ABSTRACT

Title of dissertation	EFFECTS OF THE 2014-2016 EBOLA EPIDEMIC ON INFECTIOUS DISEASE PREVENTION IN GUINEA
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Dissertation directed by	Dr. Typhanye Dyer, Associate Professor, Department of Epidemiology and Biostatistics

From 2014-2016, Ebola ravaged the three West African countries of Guinea, Sierra Leone, and Liberia. There were more than 28,000 cases and 11,000 deaths, with more than 10,600 additional deaths due to other medical conditions. We aimed to examine how utilization of infectious disease prevention services changed in Guinea over the course of the Ebola epidemic, using Andersen's model of healthcare utilization as a theoretical framework. The specific aims of this study were: 1) to examine differences in measles vaccination rates among children ages 12-35 months before and after the Ebola epidemic by wealth quintile; 2) to estimate mosquito net possession at two time points post-epidemic compared to pre-epidemic among households with at least one child under five, nationally and regionally; and 3) to quantify how much of the association between exposure to the Ebola epidemic and HIV testing prevalence can be explained by changes in urban/rural residence rates among adults in Guinea. The studies use data from the 2012 and 2018 Guinea DHS, and the 2016 MICS. Studies 1 and 2 use quasi-Poisson regression models to estimate prevalence ratios, and study 3 uses log-binomial regression models in a mediation analysis. In study 1 (n = 2,573 children ages 12-35 months), the poorest children were 54% (95% CI = 58%-67%) as likely to be vaccinated for measles in 2018 compared to 2012, and the wealthiest children were 78% (95% CI = 69%-90%) as likely. In study 2 (n = 14,756 households with at least one child under five), mosquito net possession in 2016 was 72% (95% CI = 56%-90%) higher and in 2018 was 12% (95% CI = 8%-15%) higher than in 2012. In study 3 (n = 27,809 adults), of the 4.59% (95% CI = 4%-6%) increase in the log-likelihood of ever having been tested for HIV due to being in the 2018 cohort, an estimated 0.269% of the effect (95% CI = 0.04%-1%) could be attributed to differences in urban/rural residence. Understanding these changes gives a more complete picture of the effects of epidemics on infectious disease prevention and can help public health officials plan for future epidemics.

EFFECTS OF THE 2014-2016 EBOLA EPIDEMIC ON INFECTIOUS DISEASE PREVENTION IN GUINEA

by

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Chapter 1: Introduction

1.1 Background and Rationale

Ebola virus disease, formerly known as Ebola hemorrhagic fever, is a serious illness that is often fatal in humans if left untreated.[1] Early symptoms of Ebola include fever, fatigue, muscle pain, headache, and sore throat, which quickly develop into vomiting, diarrhea, rash, impaired kidney and liver function, low white blood cell and platelet counts, elevated liver enzymes, and in some cases both internal and external bleeding.[1]

Ebola virus disease first appeared in 1976, when two simultaneous outbreaks occurred in what were then Nzara, Sudan and Yambuku, Zaire, now South Sudan and the Democratic Republic of the Congo (DRC) respectively. The World Health Organization (WHO) has records of 24 outbreaks of Ebola that occurred prior to 2014, which include four outbreaks of one case each. During this time period, the largest outbreak occurred in Uganda in 2000, where 425 cases – including suspected, probable, and confirmed cases – of Ebola were recorded. Case fatality rates varied enormously across outbreaks; in outbreaks of more than one case during this time period, they ranged from 25%, in a 2007 outbreak in Uganda with 149 cases, to 90%, in a four-month long outbreak in 2003 in the Congo with 143 cases.[1]

Within the genus *ebolavirus*, six species have been identified: *Zaire ebolavirus*, *Sudan ebolavirus*, *Bundibugyo ebolavirus*, *Taï Forest ebolavirus*, *Reston ebolavirus*, and, the recently discovered *Bombali ebolavirus*.[2] At present, *Reston ebolavirus* and *Bombali ebolavirus* are not known to infect humans.[2] Apart from one recorded case of *Taï Forest ebolavirus* in Côte d'Ivoire in 1994, three species of Ebola, *Zaire ebolavirus*, *Sudan ebolavirus*, and *Bundibugyo ebolavirus*, have been responsible for all outbreaks of Ebola. This includes the outbreak in West Africa in 2014-2016, where the *Zaire* species of Ebola spread across Guinea, Sierra Leone, and Liberia for two years.[1,3,4]

The 2014-2016 Ebola epidemic in West Africa was the 25th known outbreak since the discovery of Ebola in 1976, and it was fundamentally different in many ways. It was the largest and longest Ebola outbreak, and it was the first to involve three countries and their capital cities.[4] The index case of the West Africa Ebola epidemic was identified as an 18-month old child from Meliandou, Guinea, a remote village in the Gueckedou District in what is known as the Forest Region, and it is believed that he was infected by bats in December 2013, after he and several members of his family became sick.[5,6] However, the illness was not identified as Ebola until March 2014.[5] Initial investigations suggested a cholera, Lassa fever, or a cluster of malaria, as these diseases have many symptoms in common with Ebola.[5,7]

In mid-March 2014, the Ministry of Health in Guinea issued an alert for the unidentified illness.[8] Shortly thereafter, the Pasteur Institute in France found that the mystery was Ebola caused by *Zaire ebolavirus*. In late March 2014, just ten days after the alert for an unidentified illness went out to the public, the WHO declared an outbreak of Ebola, with 49 confirmed cases and 29 confirmed deaths from the disease at that point in time.[6] In August 2014, the WHO declared the Ebola epidemic in Guinea, Sierra Leone, and Liberia a "Public Health Emergency of International

Concern," a designation that is reserved for events with the risk of international spread or that require a coordinated international response.[5]

There are several reasons why it was difficult to contain the spread of Ebola in this particular outbreak, including weak surveillance systems, poor public health infrastructure, delayed diagnoses, and lack of knowledge in communities of how to prevent transmission.[6,9] Ebola quickly spread from Guinea to neighboring Liberia and Sierra Leone, and by July 2014, the epidemic had spread to the capitals of all three countries.[6] There was no precedent for tackling Ebola in urban areas – all previous outbreaks of the disease had only taken place in rural areas, where there was lower population density, stronger community ties, and where it was easier to implement prevention strategies.[9]

The Ebola epidemic would ravage Guinea, Sierra Leone, and Liberia for the next two years. Sierra Leone was declared Ebola-free in March 2016, and Guinea and Liberia were declared Ebola-free in June 2016.[10–12] By the end of the epidemic, there were 28,616 probable, suspected, or confirmed cases and 11,310 probable, suspected, or confirmed deaths.[13] In addition to the human toll, the epidemic had a lasting impact on all aspects of life in the three Ebola-affected countries. The economies of all three countries suffered badly due to poor private sector growth, a loss in agricultural production, and restrictions on movement of goods across borders.[14] The toll to the healthcare sector was immense, as all three affected countries lost a proportion of their healthcare workers to Ebola.[15] Children missed up to 39 weeks of school, and routine vaccinations decreased by up to 30%.[16,17] It is estimated that more than 17,800 children were orphaned due to Ebola.[16]

One of the consequences of the Ebola epidemic was the decline in visits to healthcare facilities for routine healthcare visits, and preventative healthcare for infectious diseases. Child vaccination rates declined over the period of the Ebola epidemic, resulting in measles outbreaks across the region that predominantly affected unvaccinated children.[18–23] These outbreaks were identified as early as 2015, one year into the epidemic.[19,22] Measles outbreaks are relatively common in the wake of humanitarian crises, such as epidemics, because of decreases in attendance to healthcare facilities and postponement of vaccination programs.[18,24–28]

Malaria prevention measures were also disrupted during the West African Ebola epidemic. Malaria can be fatal at all ages, however it is particularly dangerous for children as it can cause severe anemia in children. Children under the age of five years are among the most vulnerable to malaria, accounting for 67% of all malaria deaths worldwide in 2018.[29] In Guinea, 14% of children who were positive with malaria in 2018 also had severe anemia – among the highest proportion in the world. The annual prevalence of malaria in Guinea among children under the age of five is estimated to be around 30%.[30] Although malaria is endemic across Guinea, Sierra Leone, and Liberia, studies have found that malaria case management, including testing, treatment, and reporting, declined during the Ebola epidemic.[31–34] There is also evidence that malaria interventions, such as mosquito net distribution programs, were halted due to Ebola.[34,35]

The literature paints a complex picture of HIV testing, treatment, and care during and after the Ebola epidemic in West Africa. On the one hand, studies that look at shorter term repercussions of the Ebola epidemic on HIV services indicate lower testing rates, lower rates of antiretroviral treatment (ART) initiation among those who test positive for HIV in certain populations, and higher rates of defaulting on ART among those who were adherent.[36–39] On the other hand, longer term trends suggest a large increase in HIV testing rates in regions that had low Ebola case numbers compared to pre-Ebola rates, and that declines in ART adherence stabilized as cases of Ebola decreased.[37,39] Studies have also found that those living in urban areas are more likely to have been tested for HIV in Sub-Saharan African settings.[40–44] Furthermore, there is evidence that migration from rural to urban areas occurred during the Ebola epidemic at greater rates than before the epidemic.[45] Reasons for this include fear of disease, stigmatization of illness, the need for healthcare, and for economic need or opportunity.[45,46] Thus, in addition to direct repercussions caused by the Ebola epidemic, there is also a possible link between changes in HIV testing rates from before to after the Ebola epidemic that are indirectly caused by rural to urban migration.

There is ample evidence that the management of infectious diseases was disrupted during the Ebola epidemic. Vaccinations declined, interventions to distribute healthcare materials halted, and testing decreased. As epidemics continue to threaten Sub-Saharan Africa, and in the midst of the current COVID-19 pandemic, there is a need for more research that examines repercussions of epidemics on infectious disease management.

