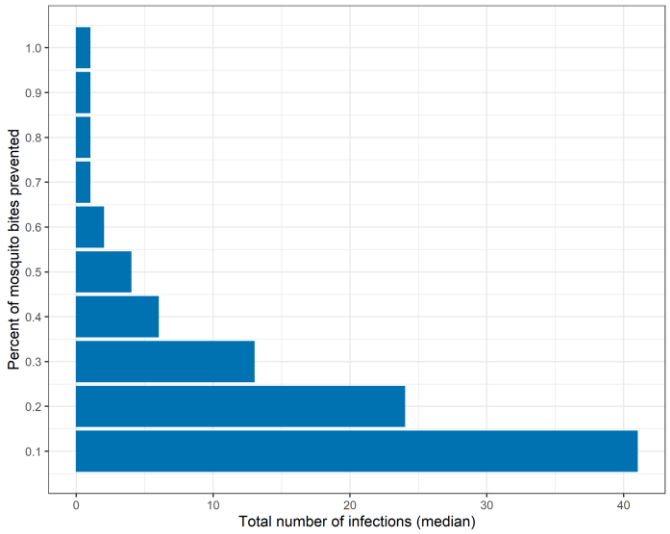


Figure 4.7 Stochastic simulation of bite prevention scenarios by percentage of bites prevented, median number of total infections



4.7 References

1. World Health Organization. Yellow fever Fact Sheet. http://www.who.int/mediacentre/factsheets/fs100/en/. Published 2016.
2. Centers for Disease Control and Prevention. Transmission | Yellow Fever | CDC. http://www.cdc.gov/yellowfever/transmission/. Published 2015. Accessed June 11, 2017.
3. World Health Organization. Eliminate Yellow fever Epidemics (EYE): a global strategy, 2017-2016. *Wkly Epidemiol Rec*. 2017;92(16):193-204. https://www.who.int/wer/2017/wer9216/en/. Accessed August 13, 2018.
4. Barrett ADT. Yellow fever live attenuated vaccine: A very successful live attenuated vaccine but still we have problems controlling the disease. *Vaccine*. 2017;35(44):5951-

5955. doi:10.1016/J.VACCINE.2017.03.032

5. Rogers DJ, Wilson AJ, Hay SI, Graham AJ. The global distribution of yellow fever and dengue. *Adv Parasitol*. 2006;62:181-220. doi:10.1016/S0065-308X(05)62006-4

6. World Health Organization. Emergencies preparedness, response - Increased risk of urban yellow fever outbreaks in Africa. *WHO*. 2015. https://www.who.int/csr/disease/yellowfev/urbanoutbreaks/en/. Accessed January 20, 2019.

7. Monath TP, Vasconcelos PFC. Yellow fever. *J Clin Virol*. 2015;64:160-173. doi:10.1016/j.jcv.2014.08.030

8. Baba MM, Ikusemoran M. Is the absence or intermittent YF vaccination the major contributor to its persistent outbreaks in eastern Africa? *Biochem Biophys Res Commun*. 2017;492(4):548-557. doi:10.1016/j.bbrc.2017.01.079

9. Monath TP. Yellow fever: an update. *Lancet Infect Dis*. 2001;1(1):11-20. doi:10.1016/S1473-3099(01)00016-0

10. Barnett ED. Yellow Fever: Epidemiology and Prevention. *Clin Infect Dis*. 2007;44(6):850-856. doi:10.1086/511869

11. Centers for Disease Control and Prevention. Prevention | Yellow Fever | CDC. https://www.cdc.gov/yellowfever/prevention/index.html. Published 2015. Accessed May 19, 2017.

12. Keusch GT, McAdam K, Cuff PA, Mancher M, Busta ER. Strengthening Capacity for Response and Research. In: *Integrating Clinical Research into Epidemic Response: The Ebola Experience*. Washington DC: National Academies Press; 2017:155-198. doi:10.17226/24739

13. World Health Organization. Emergencies preparedness, response, Yellow Fever – Democratic Republic of the Congo, 11 April 2016. WHO. http://www.who.int/csr/don/11-april-2016-yellow-fever-drc/en/. Published 2016. Accessed May 19, 2017.

14. World Health Organization. Emergencies preparedness, response, Yellow fever – Democratic Republic of the Congo, 2 June 2016. WHO. http://www.who.int/csr/don/02-june-2016-yellow-fever-drc/en/. Published 2016. Accessed May 19, 2017.

15. Otshudiema JO, Ndakala NG, Mawanda E-TK, et al. Yellow Fever Outbreak - Kongo Central Province, Democratic Republic of the Congo, August 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(12):335-338. doi:10.15585/mmwr.mm6612a5

16. World Health Organization. *Situation Report - Yellow Fever - 28 October 2016.*; 2016. http://apps.who.int/iris/bitstream/handle/10665/250661/yellowfeversitrep28Oct16-eng.pdf?sequence=1. Accessed June 19, 2018.

17. Ingelbeen B, Weregemere NA, Noel H, et al. Urban yellow fever outbreak—Democratic Republic of the Congo, 2016: Towards more rapid case detection. Beasley DWC, ed. *PLoS Negl Trop Dis*. 2018;12(12):e0007029. doi:10.1371/journal.pntd.0007029

18. Kraemer MUG, Faria NR, Reiner RC, et al. Spread of yellow fever virus outbreak in Angola and the Democratic Republic of the Congo 2015–16: a modelling study. *Lancet*

Infect Dis. 2016. doi:10.1016/S1473-3099(16)30513-8

19. Zhao S, Stone L, Gao D, He D. Modelling the large-scale yellow fever outbreak in Luanda, Angola, and the impact of vaccination. Rodriguez-Barraquer I, ed. *PLoS Negl Trop Dis*. 2018;12(1):e0006158. doi:10.1371/journal.pntd.0006158
20. Yusuf TT, Daniel DO. Mathematical Modeling of Yellow Fever Transmission Dynamics with Multiple Control Measures. *Asian Res J Math*. May 2019:1-15.
21. Raimundo SM, Amaku M, Massad E. Equilibrium Analysis of a Yellow Fever Dynamical Model with Vaccination. 2015. doi:10.1155/2015/482091
22. Andraud M, Hens N, Marais C, Beutels P. Dynamic Epidemiological Models for Dengue Transmission: A Systematic Review of Structural Approaches. *PLoS One*. 2012. doi:10.1371/journal.pone.0049085
23. Nishiura H. Mathematical and Statistical Analyses ofthe Spread of Dengue. *Dengue Bull*. 2006;30:51-67. message:%3C4D8040D1.2000800@emory.edu%3E%5Cnpapers2://publication/uuid/41B30B48-DE61-4646-AB72-E3FF8190566F.
24. Luz PM, Struchiner CJ, Galvani AP. Modeling Transmission Dynamics and Control of Vector-Borne Neglected Tropical Diseases. Brooker S, ed. *PLoS Negl Trop Dis*. 2010;4(10):e761. doi:10.1371/journal.pntd.0000761
25. Brauer F, Castillo-Chavez C, Mubayi A, Towers S. Some models for epidemics of vector-transmitted diseases. *Infect Dis Model*. 2016;1(1):79-87. doi:10.1016/j.idm.2016.08.001
26. WHO | Democratic Republic of the Congo. https://www.who.int/csr/don/archive/country/cod/en/. Accessed June 19, 2020.
27. DRC Ebola outbreak crisis update | MSF. https://www.msf.org/drc-ebola-outbreak-crisis-update. Accessed June 19, 2020.
28. Shearer FM, Moyes CL, Pigott DM, et al. Global yellow fever vaccination coverage from 1970 to 2016: an adjusted retrospective analysis. *Lancet Infect Dis*. 2017;17(11):1209-1217. doi:10.1016/S1473-3099(17)30419-X
29. The World Bank. Congo, Dem. Rep.| Data. http://data.worldbank.org/country/congo-dem-rep. Published 2015. Accessed June 11, 2017.
30. Massad E, Bezerra Coutinho FA, Burattini MN, Lopez LF, Struchiner CJ. Yellow fever vaccination: How much is enough? *Vaccine*. 2005;23(30):3908-3914. doi:10.1016/j.vaccine.2005.03.002
31. Ribeiro AF, Tengan C, Sato HK, et al. A public health risk assessment for yellow fever vaccination: A model exemplified by an outbreak in the state of São Paulo, Brazil. *Mem Inst Oswaldo Cruz*. 2015. doi:10.1590/0074-02760140345
32. Johansson MA, Arana-Vizcarrondo N, Biggerstaff BJ, Staples JE. Incubation Periods of Yellow Fever Virus. *Am J Trop Med Hyg*. 2010;83(1):183-188. doi:10.4269/ajtmh.2010.09-0782
33. Johansson MA, Vasconcelos PFC, Staples JE. The whole iceberg: estimating the incidence of yellow fever virus infection from the number of severe cases. *Trans R Soc*