1.2 Objective of the Research

The Ebola epidemic in West Africa disrupted the already fragile healthcare systems of Guinea, Sierra Leone, and Liberia. The effects on healthcare during and after the epidemic were wide-reaching, and were not limited to the mortalities and morbidities caused directly by Ebola. Studies show that all aspects of healthcare delivery, access, management, and utilization were affected by the epidemic. Vaccination rates for childhood illnesses decreased, resulting in several measles outbreaks.[16,18–23] There were documented declines in healthcare facility visits for inpatient care, outpatient care, deliveries, antenatal care, cases of fever, and management of infectious diseases such as malaria, HIV, and TB.[31,38,47–52] The extent to which infectious disease healthcare, utilization, and management was disrupted during the Ebola epidemic has not been fully explored.

The overall aim of this study is to examine how utilization of infectious disease prevention services changed in Guinea over the course of the Ebola epidemic. The specific aims of this study are:

1) to examine differences in measles vaccination rates among children ages 12-35 months before and after the Ebola epidemic by wealth quintile;
2) to estimate mosquito net possession at two time points after the Ebola epidemic compared to pre-epidemic rates among households with at least one child under the age of five years in Guinea overall and by region; and
3) to quantify how much of the association between exposure to the Ebola epidemic and HIV testing can be explained by differences in urban/rural residence rates among adults in Guinea by testing urban/rural residence as a mediator in the association between cohort and HIV testing.

The aims of this study support some of the specific targets laid out in the United Nations Sustainable Development Goals. The United Nations Sustainable

Development Goals are a set of 17 goals for sustainable development, and were adopted by all member states in 2015. At their core, the goals recognize the interconnected nature of different developmental concepts, such as ending poverty and combatting climate change.[53] The aims of this study are particularly pertinent to goals that aim to promote good health and wellbeing (goal 3) and reduce inequalities (goal 10).

1.3 Theoretical Framework and Hypotheses

Within the framework of the study, we hypothesize the following:

1) those born during and immediately after the Ebola epidemic have a lower likelihood of being vaccinated for measles than those born before the Ebola epidemic and that the effect will be greater in the poorer wealth quintiles than in the wealthier wealth quintiles;
2) households with at least one child under the age of five years will have a lower likelihood of having a mosquito net in the home in 2016, but the likelihood of mosquito net possession will increase in 2018 when compared to 2012 levels and there will be differences in regions that had higher incidences of Ebola when compared to regions with lower incidences of Ebola; and
3) some of the association between exposure to the Ebola epidemic and HIV testing can be explained by differences in urban/rural residence.

The Andersen healthcare utilization model provided the theoretical framework for these studies.[54,55] Andersen's original conceptual model, which was developed in 1968, was developed to explain the process and the factors that lead to healthcare service usage.[54] Andersen's original model was made up of three elements: *environmental factors*, including the healthcare system and external environment; *personal characteristics*, including predisposing characteristics, enabling resources, and need; and *health behavior*, including personal health choices.

The more recent iteration of the Andersen model, developed in 1995, includes health outcomes and feedback loops.[55] It is made up of four elements: environmental factors, population characteristics, health behavior, and outcomes. The environmental factors explain the environmental context of the healthcare problem. Population characteristics are made up of predisposing characteristics, including demographics; enabling resources – factors that enable healthcare utilization in the study sample; and need – reasons why this particular type of healthcare utilization is needed among the study population. In this project, the health behaviors of interest in the three studies are:

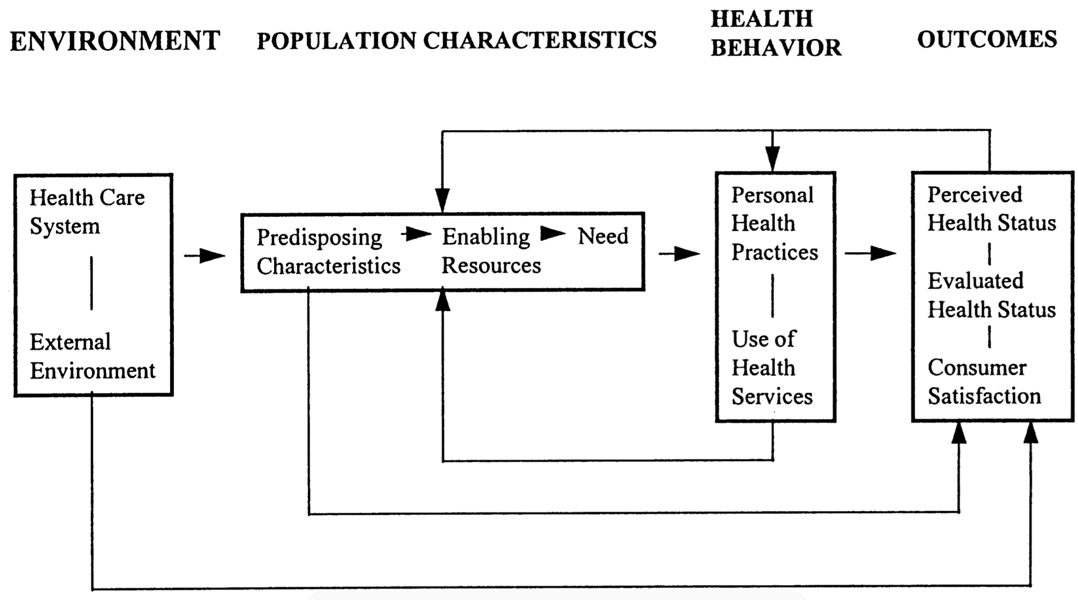
1) a child between the ages of 12-35 months receiving a measles vaccination;
2) a household with at least one child under the age of five years owning a mosquito net; and
3) an adult receiving an HIV test.

These studies use the more recent iteration of Andersen's model as a framework to gain a more holistic understanding of the processes of healthcare service utilization and their outcomes.

1.4 Innovation and Significance

This research is a novel and innovative approach to analyzing the effects of an epidemic on infectious disease management and prevention efforts. Considering an epidemic as an exposure, and modelling it as such allows us to quantify effects of the epidemic. With the current COVID-19 pandemic, there is a need for more research on past epidemics and pandemics that can help us understand some of the possible repercussions we face with COVID-19, especially in Sub-Saharan African settings. These approaches have the potential to inform epidemic and pandemic research in understanding the effects on infectious disease management and prevention efforts.

Figure 1.1. Andersen model of healthcare utilization (1995)



Chapter 2: Methods

2.1 Study Design

All three studies have cross-sectional study designs. The three studies use data from two Demographic and Health Survey (DHS) datasets and the Multiple Indicator Cluster Survey (MICS). DHS and MICS surveys are both nationally representative household surveys that ask questions on a wide range of demographic and health topics, and are completed approximately every five years to allow for comparisons over time.[56] MICS surveys differ slightly to DHS surveys in that they focus primarily on women and children.[57] Data from DHS and MICS surveys have been analyzed together and compared in many studies on Sub-Saharan African populations.[58–61] These studies use data from the 2012 and 2018 Guinea DHS surveys, and the 2016 Guinea MICS.[62–64]

The 2012 Guinea Demographic and Health Survey

Data for the 2012 Guinea DHS surveys were collected between June and October 2012 by the Institut National de la Statistique and the Ministère du Plan, in collaboration with the Ministère de la Santé et de l'Hygiène Publique. The 2012 Guinea DHS identified 7,200 eligible households to participate in the survey, of which 7,109 participated. 9,331 eligible women ages 15-49 were identified for individual survey, of which 9,142 were surveyed. 3,910 eligible men ages 15-59 were identified for individual survey, of which 3,782 were surveyed. Data on 7,039 children from the sampled households were collected as part of the survey.[65] The 2012 Guinea DHS used the DHS VI version of the surveys.

The 2018 Guinea Demographic and Health Survey

Data for the 2018 Guinea DHS were collected between March and June 2018 by the Institut National de la Statistique, and the Ministère du Plan et du Développement Économique, in collaboration with the Ministère de la Santé. The 2018 Guinea DHS identified 8,020 eligible households to participate in the survey, of which, 7,912 participated. 10,987 eligible women ages 15-49 were identified for individual survey, of which 10,874 were surveyed. 4,235 eligible men ages 15-59 were identified for individual survey, of which 4,117 men were surveyed. Data on 7,951 children were collected as part of the survey from the sampled households.[66] The 2018 Guinea DHS used the DHS VII version of the survey.

The 2016 Guinea Multiple Indicator Cluster Survey

Data for the 2016 Guinea MICS were collected between August and November 2016 by the Institut National de la Statistique, in collaboration with the Programme National de lutte contre le Paludisme and the Institut National de Santé Publique. The 2016 Guinea MICS identified 8,400 eligible households to participate in the survey, of which, 8,081 participated. 10,245 eligible women ages 15-49 were identified for individual survey, of which 9,663 were surveyed. 7,650 eligible children were identified, about whom data on 7,359 children were collected.[67] The 2016 Guinea MICS is part of the MICS5 round of surveys.

Selection criteria

For study 1, the study sample comprised all children ages 12-35 months in from the 2012 Guinea DHS and 2018 Guinea DHS, and included data from the children and their mothers. Participants were included based on the age of the child in months at the time of their household being surveyed. The base population in both datasets is all children between the ages of 0 and 59 months who were alive at the time of data collection and lived in a household that participated in the survey.

For study 2, the study sample comprised all households with at least one child under the age of five years from the 2012 Guinea DHS, the 2016 Guinea MICS, and the 2018 Guinea DHS. Both the DHS and MICS surveys ask how many children under the age of five live in the household, and code this as a continuous variable. The sample population was selected based on a response of greater than 0 to this question. The base population is all participating households in the survey.

For study 3, the study sample comprised all adults, defined as females aged 15-49 and males aged 15-59, in the 2012 Guinea DHS and the 2018 Guinea DHS.

Dependent variables

For study 1, the dependent variable was having received the first measles vaccination. The variable indicating whether a child as received their first measles vaccination is coded with the following six categories: “no,” “vaccination date on card,” “reported by mother,” “vaccination marked on card,” “don’t know,” or “missing.” The variable was recoded as a binary variable, with “no” indicating that they have not received the measles vaccine, “vaccination date on card,” “reported by mother,” and “vaccination marked on card” indicating the child has received the measles vaccine. Those who replied “don’t know” were not included in the study sample. There were no missing values for this variable.

For study 2, the dependent variable was whether the household possesses at least one mosquito net. The 2016 Guinea MICS asks, “Does your household have any mosquito nets that can be used while sleeping?” This is a binary variable coded as “yes” or “no.” The 2018 Guinea DHS asks, “Does the household have a mosquito net for sleeping?” This is a binary variable coded as “yes” or “no.”

For study 3, the dependent variable is having ever been tested for HIV during the participant’s lifetime. All participants of the 2012 and 2018 Guinea DHS surveys of all age groups were asked, “Have you ever been tested for HIV?” or “Have you ever been tested for the AIDS virus?” This variable is a binary variable coded as “yes” or “no.”

Independent variables

The independent variables for all three studies was cohort. Study participants were categorized into one of three cohorts according to whether they were part of the 2012 Guinea DHS, the 2016 Guinea MICS, or the 2018 Guinea DHS. Cohorts were proxies for exposure to the Ebola epidemic, with the 2012 cohorts considered “unexposed,” and the 2016 and 2018 cohorts considered “exposed.” In studies 1 and 3 this was a binary variable with subjects’ cohort membership corresponding to either 2012 or 2018. Study 2 uses all three levels of cohort membership as the independent variable.

Potential confounding variables, effect modifiers, and mediators

The following variables were assessed as confounders in at least one of the three studies. Unless otherwise stated, the variable is measured in the same way in the DHS and MICS datasets.

- Age of survey participant: A continuous variable that indicates the age in years of the participant, or age in months of a child up to 59 months of age. Participant age is calculated from the variables for month of birth and year of birth and to month and year of interview.

- Sex of survey participant: A binary variable indicating the sex, either “Female” or “Male.”
- Number of antenatal care visits by mother: A continuous variable that indicates how many antenatal visits a woman had while pregnant, with a categorical option for “don’t know.”
- Number of children ever born to mother: A continuous variable that indicates how many children a woman has given birth to.
- Highest education level: An ordinal variable in the DHS datasets with four categories: “No education,” “Primary,” “Secondary,” and “Higher.” It was recoded as a binary variable with the categories “none/primary” and “secondary/higher.” In the MICS data, there are two variables that deal with educational attainment. The first asks, “Has (name) ever attended school or pre-school?,” and is a binary question with the options, “yes,” or “no.” Those who responded affirmatively to the question about attending school or pre-school are asked, “What is the highest level of school (name) has attended?” This is an ordinal variable with the following categories: “Maternelle,” “Primaire,” “Collège,” “Lycée,” “Prof/T – A,” “Prof/T – B,” and “Supérieur.” Responses from these two questions were combined to create one binary variable that indicates the highest level of education attained. Those that responded that they did not attend school, or that their highest level of education was “Maternelle,” or “Primaire” were categorized as having a highest educational attainment of

"none/primary." Those who responded that their highest level of education was "Collège," "Lycée," "Prof/T – A," "Prof/T – B," or "Supérieur" were categorized as having a highest educational attainment of "secondary/higher."

- Number of people living in household: A continuous variable that records the number of people in the household.
- Number of children under the age of five living in household: A continuous variable that records the number of children under the age of five years living in the household.
- Urban/rural residence: A binary variable with the categories "Urban" and "Rural," which indicates whether the household is in a rural or urban setting. This variable is coded according to whether the cluster or sample point is defined as urban or rural, and is not the survey participant's classification.
- Wealth index: A categorical variable in the DHS datasets with five levels, coded as a value between 1 and 5, representing "Poorest," "Poorer," "Middle," "Wealthier," and "Wealthiest." The wealth index is a composite measure of a household's cumulative living standard, and is calculated using data on a household's ownership of selected assets, materials used for housing construction, and types of water access and sanitation facilities. Scores are generated using principal components analysis.

2.2 Assessment of Potential Biases

The most common types of bias that occur in survey data are social-desirability bias, recall bias, and interviewer bias. Social-desirability bias occurs when a survey participant responds in such a way that is deemed more socially desirable and does not reflect the truth. In all three studies, social desirability bias could have occurred if mothers responded that children had been vaccinated for measles when they had not, heads of households responded that they had a mosquito net in the home when they did not, and adults responded affirmatively to having been tested for HIV when they had not.

Recall bias occurs when survey participants do not accurately remember if an event occurred. Results from studies 1 and 3 are potentially susceptible to recall bias, as mothers might not accurately remember whether their child had a measles vaccine, and adults might not remember if they had been tested for HIV.

Although those carrying out the MICS and DHS fieldwork are trained to conduct interviews consistently and objectively, there is potential interviewer bias. However, the data were collected via structured interviews with closed-end questions and specified response options, which generally minimizes interviewer bias. Because there is no way to assess whether social-desirability bias, recall bias, or interviewer bias occurred, we took these into consideration when interpreting results.

Confounding bias was assessed for each study. Potential confounders were initially selected for assessment based on the literature and prior research. For each study, we ran a model with the independent variable and the dependent variable only. For each potential confounder, the model was run with the independent variable, dependent variable, and the potential confounder. The effect of the independent variable on the dependent variable was compared in both models, and if there is a 10% or greater change in effect size, measured by the prevalence ratio, the variable was treated as a confounder. Survey weights were applied to confounder assessments.

2.3 Statistical approaches

Descriptive statistics

Each of the three studies provides a table that describes the study sample. Subjects were stratified by year of data collection, defined as cohort. Differences in demographic, social, economic, and geographic factors were reported between corresponding groups. For continuous variables, the mean value and standard deviation was reported for each of the stratified categories, and a t-test was conducted to quantify mean differences between groups. Normality was tested for each continuous variable. For binary and categorical variables, the proportion of exposure within each group was reported and a chi-squared test was conducted to quantify differences between groups. Results of the t-tests and chi-squared tests were reported. Survey weights were applied to descriptive statistics.

Power Analyses

We used power analyses to determine the minimum required sample size for the models in each study in order to achieve a power of 0.80. Survey weights were applied to all power calculations.

For study 1, using the full model and all confounders, we estimated the measles vaccination rate under the null hypothesis to be $e^{-0.42} = 0.66$, with an estimated relative decrease of $e^{-0.76} = 0.47$. We calculated that a minimum sample size of 60 subjects would be required to achieve a power of at least 0.80. Given the sample size of the study sample was estimated to be greater than 2,500 subjects, it was reasonable to conclude that the analyses would detect an effect with a power of at least 0.80.

For study 2, for the purpose of calculating sample size we created a binary variable for cohort by combining the 2016 and 2018 cohorts, the two cohorts exposed to the Ebola epidemic. We estimated that the rate of mosquito net possession under the null hypothesis was $e^{0.28} = 1.32$, with an estimated relative decrease of $e^{-0.55} = 0.58$. Using these estimates, we calculated a minimum sample size of 42 subjects would be required to achieve a power of at least 0.80. Given that the study sample was estimated to be greater than 14,000, it was reasonable to conclude that the analyses would detect an effect with a power of at least 0.80.

For study 3, we used Sobel's method of determining sample size for mediation analysis.[68] The model that was used in the power analysis included cohort as the independent variable (x), ever having been tested for HIV as the dependent variable (y), urban/rural residence as the mediator (m), and age and sex as potential confounders. Using Sobel's method, a sample size of 23,160 participants would be required to achieve a power of 0.80 in the analyses. Given the sample size was expected to be greater than 27,000, it was reasonable to conclude that the analyses would have a power of at least 0.80.

Power analyses for studies 1 and 2 were conducted using the package *Basic and Advanced Statistical Power Analysis* (*WebPower*), and power analyses for study 3 were conducted using the package *Power/Sample Size Calculation for Mediation Analysis* (*powerMediation*) in R.[69,70]

Missing Data

Complete-case analysis was used for variables with less than or equal to 5% missing values. For variables with greater than 5% missing values, the data were analyzed to determine the missing data pattern by testing associations between the independent and dependent variables and missingness. We determined whether the data were missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR).

The only variable that contained greater than 5% missing data was the number of antenatal care visits made by a mother, analyzed as a confounder in study 1. 9% of the data for the number of antenatal care visits was missing. Chi-square tests indicated no association between missingness and the independent variable, cohort ($p = 0.4$), however, missingness was associated with the dependent variable, measles vaccination status ($p = 0.02$). The missing mechanism of the data was therefore MAR. We used multiple imputation to impute missing values of the variable for antenatal care visits.

2.4 Assessment of Potential Mediation Effects or/and Interaction Effects

Study 1 considered wealth index as a potential effect modifier in the association between cohort and measles vaccination status. We considered wealth index as a categorical variable with five levels: poorest, poorer, middle, wealthier, and wealthiest. Wealth index was tested as an effect modifier using interaction terms for cohort and each category of wealth index, with 2012 as the reference group for cohort, and "middle" as the reference group for wealth index to allow for more comparison between the two poor groups and the two wealthy groups. A term for the main effects of wealth index was also included in the analysis. We tested for effect modification using a likelihood ratio test. Likelihood ratio tests test the goodness of fit of two models, where one is a nested version of the other, and if the difference of the two models is found to be significant, the variable is treated as an effect modifier. Wealth index was found to be an effect modifier, and because it was a five-level categorical variable, we stratified results by each level of wealth. Study 1 did not consider any mediators, and study 2 did not consider any effect modifiers or mediators.