Trop Med Hyg. 2014;108(8):482-487. doi:10.1093/trstmh/tru092

34. Van Den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math Biosci*. 2002;180(1-2):29-48. doi:10.1016/S0025-5564(02)00108-6

35. Zhao S, Musa SS, Hebert JT, et al. Modelling the effective reproduction number of vector-borne diseases: The yellow fever outbreak in Luanda, Angola 2015-2016 as an example. *PeerJ*. 2020;2020(2). doi:10.7717/peerj.8601

36. Gillespie DT. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. *J Comput Phys*. 1976;22(4):403-434. http://web.mit.edu/endy/www/scraps/signal/JCompPhys(22)403.pdf. Accessed July 22, 2020.

37. Gillespie DT. Exact stochastic simulation of coupled chemical reactions. *J Phys Chem*. 1977;81(25):2340-2361. doi:10.1021/j100540a008

38. Gillespie DT. Approximate accelerated stochastic simulation of chemically reacting systems. *J Chem Phys*. 2001;115(4):1716-1733. doi:10.1063/1.1378322

39. WHO and UNICEF. *Democratic Republic of the Congo: WHO and UNICEF Estimates of Immunization Coverage: 2017 Revision*.; 2018. https://www.who.int/immunization/monitoring_surveillance/data/cod.pdf. Accessed March 10, 2019.

40. Kandel N, Chungong S, Omaar A, Xing J. Health security capacities in the context of COVID-19 outbreak: an analysis of International Health Regulations annual report data from 182 countries. *Lancet*. 2020;395(10229):1047-1053. doi:10.1016/S0140-6736(20)30553-5

41. World Health Organization. *Thematic Paper on the Status of Country Preparedness Capacities Background Report Commissioned by the Global Preparedness Monitoring Board (GPMB) .*; 2019. https://apps.who.int/gpmb/assets/thematic_papers/tr-2.pdf. Accessed July 23, 2020.

42. World Health Organization. WHO recommended surveillance standard of yellow fever. *WHO*. 2015. http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/YF_standards/en/. Accessed June 18, 2018.

43. Reiner RC, Perkins TA, Barker CM, et al. A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970-2010. *J R Soc Interface*. 2013;10(81):20120921-20120921. doi:10.1098/rsif.2012.0921

44. Wu JT, Peak CM, Leung GM, Lipsitch M. Fractional dosing of yellow fever vaccine to extend supply: a modelling study. *Lancet*. 2016;388(10062):2904-2911. doi:10.1016/S0140-6736(16)31838-4

45. Hamlet A, Jean K, Perea W, et al. The seasonal influence of climate and environment on yellow fever transmission across Africa. Al-Salem WS, ed. *PLoS Negl Trop Dis*. 2018;12(3):e0006284. doi:10.1371/journal.pntd.0006284

Chapter 5: Conclusion and Public Health Significance

Yellow fever is an ancient disease that has been causing outbreaks since the 15th century. Ensuring adequate use of prevention strategies and preparedness for outbreaks can significantly limit morbidity and mortality from yellow fever. Despite routine immunization, cases still occur sporadically throughout the Democratic Republic of the Congo (DRC) and along with an outbreak in 2016 when there were 78 cases of yellow fever confirmed in three provinces. The outbreak potential of yellow fever was reestablished after the outbreak in DRC and neighboring Angola, combined with a concurrent outbreak in Brazil. As a result, the existing strategic framework was revised, and the Eliminate Yellow Fever Epidemics (EYE) Global Strategy for 2017-2026 was developed. The three primary objectives are global and comprehensive, including 1) To protect at-risk populations, 2) To prevent international spread of the disease, and 3) To contain outbreaks rapidly.[1] Investigating the susceptibility to yellow fever and risk of transmission in DRC would help meet the EYE Global Strategy objectives.