Study 3 is a mediation analysis that analyzed the role of urban/rural residence as a mediator in the association between cohort and ever having been tested for HIV among adults. Three models were constructed:

- model 1, direct effect of independent variable on dependent variable: log-binomial model with cohort as the independent variable, and ever having been tested for HIV as the dependent variable, controlling for age and sex;
- model 2, effect of independent variable on mediator: a log-binomial model with cohort as the independent variable, urban/rural residence as the dependent variable, and age and sex as confounders;
- model 3, effect of mediator on dependent variable, controlling for independent variable: a log-binomial model with urban/rural residence as the independent variable, ever having been tested for HIV as the dependent variable, urban/rural residence*cohort as the interaction term (informed by results of the likelihood ratio test), and cohort, age, and sex as confounders.

We used R's causal mediation package, *Causal Mediation Analysis* (*mediation*), to determine the mediated effect of urban/rural residence on the association between cohort and ever having been tested for HIV, controlling for age and sex. To test whether the association between cohort and having ever been tested for HIV is significantly explained by differences in urban/rural residence, we used Vanderweele's method with a bootstrap approach.[71] Confidence intervals were generated by bootstrapping using 1,000 repetitions.

2.5 Model Specification

For studies 1 and 2, we constructed quasi-Poisson models to estimate prevalence ratios. Quasi-Poisson models use a log function to estimate prevalence ratios for binary data. Possible confounders and effect modifiers were included as appropriate. The quasi information criterion (QIC) was used to determine the model fit. The QIC is a measure of relative goodness of fit, and can be used to compare two or more models. Generally speaking, a model with the lowest QIC indicates the best fit.

For study 1, measles vaccination was the binary dependent variable and cohort was the binary independent variable in the quasi-Poisson model. Possible confounders were: age of child in months, sex of child, age of mother in years, education level of mother, total number of children born to mother, wealth index, and urban/rural residence. Wealth index was also tested as an effect modifier.

For study 2, we constructed quasi-Poisson models. Having at least one mosquito net in the home was the binary dependent variable, and cohort was the categorical independent variable. Possible confounders were: number of people living in the household, number of children under the age of five years living in the household, sex of head of household, age of head of household, education level of head of household, and urban/rural residence.

Study 3 was a mediation analysis and analyzes urban/rural residence as a possible mediator in the association between cohort and having ever been tested for HIV, controlling for age and sex. We used log-binomial models for the analysis. Details of the analyses for study 3 can be found in section 2.4, "Assessment of potential mediation effects or/and interaction effects."

Survey weights were applied to all models. All analyses were conducted using R version 4.0.3.[72]

2.6 Assessment of Model Assumptions

To assess multicollinearity, we calculated the variance inflation factor for each variable in each model. A general rule of thumb is that a variance inflation factor of less than 10 indicates that there are no issues with collinearity in the model. There was no evidence of variance inflation. Potential outliers were identified by calculating and plotting the Cook's Distance. Each model had a maximum of six overly influential points in the model, according to Cook's Distance values. As these points represented a very small proportion of the total study samples, and there was no indication that data were recorded incorrectly, they were included in the analyses.

Mediation analysis requires certain conditions to show a mediated effect. Firstly, the independent variable (cohort) must have a significant effect on the mediator (urban/rural residence). The second condition is that the mediator (urban/rural residence) must have a significant effect on the dependent variable (ever having been tested for HIV) when controlling for the independent variable (cohort).[73] Details of the analyses for study 3 can be found in section 2.4, "Assessment of potential mediation effects or/and interaction effects."

2.7 Strengths and Limitations

An inherent limitation of the cross-sectional study design is temporality. These studies aim to overcome this limitation by analyzing data that were collected at different time points, which infers temporality. Additionally, although these studies are framed in the context of the Ebola epidemic, cause and effect cannot be inferred. That is to say, it cannot be said that the Ebola epidemic was the sole cause in the changes in healthcare utilization and infectious disease prevention efforts without taking into account other social, economic, and political factors that could have been unrelated to the Ebola epidemic that could have also played a role in the change.

The main strength of these studies is the large sample size and the use of nationally representative datasets. This enhances the generalizability of the results of the study. Additionally, with the ongoing COVID-19 pandemic, there is a need for more research that examines the association between epidemics and pandemics and healthcare in Sub-Saharan African settings.

Chapter 3: Modeling the effect of the Ebola epidemic on measles vaccination among children in Guinea

Abstract

From 2014 to 2016, Ebola ravaged the three West African countries of Guinea, Sierra Leone, and Liberia in what was the worst epidemic of Ebola since the discovery of the virus. Child vaccination rates declined, resulting in measles outbreaks across the region that predominantly affected unvaccinated children. Measles is highly contagious, and maintaining vaccine coverage among vulnerable populations is a priority. The aim of this study is to understand the effect of the Ebola epidemic on measles vaccination among children ages 12-35 months in Guinea, using Andersen's model of healthcare utilization as a theoretical framework. The study uses DHS data from 2012 and 2018, which serve as proxies for being unexposed or exposed to the Ebola epidemic of 2014-2016. Children in the 2012 cohort (n = 1,269) were born in 2009-2011, while those in the 2018 cohort (n = 1,304) were born in 2015-2017. We used quasi-Poisson models to measure the effect cohort membership on measles vaccination, controlling for confounders, stratified by wealth index. The likelihood of being vaccinated for measles among the poorest children in the 2018 cohort was 54% (95% CI = 58%-67%) that of the poorest children in the 2012 cohort, while the likelihood of being vaccinated for measles among the wealthiest children in the 2018 cohort was 78% (95% CI = 69%-90%) what it was for the same group of children in the 2012 cohort. These findings have implications for vaccination programs in the context of future epidemics.

3.1 Background

From 2014 to 2016, Ebola ravaged the three West African countries of Guinea, Sierra Leone, and Liberia in what would be the worst epidemic of Ebola since the discovery of the virus. Over the course of two years, there were more than 28,000 cases and 11,000 deaths of Ebola across the three countries.[13] In addition to the human toll, the epidemic had a lasting impact on all aspects of life in Guinea, Sierra Leone, and Liberia. The economies of all three countries suffered badly due to poor private sector growth, a loss in agricultural production, and restrictions on movement of goods across borders.[14] The toll to the healthcare sector was also immense; Guinea, Sierra Leone, and Liberia lost an estimated 1.5%, 6.9%, and 8.1% of their healthcare workers to Ebola, respectively.[15] Children missed an average of 33 weeks of school in Guinea and 39 weeks of school in Sierra Leone, and it is estimated that more than 17,800 children were orphaned due to Ebola.[16,17,74,75] In addition socioeconomic effects, there were an estimated 10,600 additional deaths across the three countries due to untreated medical conditions, such as malaria, tuberculosis, and HIV/AIDS, due to the decrease in healthcare facility visits for routine medical care.[31,49]

Child vaccination rates also declined over the period of the Ebola epidemic, resulting in several recorded measles outbreaks across the region that predominantly affected unvaccinated children.[18–23] Measles outbreaks often follow humanitarian crises, such as war, natural disasters, famine, or epidemics.[18,24–27] Reasons for this include a decrease in attendance rates to healthcare facilities for routine consultations and outpatient services, as well as the postponement and cancelation of vaccination programs.[28] Measles is also highly contagious, with a basic reproductive number (R_0)

of 12-18, higher than other infectious diseases, though studies suggest that the R_0 for measles could be much higher in Africa.[76–78] In the absence of any vaccination coverage, measles outbreaks occur approximately every 2-4 years, but with a vaccination coverage of around 80%, the time between outbreaks is lengthened to 4-8 years.[79] Maintaining vaccine coverage among vulnerable populations, such as children, is therefore a priority.

Measles outbreaks were identified in the Ebola-affected countries as early as 2015, in the middle of the Ebola epidemic.[19,22] In Sierra Leone, one study identified measles in 16% of Ebola-negative patients presenting at an Ebola treatment center in Freetown, Sierra Leone, between December 2014 and June 2015, while 284 cases of measles were identified in Lola Prefecture, Guinea over the period from January to April 2015, representing the beginnings of potential outbreaks.[19,20] In 2015, researchers predicted that 6-18 months of disruptions to measles vaccination programs due to the Ebola epidemic would lead to 2,000-16,000 additional measles deaths across Guinea, Sierra Leone, and Liberia.[22]

Recent studies and reports suggest that Guinea may have seen a greater decline in measles vaccination coverage than either Liberia or Sierra Leone. In a retrospective study of measles vaccination coverage in the three Ebola-affected countries published in 2020, it was found that on the national level, the mean monthly vaccination rates for measles decreased only in Guinea and Liberia during the Ebola epidemic when compared to 2012 vaccination levels. Mean monthly measles vaccination rates declined by 33% in Guinea and 30% in Liberia in 2014 when compared to 2012 levels, and by 26% in Guinea and 25% in Liberia in 2015 when compared to 2012 levels. Conversely, in Sierra Leone, measles vaccination rates increased by 1% in 2014 and 3% in 2015 when compared to 2012 levels.[21] In 2016, the year the Ebola epidemic ended, Guinea's mean monthly vaccination rate for measles was 9% lower than it had been in 2012, while Liberia's was 13% higher, and Sierra Leone's was 14% higher.[21] A 2014 United Nations Development Programme report that assessed the socioeconomic impacts of the Ebola epidemic found that overall healthcare facility attendance for childhood vaccinations in Guinea declined 30% from 2013 to 2014.[28]

The percentage of children vaccinated for measles in Guinea was already low. An evaluation of a 2012 measles mass vaccination campaign estimated that 75% of children in Guinea had been vaccinated for measles, which is not considered high enough to contain a measles outbreak.[80] There were regional differences in the estimates of vaccination coverage; while 93% of children in Boké Region were vaccinated for measles in 2012, only 53% of children in Mamou Region were estimated to be vaccinated.[80] When looking at the population as a whole, the WHO-UNICEF estimates that overall measles vaccination coverage in Guinea declined from 58% in 2012, to 50% in 2014, to 47% 2016.[81]

There are many socioeconomic, demographic, and geographic factors associated with childhood vaccination in low-income settings. A study across 12 East African countries found several factors that were associated with complete childhood vaccination, including maternal age, maternal education level, number of antenatal care visits, and wealth.[82] In a study of childhood vaccination coverage in Ethiopia, factors that were found to be associated with full or single vaccination status were maternal education level, wealth, and living in an urban area.[83] Studies that researched Sub-Saharan African populations also found that child vaccination varied by region.[84,85] Studies in other settings have found similar factors to be associated with childhood vaccination. A study of vaccination coverage among children in Bangladesh found that the socioeconomic factors that were associated with having received all basic vaccinations were being in a higher wealth quintile, living in an urban area, being a local resident as opposed to a visitor, and being born outside of the home.[86] The socioeconomic factors of the children's mothers that were associated with children having received all basic vaccinations were having a higher level of education and having had a greater number of antenatal visits.[86] A study based in rural Vellore, India, found that children were more likely to be fully vaccinated if they received their vaccinations in public facilities, if their parents strongly agreed or agreed that they understood the schedule set out by the national vaccination program in India, and if their parents reported having learned about the national vaccination program during antenatal visits.[87] In some countries, ethnicity has also been found to be associated with having received vaccinations among children.[88,89]

The literature on measles vaccination during and after the Ebola epidemic focuses primarily on measles vaccination coverage and the resulting measles outbreaks. Several studies examine specific geographic areas, such as the Lola Prefecture in Guinea, or Freetown, Sierra Leone.[18–20] Other studies examine differences in measles vaccination rates and subsequent measles outbreaks in Guinea, Sierra Leone, and Liberia on the national level. There have also been several studies on socioeconomic, demographic, and geographic factors associated with receiving childhood vaccinations in other settings.[78,84–87,89] However, to our knowledge, there have not been any studies that model the Ebola epidemic as an exposure for being vaccinated for measles, nor have there been any studies to model an epidemic or pandemic as an exposure for vaccination. With the ongoing COVID-19 pandemic, this study contributes to the understanding of the effects and repercussions of disease outbreaks on vaccination coverage in Sub-Saharan settings.

The aim of this study is to analyze whether those born during and immediately after the Ebola epidemic have a lower likelihood of being vaccinated for measles than those born prior to the Ebola epidemic. The measles vaccine is one of the six original vaccines that was included in vaccination programs, and is considered one of the eight "basic" vaccines by the Demographic and Health Surveys Program.[90,91] We hypothesized that those born during and immediately after the Ebola epidemic would have a lower likelihood of being vaccinated for measles than those born before the Ebola epidemic.

3.2 Methods

This study utilized Andersen's model of healthcare utilization as a theoretical basis for analyzing the process and factors that lead to children being vaccinated for measles.[55] The most recent iteration of the Andersen model, developed in 1995, is made up of four elements: environmental factors, population characteristics, health behavior, and outcomes. The environmental factors explain the environmental context of the healthcare problem, in this case, the healthcare system. Population characteristics are made up of predisposing characteristics, including demographics; enabling resources, including factors that enable healthcare utilization in the study population; and need, including reasons why this particular type of healthcare utilization is needed among the study population. The health behavior of interest is a child receiving a measles vaccination, which involves a parent or caretaker attending a clinic for preventative care. The outcome is immunity to measles. Figure 3.1 illustrates how Andersen's model is applied to this study.

This was a cross-sectional study that used data from two Demographic and Health Survey (DHS) datasets: the 2012 and 2018 Guinea DHS surveys.[62,63] DHS surveys are nationally representative household surveys that asks questions on a wide range of demographic and health topics.[56]

The study sample comprised all children ages 12-35 months in both the 2012 Guinea DHS and 2018 Guinea DHS, and included data from the children and their mothers. Participants were included based on the age of the child in months at the time of their household being surveyed. The base population in both datasets is all children between the ages of 0 and 59 months who were alive at the time of data collection and lived in a household that participated in the survey. Children were categorized into two cohorts corresponding to when data were collected on them: 2012 and 2018. The two time periods serve as proxies for exposure status to the Ebola epidemic, with the 2012 cohort being unexposed, and the 2018 cohort being exposed. Children in the 2012 cohort were born between 2009 and 2011, and children in the 2018 cohort were born between 2015 and 2017.

The outcome variable of this study was having received the first measles vaccination. The variable indicating whether a child as received their first measles vaccination is coded with the following six categories: "no," "vaccination date on card," "reported by mother," "vaccination marked on card," "don't know," or "missing." The variable was recoded as a binary variable, with "no" indicating that they have not received the measles vaccine, "vaccination date on card," "reported by mother," and "vaccination marked on card" indicating the child has received the measles vaccine. Those who replied "don't know" were not included in the study.

This study considered the following variables as potential confounders: age of child in months (continuous), sex of child (binary: female, male), wealth index (categorical: poorest, poorer, middle, wealthier, wealthiest), urban/rural residence (binary: urban, rural), age of the mother in years (continuous), number of antenatal care visits (continuous), education level of the mother (binary: none/primary, secondary/higher), and number of children born to the mother (continuous). To determine whether a variable would be included in the model as a confounder, we ran a model with the independent variable (cohort) and the dependent variable (measles vaccination) only. For each potential confounder, the quasi-Poisson model was run with the independent variable, dependent variable, and the potential confounder. The effect of the independent variable on the dependent variable was compared in both models, and if there was a 10% or greater change in effect size, measured by the prevalence ratio, the variable was treated as a confounder. Variables were considered confounders if there is strong evidence in the literature to suggest they are.

We also tested wealth index as an effect modifier using interaction terms for cohort and each category of wealth index, with 2012 as the reference group for cohort, and "middle" as the reference group for wealth index. A term for the main effects of the wealth index was also included in the analysis. We tested for effect modification using a likelihood ratio test. Likelihood ratio tests test the goodness of fit of two models, where one is a nested version of the other. Wealth index was found to be an effect modifier in the association between cohort and likelihood of measles vaccination. Because wealth index is a categorical variable with five levels, we stratified the results by each level.

We constructed quasi-Poisson regression models, which use a log function to estimate prevalence ratios. When modeling a common outcome, such as mosquito net possession, odds ratios calculated from logistic regression models are often inflated, thus it is recommended to use either a log-binomial model or modified or quasi-Poisson model.[92–94] Measles vaccination was the binary dependent variable, and cohort as the binary independent variable.

We calculated the percent of missing values for the independent variable, dependent variable, and each potential confounder. The only variable that contained missing data was the number of antenatal care visits by the mother, therefore the missing pattern of the data was univariate. 9% of the data for the number of antenatal care visits was missing. Chi-square tests indicated no association between missingness and the independent variable, cohort ($p = 0.4$), however, missingness was associated with the dependent variable, measles vaccination status ($p = 0.02$). The missing mechanism of the data was therefore missing at random (MAR). We used multiple imputation to impute missing values of the variable for antenatal care visits using the package, *Multivariate Imputation by Chained Equations* (*mice*) in R.[95]

Multicollinearity was assessed using variance inflation factors. We used the quasi information criterion (QIC) to aid with determining the model fit. The QIC is a measure of relative goodness of fit, and can be used to compare two or more models. Generally speaking, a model with the lowest QIC indicates the best fit. QIC was calculated using the *Generalized Estimating Equation* (*geepack*) package in R.[96,97] All analyses were conducted using R version 4.0.3.[72]

3.3 Results

There were 1,269 children ages 12-35 months in the 2012 Guinea DHS and 1,304 children ages 12-35 months in the 2018 Guinea DHS. The ages of the children and their mothers differed significantly between cohorts. Children had a mean age of 22.47 months in the 2012 cohort and 21.83 months in the 2018 cohort (p = 0.02), and mothers had a mean age of 28.13 years in the 2012 cohort and 29.07 years in the 2018 cohort (p = 0.0009). The mean number of antenatal care visits by mothers decreased significantly, from 4.07 visits among the 2012 cohort to 2.94 visits among the 2018 cohort (p < 0.0001), while the proportion of mothers with secondary or higher education increased significantly, from 10% among the 2012 cohort, to 15% among the 2018 cohort (p = 0.0002). The percentage of children ages 12-35 months who had received their first measles vaccination was 65% in the 2012 cohort, and 40% in the 2018 cohort (p < 0.0001). The characteristics that were not significantly different across cohorts were the sex of child, proportion in each level of wealth index, and the proportion living in urban areas. Table 3.1 details the study population.

The unadjusted prevalence ratio for having been vaccinated for measles among those in the 2018 cohort (i.e., exposed to the Ebola epidemic) was 0.62 (95% CI = 0.58-0.67). Education level of the mother and the number of antenatal visits that the mother had both satisfied the criteria for confounding. Urban/rural residence was included based on prior literature. Wealth index was found to be an effect modifier, so results were stratified but each level of wealth index.