The DRC is the largest country in sub-Saharan Africa and the health delivery system faces many challenges due to poor infrastructure and competing priorities for prevention. Outbreaks of many diseases including yellow fever, cholera, the worst outbreak of measles in DRC's history, vaccine-derived polio, the 11th Ebola outbreak on record, and, now, the ongoing coronavirus disease 2019 (COVID-19) pandemic continue to occur and require attention and priority.[2,3] Additionally, the DRC has many isolated villages and health centers, resulting in difficulty detecting and controlling disease outbreaks throughout the country. The Expanded Program for Immunization (EPI) also experiences challenges due to the vast country size and existence of remote health districts and health centers where immunization activities are conducted and immunization data is collected. Longer distances can also lead to deficiencies in

vaccine storage during transport. Unfortunately, COVID-19 is expected to interrupt many health services even further, including vaccination. This is expected to exacerbate gaps in vaccination coverage and leave millions of children at risk of vaccine-preventable infectious diseases.[4,5] Given the challenges with detecting and controlling disease outbreaks throughout DRC, it is crucial to understand the state of yellow fever immunity, and it would be advantageous to develop alternative ways to identify targets for enhanced surveillance and develop efficient interventions to prevent yellow fever transmission.

Existing estimates of yellow fever vaccination coverage vary, but using the DHS survey from 2013-14, the estimated vaccination coverage among children is approximately between 69.9% and 82.9%. Although using the vaccination card indicated very favorable vaccination coverage, only about 16.5% of children presented a vaccination card and the number of children with a vaccination card declined with older age. The EYE Global Strategy emphasizes that documentation of vaccination needs to be improved to capture the coverage level in the community accurately, therefore, revising vaccination certificates should be a priority.[1] Children missing a vaccination card may represent an unvaccinated population. It would be helpful to understand the barriers to retaining vaccination cards in DRC to improve the use of this important record-keeping mechanism. Additionally, a recent Multiple Indicator Cluster Surveys (MICS) survey in 2017-18 indicated that vaccination coverage among children ages 12 to 23 months and 24 to 35 months might be lower (52.6% and 63.0%, respectively).[6] In general, estimates of vaccination coverage are lower than necessary to prevent outbreaks and are potentially declining. Fortunately, vaccination can be improved. This research elucidates that focusing on a continuum of care starting with maternal antenatal care followed by delivery at an institution, especially government and public facilities, may ultimately impact childhood

vaccination. Improving mother's degree of education and decreasing poverty can improve the overall health of the community and increase yellow fever vaccination coverage in DRC.

Analyzing patterns in the spatial distribution of yellow fever assists with identifying target areas for enhanced surveillance. This research identifies geographic patterns in reported yellow fever cases in DRC. Yellow fever cases are not reported at random but are clustered among health zones, especially in the Central, North, and North West. These results are especially useful for public health to detect and locate areas that may need targeted intervention, public health messaging, and health system enhancement.[7,8] Using geographic data and spatial analysis are increasingly popular tools in public health and epidemiology, especially for addressing questions about environmental risk, however, high-quality spatial data is not readily available, especially for yellow fever. Lastly, this research could not completely elucidate the relationship between health care capacity and cold chain quality, vaccination coverage, and yellow fever cases. It indicates the need for additional research to investigate this important factor in DRC further.