When adjusting for urban/rural residence, highest education level attained by the mother, and the number of antenatal care visits by the mother, the biggest effect of being in the 2018 cohort versus the 2012 cohort was seen in the poorest group (group 1). In the poorest group, children in the 2018 cohort had just over half the likelihood of having been vaccinated for measles than the 2012 cohort (aPR = 0.54, 95% CI = 0.43-0.67), whereas in the wealthiest group (group 5), children in the 2018 cohort had around three-quarters of the likelihood of being vaccinated for measles than those in the 2012 cohort (aPR = 0.78, 95% CI = 0.69-0.90). Additionally, the number of antenatal care visits was significant at all levels except in the wealthiest group, and the effect declined from the poorest group, where it was associated with a 13% increase in the likelihood of having been vaccinated for measles, to the wealthier group (group 4), where it was associated with a 7% increase in the likelihood of having been vaccinated for measles. The highest level of education attained by the mother was only significant in the wealthiest group, where children of mothers who had secondary or higher education were 19% more likely to be vaccinated for measles than children of mothers with no or only primary education.

3.4 Discussion

Results of this study reveal the devastating effect of the Ebola epidemic on measles vaccination coverage among children between the ages of 12-35 months in Guinea. Children in the 2018 cohort, born between 2015 and 2017, had a lower prevalence of measles vaccination than children in the 2012 cohort. This result is in line with studies that show a decline in measles vaccination across the three countries affected by the 2014-2016 Ebola epidemic, and helps explain some of the reasons for the measles outbreaks that were identified in the region.[18–23]

In addition to estimating the likelihood of measles vaccination using cohort as a predictor, this study also shows that antenatal care visits are associated with higher likelihood of being vaccinated for measles, and that the effect is greater among poorer groups. It is possible that women in wealthier groups are already connected to the healthcare system and receive regular healthcare, so prenatal care visits would not have affected their likelihood to get their children vaccinated. Additionally, higher levels of education among mothers are associated with a higher likelihood of measles vaccination among children, but only for the wealthiest group. This could have to do with the quality of education received at different levels of wealth, and perhaps indicates that a girl or woman who has attained secondary or higher education in the poorer groups might still not have access to the same level of education or educational resources as girls and women who attain the same level of education in the wealthiest group. When applying the Andersen model to these findings, the factors that were most associated with measles vaccination among children were found to be enabling resources in the Andersen model, with antenatal care visits falling under the category of "previous healthcare use." Researchers can use these results to inform how to best increase child vaccination rates.

The main strength of this study is the large sample size and the use of nationally representative datasets, which enhances the generalizability of the results of the study. An inherent limitation of the cross-sectional study design is temporality. Although the cohort variable infers temporality, no conclusions can be made about temporality. Additionally, although this study is framed in the context of the Ebola epidemic, cause and effect cannot be inferred. That is to say, it cannot be said that the Ebola epidemic was the sole cause in the changes in measles vaccination coverage among children ages 12-35 months in Guinea from 2012 to 2018 without taking into account other social, economic, and political factors that could have been unrelated to the Ebola epidemic that could have also played a role in the change.

Ebola continues to be a threat in Sub-Saharan Africa, and since 2016, there have been three further epidemics of Ebola in the region, all in the Democratic Republic of the Congo, and with cases also seen in Uganda. Additionally, as cases of COVID-19 continue to increase worldwide, this study will be useful in assessing the possible disruptions to infectious disease management in Sub-Saharan African settings. As of writing, Guinea has had 19,084 confirmed cases of COVID-19, and 113 deaths.[98] Africa, generally, has not been hit as badly as other regions, however, it is imperative to consider the wide-reaching, and long-term effects it could have on infectious disease prevention. This study can help inform further research into how childhood vaccinations can be affected by further epidemics and pandemics.

Table 3.1. Study sample characteristics: children ages 12-35 months (n = 2,573)

	2012 cohort	2018 cohort	*p*-value
Total number	1,269	1,304	
Mean age in months	22.47 (±6.85)	21.83 (±6.87)	*0.02*
Sex (% female)	49%	48%	0.66
Wealth index			
1 (poorest)	22%	24%	0.28
2 (poorer)	23%	23%	0.73
3 (middle)	21%	19%	0.19
4 (wealthier)	19%	18%	0.63
5 (wealthiest)	15%	16%	0.27
Urban/rural (% urban)	26%	29%	0.09
Mean age of mother in years	28.13 (±7.21)	29.07 (±7.05)	*0.0009*
Mean number of antenatal care visits by mother	4.07 (±2.71)	2.94 (±2.03)	*<0.0001*
% mother with secondary or higher education	10%	15%	*0.0002*
Mean total children ever born to mother	3.76 (±2.32)	3.67 (±2.12)	0.34
% received measles vaccination	65%	40%	*<0.0001*

Table 3.2. Unadjusted and adjusted prevalence ratios (95% CI) of measles vaccination status in Guinea in 2018 cohort compared to 2012 cohort, stratified by wealth index (n = 2,573)

	PR	**aPR Wealth = 1**	**aPR Wealth = 2**	**aPR Wealth = 3**	**aPR Wealth = 4**	**aPR Wealth = 5**
Cohort (ref = 2012)	0.62 (0.58-0.67)	0.54 (0.43-0.67)	0.57 (0.48-0.68)	0.69 (0.57-0.82)	0.66 (0.56-0.79)	0.78 (0.69-0.90)
Urban/rural residence (ref = rural)		1.04 (0.24-2.82)	1.38 (0.71-2.40)	1.15 (0.85-1.51)	1.02 (0.86-1.21)	0.79 (0.56-1.17)
Mother's education (ref = none/primary)		0.36 (0.08-1.00)	1.32 (0.93-1.81)	1.28 (0.91-1.75)	1.08 (0.87-1.33)	1.19 (1.05-1.34)
Number of antenatal care visits by mother		1.13 (1.07-1.18)	1.08 (1.04-1.12)	1.04 (1.00-1.08)	1.07 (1.03-1.10)	1.02 (0.99-1.04)

Figure 3.1. Andersen’s model of healthcare utilization: measles vaccination

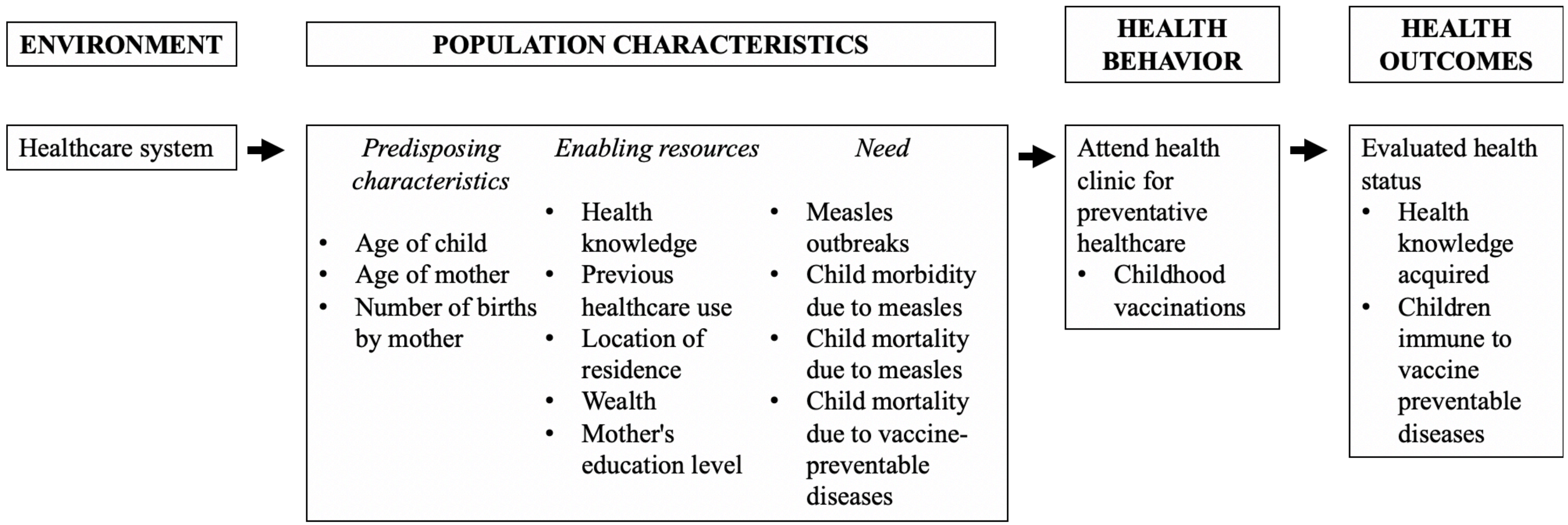
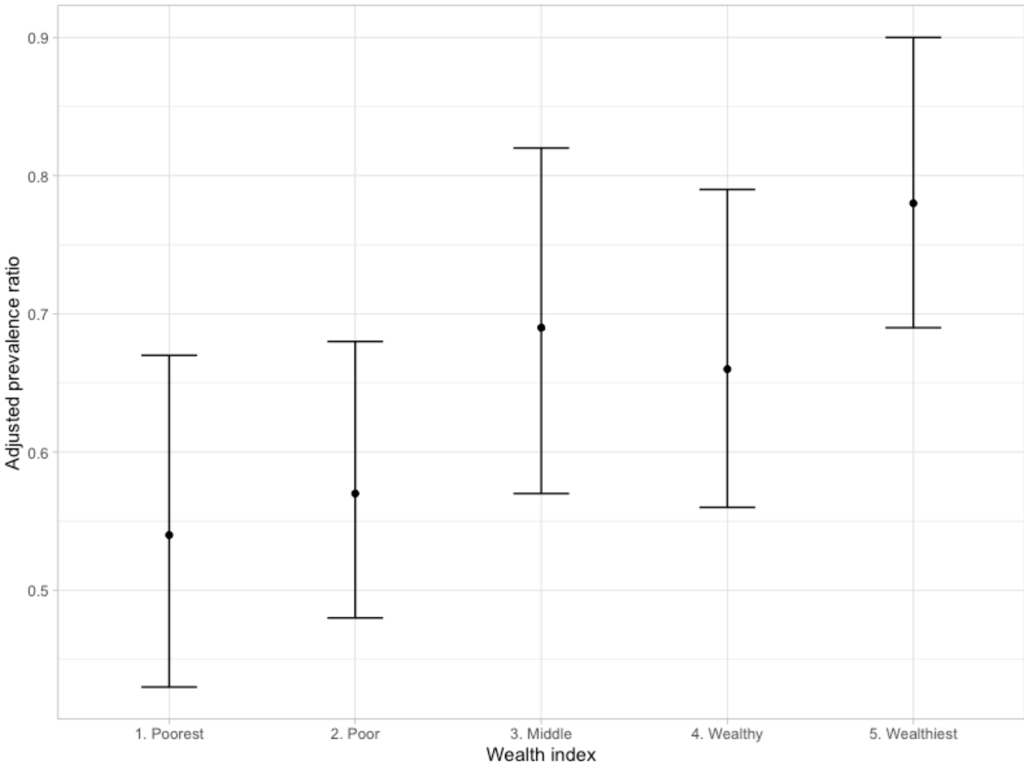


Figure 3.2. Plot of adjusted prevalence ratios of measles vaccination status in Guinea in 2018 cohort compared to 2012 by wealth index (n = 2,573)



Chapter 4: Possession of mosquito nets for malaria prevention in Guinea at two time points after the Ebola epidemic

Abstract

The 2014-2016 Ebola epidemic in West Africa changed all aspects of life in Guinea, Sierra Leone, and Liberia. In addition to the human toll caused directly by Ebola, there were also an estimated 10,600 additional deaths across the three countries due to untreated medical conditions, such as malaria, due to a decrease in healthcare facility visits for routine medical care. Malaria is endemic in the region, and although it can be fatal at all ages, it particularly affects children under the age of five years. The WHO recommends sleeping under insecticide-treated nets as the main method for malaria prevention in Sub-Saharan Africa. Maintaining access to mosquito nets in the region among vulnerable populations is therefore a priority. This aim of this study is to quantify mosquito net possession by region in 2016 and 2018 when compared to 2012 among households with at least one child under the age of five years. There were 14,756 households across the three time points. Compared to the 2012 baseline level, mosquito net possession among households in 2016 was 72% (95% CI = 56%-90%) higher than at baseline and in 2018 it was 12% (95% CI = 8%-15%) higher than at baseline. Mosquito net possession declined in all regions from 2016 to 2018, with the biggest declines in Conakry, Kankan, and N'Zérékoré, which had the highest estimated incidence rates of Ebola over the course of the epidemic. Results from this study can help inform future research on malaria outbreaks.

4.1 Background

The 2014-2016 Ebola epidemic in West Africa changed all aspects of life in Guinea, Sierra Leone, and Liberia. Over the course of two years, there were more than 28,000 cases, and 11,000 deaths of Ebola across the three countries.[13] The economies of all three countries suffered due to agricultural loss and restrictions on movement of goods across borders.[14] Children missed up to 39 weeks of school, and it is estimated that more than 17,800 children were orphaned because of Ebola.[16,17,74,75] In addition to socioeconomic effects, the toll to the healthcare sector was also immense. Guinea, Sierra Leone, and Liberia lost an estimated 1.5%, 6.9%, and 8.1% of their healthcare workers to Ebola, respectively.[15] There were also an estimated 10,600 additional deaths across the three countries due to untreated medical conditions, such as malaria, due to the a decrease in healthcare facility visits for routine medical care.[31,49]

Malaria is a vector-borne infectious disease caused by parasites that are transmitted to people through the bites of infected mosquitoes.[99] In 2018, an estimated 93% of the world's 228 million malaria cases were found in the WHO African region, with a smaller proportion of cases found in the WHO South-East Asia and Eastern Mediterranean regions.[29] Malaria can be fatal at all ages, however, it can cause severe anemia in children. Children under the age of five years are among the most vulnerable, accounting for 67% of all malaria deaths worldwide in 2018.[29] In Guinea, 14% of children who were positive with malaria in 2018 also had severe anemia – among the highest proportion in the world. In most other Sub-Saharan African countries, severe anemia ranges from 5% to 10% among children with malaria.[29] Among children under the age of five years in Guinea, the annual prevalence of malaria is estimated to be around 30%, though there is substantial regional variation, with 30% prevalence in the region of N'Zérékoré and 25% prevalence in the region of Faranah, and a prevalence of 2% in Conakry, the capital city.[30]

There are several ways in which malaria infection can be prevented, including vector control, chemoprevention, and in some cases, larval source management or other environmental modifications. The "core interventions" recommended by the WHO for the prevention of malaria are sleeping under an insecticide-treated net and indoor residual spraying, with insecticide-treated nets being the main method for malaria prevention in Sub-Saharan Africa.[29] It is therefore a priority to maintain accessibility to mosquito nets in this region for vulnerable populations.

Although malaria is endemic across Guinea, Sierra Leone, and Liberia, studies have found that malaria case management, including testing, treatment, and reporting, declined during the Ebola epidemic.[31–34] Malaria admissions for children under the age of five declined up to 39% in Sierra Leone, while in Guinea, it is estimated that there was a reduction of 74,000 suspected cases of malaria presenting at public health facilities than would have been expected.[100,101] A study that analyzed changes in malaria case management in Guinea during the Ebola epidemic found that the number of patients treated with oral antimalarials decreased by 24% and injectable antimalarials by 30% from the previous year. They also found that in Ebola-affected prefectures, only about half (48%) of the surveyed clinics were treating malaria cases, compared to almost all surveyed clinics in Ebola-unaffected prefectures.[101]

Reasons for the decline in malaria reporting and treatment are complex. Symptoms for malaria are virtually the same as the earliest symptoms of Ebola, and there are reports that people with malaria might have been turned away by healthcare workers out of fear of Ebola, or referred to Ebola treatment centers, which could have disincentivized seeking care.[32] Additionally, in November 2014, the WHO issued a guidelines for "temporary malaria control measures in Ebola-affected countries," which mandated the use of personal protective equipment when conducting malaria diagnostic testing, making malaria testing more difficult and burdensome for healthcare workers.[102] The document also lays out guidelines for safely distributing insecticidal nets, however, there is evidence that many intervention programs were halted due to Ebola. A Médecins Sans Frontières intervention in Guéckédou Prefecture in the N'Zérékoré Region, where the Ebola epidemic started, ended earlier than anticipated in 2014 due to Ebola, and news reports from the time suggest malaria prevention efforts, including net distribution, came to a standstill during the epidemic.[34,35]

Despite recommendations from the WHO that insecticide-treated nets are the most effective method for malaria prevention in Sub-Saharan Africa, and despite evidence that malaria prevention efforts decreased during the Ebola epidemic in Guinea, to our knowledge, there are no studies that analyze mosquito net possession during or after the Ebola epidemic. The studies that do examine changes in malaria management during the Ebola epidemic focus on decreases in malaria admissions, malaria testing, and lower than expected reported cases of malaria, but they do not focus on analyzing how methods of malaria prevention changed during this time.

Additionally, while it is important to examine changes in malaria management that occurred over the course of the Ebola epidemic, no study takes into consideration the potential longer-term impacts of the epidemic on malaria management. Analyzing longer-term impacts to malaria management on a regional level gives a more complete picture of the effects of the Ebola epidemic on malaria prevention. This study aimed to fill this research gap. Mosquito net possession was analyzed by region in Guinea using data collected in the months immediately after the Ebola epidemic, in 2016, and two years later, in 2018.

This study aims to answer the following questions: Is there a difference in household mosquito net possession in Guinea in 2016 and 2018 when compared to the pre-Ebola baseline from 2012? Is there a difference among households in regions that experienced the highest levels of Ebola infection versus those that had low levels of Ebola infection? We hypothesize that there is an association between household region and possession of mosquito nets at both time periods and that households in regions that had higher rates of Ebola cases will have lower likelihood of having a mosquito net in the home.

4.2 Methods

This study utilizes Andersen's model of healthcare utilization as a theoretical basis for analyzing the process and factors that lead to possession of a mosquito net among households with at least one child under the age of five years.[55] The most recent iteration of the Andersen model, developed in 1995, is made up of four elements: environmental factors, population characteristics, health behavior, and outcomes. The environmental factors explain the environmental context of the healthcare problem, in this case, the healthcare system and programs that distribute mosquito nets. Population characteristics are made up of predisposing characteristics, including demographics; enabling resources, including factors that enable mosquito net possession in the study population; and need, including reasons why mosquito nets are needed among the study population. The health behavior of interest is a household possessing a mosquito net. The outcome is decreased malaria prevalence. Figure 4.1 illustrates how Andersen's model is applied to this study.

We used data from the 2012 Guinea DHS, the 2016 Guinea MICS, and the 2018 Guinea DHS. DHS and MICS surveys are nationally representative household surveys that ask questions on a wide range of demographic and health topics. DHS and MICS surveys are similar in scope, though MICS surveys focus primarily on women and children. [57,63,64]

This is a cross-sectional study using data from 2012, 2016, and 2018. The study sample comprised all households with at least one child under the age of five years from all three time periods. Both the DHS and MICS surveys ask how many children under the age of five live in the household, and code this as a continuous variable. The sample population was selected based on a response of greater than zero to this question.