When an outbreak is detected in DRC, current interventions typically only consist of reactive vaccination campaigns and sporadic vector control, which are supported by outside organizations such as CDC or WHO. Vaccination campaigns can be costly and logistically challenging to implement and, as a result, are often implemented after an outbreak has already begun to decline. The campaigns typically seek to vaccinate as many people as possible. However, based on the simulations in this research, this strategy may not have been the most effective. Systematically improving the population immunity through routine immunization would be a more efficient use of the health systems resources and would be effective for preventing outbreaks. Higher initial population immunity to yellow fever would help reduce

cases during outbreaks of yellow fever by as much as 90% if at least 70% to 80% yellow fever immunity could be achieved. While early detection is paramount, the outbreak response relies on having an existing stable health infrastructure and the availability of significant human resources, financing, and the ability to manage emergency logistics, however, many low-income countries still need additional support to strengthen these systems.[9,10] Routine mosquito control could also be implemented to aid preparedness efforts and help prevent outbreaks from occurring. Existing programs for distribution of insecticide-treated or other bed nets for malaria prevention could be augmented by adding protection for daytime biting mosquitoes.

This research used existing and mostly publicly available data, including a large population-based and validated dataset and the country's IDSR surveillance data, in new and unique ways to examine the background situation and risk factors that facilitated the 2016 DRC yellow fever outbreak and identify opportunities to more effectively mitigate or prevent future outbreaks. This research identified potential deficiencies in yellow fever vaccination and predictors of vaccination coverage that can be targeted for interventions. Lastly, there may be areas in DRC with increased transmission and where outbreaks may be more likely, however, outbreaks may be prevented by investing in a widespread prevention infrastructure.

5.1 References

1. World Health Organization. Eliminate Yellow fever Epidemics (EYE): a global strategy, 2017-2016. *Wkly Epidemiol Rec*. 2017;92(16):193-204. https://www.who.int/wer/2017/wer9216/en/. Accessed August 13, 2018.
2. WHO | Democratic Republic of the Congo. https://www.who.int/csr/don/archive/country/cod/en/. Accessed June 19, 2020.
3. DRC Ebola outbreak crisis update | MSF. https://www.msf.org/drc-ebola-outbreak-crisis-update. Accessed June 19, 2020.
4. Infectious Disease Vulnerability in DR Congo | UNICEF USA. https://www.unicefusa.org/stories/ebola-measles-and-now-covid-19-dr-congo-

crisis/37185. Accessed June 19, 2020.

5. At least 80 million children under one at risk of diseases such as diphtheria, measles and polio as COVID-19 disrupts routine vaccination efforts, warn Gavi, WHO and UNICEF. https://www.who.int/news-room/detail/22-05-2020-at-least-80-million-children-under-one-at-risk-of-diseases-such-as-diphtheria-measles-and-polio-as-covid-19-disrupts-routine-vaccination-efforts-warn-gavi-who-and-unicef. Accessed June 19, 2020.
6. INS. *Multiple Indicator Cluster Survey (MICS), 2017-2018, Survey Results Report. Kinshasa, Democratic Republic of the Congo*. Kinshasa; 2019. https://mics-surveys-prod.s3.amazonaws.com/MICS6/West and Central Africa/Congo%2C Democratic Republic of the/2017-2018/Survey findings/Congo%2C Democratic Republic of the%2C 2017-18 MICS SFR_French.pdf. Accessed July 8, 2020.
7. Kanaroglou P, Delmelle E, Paez A, eds. *Spatial Analysis in Health Geography*. Surrey, England: Ashgate Publishing Limited; 2015.
8. Jerrett M, Gale S, Kontgis C. Spatial modeling in environmental and public health research. *Int J Environ Res Public Health*. 2010;7(4):1302-1329. doi:10.3390/ijerph7041302
9. Keusch GT, McAdam K, Cuff PA, Mancher M, Busta ER. Strengthening Capacity for Response and Research. In: *Integrating Clinical Research into Epidemic Response: The Ebola Experience*. Washington DC: National Academies Press; 2017:155-198. doi:10.17226/24739
10. Kandel N, Chungong S, Omaar A, Xing J. Health security capacities in the context of COVID-19 outbreak: an analysis of International Health Regulations annual report data from 182 countries. *Lancet*. 2020;395(10229):1047-1053. doi:10.1016/S0140-6736(20)30553-5