The dependent variable was whether the household possesses at least one mosquito net. Both the DHS and MICS surveys ask if the household has a mosquito net that can be used for sleeping. Both surveys code this as a binary variable with "yes" or "no" options. There is also a category for "missing."

The independent variable is cohort. The study sample was categorized into one of three cohorts corresponding to when data on the household were collected, in either 2012, 2016, or 2018. The 2012 cohort served as a baseline for comparison of mosquito net possession immediately after the Ebola epidemic, in 2016, and two years after the Ebola epidemic, in 2018. Results were stratified by region to allow for comparison with regional Ebola incidence rates. Guinea has eight regions, which includes the capital city of Conakry as its own region. DHS and MICS data are collected on the regional level. The eight regions of Guinea are: Boké, Conakry, Faranah, Kankan, Kindia, Labé, Mamou, and N'Zérékoré.

This study considered the following variables as confounders: urban/rural residence (binary: urban, rural), number of people in the household (continuous), the sex of the head of household (binary: female, male), the age of the head of household (continuous), and the highest education level attained of the head of household (binary: none/primary, secondary/higher), and the number of children under the age of five in the household (continuous). Wealth was not included because wealth quintiles were not measured in the 2016 Guinea MICS survey.

To assess for confounding, a model was run with the independent variable (cohort) and the dependent variable (possession of at least one net) only. For each potential confounder, the model was run with the independent variable, dependent variable, and the potential confounder. If there was a 10% or greater change in effect size, measured by the prevalence ratio, the variable was treated as a confounder. Variables were also be considered as confounders if there is strong evidence in the literature to suggest they are. There is no indication that any of these variables would act as mediators.

The only variable that contained missing data was the highest education level of the head of household in the 2016 MICS dataset, which had 12 missing records, representing 0.2% of the total data for that variable. Complete case analysis was therefore used. The variance inflation factors indicated no multicollinearity among variables in the models.

We constructed quasi-Poisson regression models with cohort as the independent variable (reference = 2012 cohort) and mosquito net possession as the binary dependent variable. Quasi-Poisson regression models use a log function to estimate prevalence ratios. When modeling a common outcome, such as mosquito net possession, odds ratios calculated from logistic regression models are often inflated, thus it is recommended to use either a log-binomial model or modified or quasi-Poisson model.[92–94]

We used the quasi information criterion (QIC) to determine the model fit. The QIC is a measure of relative goodness of fit, and can be used to compare two or more models. Generally speaking, a model with the lowest QIC indicates the best fit. Results of the two models will be compared to each other, and will be compared to Ebola case data on the prefecture level. QIC was calculated using the *Generalized Estimating Equation Package* (*geepack*) in R.[96,97]All analyses will be conducted using R version 4.0.3.[72]

4.3 Results

There were 14,756 households across the three time periods with at least one child under the age of five years; 4,614 in the 2012 cohort, 4,866 in the 2016 cohort, and 5,276 in the 2018 cohort. The samples were distributed across regions, with the greatest proportion of households located in N'Zérékoré and Kindia (16%-17%). At all three time points, the smallest proportion of households were located in Faranah and Mamou (7%-9%). The proportion of households located in urban areas ranged from 29% to 34%. The mean number of people per household ranged between 6.96 (±3.56) to 7.44 (±3.73). This included a mean number of children under the age of five years of between 1.57 (± 0.82) and 1.84 (±1.01).

With regards to the heads of the households, the proportion of female heads of households ranged from 15% to 16%, and the mean age of the head of household ranged from 44.33 (± 13.41) years to 46.75 (± 14.1) years. The proportion of heads of households with secondary or higher education ranged from 18% to 23%. In 2012, the baseline year, 56% of households were in possession of at least one mosquito net. In 2016, 86% of households were in possession of at least one mosquito net, while in 2018, 63% of households were in possession of at least one mosquito net. The characteristics of the sample households are detailed in Table 4.1.

Urban/rural residence was included as a confounder, though it was not included in the model for Conakry when the results were stratified by region, as Conakry is the capital city and there are no rural areas in the region. The unadjusted likelihood of having a mosquito net in 2016 was 53% (95% CI = 49%-58%) higher than the 2012 baseline level, and in 2018 it was 11% (95% CI = 8%-15%) higher than the baseline level. The adjusted likelihood, which controlled for the highest urban/rural residence, was 54% (95% CI = 50%-58%) higher than the baseline level in 2016, and 12% (95% CI = 1%-25%) higher the baseline level in 2018.

When stratifying by region, the region with the highest likelihood of mosquito net possession in 2016 was Boké, where households had a 77% (95% CI = 65%-91%) greater likelihood of having a mosquito net in the home compared to baseline. The region with the lowest mosquito net possession in 2016 was Kankan, where mosquito net possession was 28% (95% CI = 19%-37%) higher than the baseline level. In 2018, the region with the highest likelihood of mosquito net possession was Kindia, with a 42% (95% CI = 30%-55%) greater likelihood than the baseline level, and the region with the lowest mosquito net possession was Kankan, which had a 10% (95% CI = 2%-17%) decrease in the likelihood of mosquito net possession compared to the baseline level.

The likelihood of mosquito net possession decreased significantly from 2016 to 2018 in all regions when compared to the 2012 baseline. The biggest decline was in N'Zérékoré, where households had a 74% (95% CI = 61%-88%) higher likelihood of having a mosquito net in 2016, but only an 11% (95% CI = 2%-20%) higher likelihood in 2018 when compared to 2012 levels. Kankan also saw a large decline in mosquito net possession. In 2018, the region had a 28% (95% CI = 19%-37%) greater likelihood of having a mosquito net compared to the baseline, but in 2018, the likelihood was 10% (95% CI = 2%-17%) lower than at 2012 than in 2012. Conakry, the capital city, also saw a large decline, with a 72% (95% CI = 56%-90%) greater likelihood of mosquito net possession in households in 2016, and only a 12% (95%

CI = 1%-25%) greater likelihood in 2018. These results are detailed in Table 4.3, and depicted in Figure 4.3.

4.4 Discussion

A surprising finding from this study was the lower likelihood of mosquito net possession among households in 2018, two years after the end of the Ebola epidemic, than in 2016, immediately after the end of the Ebola epidemic, when both were compared to baseline. There are several possible explanations that could account for the apparent decline in mosquito net possession from 2016 to 2018 when compared to 2012, including the time of year that data on the samples were collected. Malaria is endemic in Guinea with year-round transmission, however transmission is higher during the rainy season, which occurs annually approximately from June to November.[32] The 2012 Guinea DHS data were collected in June 2012 to October 2012, and the 2016 Guinea MICS data were collected from August 2016 to November 2016, which were both during the rainy season and therefore during the time of greater malaria transmission.[65,67] The 2018 Guinea DHS data, however, were collected from March to June, most of which is during the dry season when there is lower malaria transmission. There could be lower mosquito net possession during the dry season than the rainy season, although there is limited literature on this topic.

Another possible explanation for this difference in mosquito net possession is that although there is evidence that some mosquito net distribution programs were halted because of Ebola, it is possible there were unrecorded or unpublicized programs or local efforts to distribute mosquito nets to households. Furthermore, mosquito net possession was a self-reported variable. Each survey has a variable for the interviewer to indicate that the mosquito net was observed, however these data were not recorded. It is possible that the difference reflects bias that was introduced at the data collection stage. There is the possibility of social-desirability bias, in which survey participants would have responded erroneously to having a mosquito net in the home because they believed they should. Additionally, although those carrying out the MICS and DHS fieldwork are trained to conduct interviews consistently and objectively, there is potential interviewer bias. The data collected for the surveys were collected via structured interviews with closed-end questions and specified response options. Because we cannot assess whether social-desirability bias or interviewer bias occurred, we can only consider the possibility. However, there is no explanation for why it would have occurred at different rates in 2016 versus 2018.

N'Zérékoré, Kindia, and Conakry saw the biggest declines in mosquito net possession from 2016 to 2018. These three regions also had the highest incidence rates of Ebola per 100,000 over the course of the epidemic. N'Zérékoré had between 45.14 and 313.78 cases per 100,000, Kindia had between 22.13 and 109.03 cases per 100,000, and Conakry had between 30.04 and 239.83 cases of Ebola per 100,000 over the course of the epidemic. However, without official case numbers, we can only glean the severity of the epidemic on the regional level with ranges of cases, which are, in some cases, very wide. Regional differences of malaria infection risk do not explain these differences, as N'Zérékoré has an estimated annual malaria prevalence of 30% among children between six and 59 months, while in Conakry it is 2%.[30] Using Andersen's model, in addition to location of residence, health knowledge and wealth are also enabling factors for mosquito net possession. Researchers can use these findings to understand factors associated with mosquito net ownership and design mosquito net programs to be more effective and efficient.

An inherent limitation of the cross-sectional study design is temporality. The aim of this study is to examine the role of the Ebola epidemic in the possession of mosquito nets across Guinea immediately after and two years after the epidemic. Although cause and effect with regards to time usually cannot be inferred with a cross-sectional study design, using data collected at three different time points mitigates this limitation.

Another limitation of this study is the analysis of variables that indicate possession of at least one mosquito net in the home, rather than use of a mosquito net. Data were not collected in 2016 on use of mosquito nets, therefore it is not possible to analyze use. Studies have shown that mosquito net use varies greatly, however recent studies looking at mosquito net possession and use suggest that the majority of children that live in a household with at least one mosquito net sleep under it.[103,104] Therefore, mosquito net possession can be treated as a proxy for use among children under the age of five.

The primary strength of the study is the data that are used for analyses. The MICS and DHS data are nationally representative, which make the findings generalizable on the country-level. Another strength of this study is points in time at which data were collected. Data collected for the 2016 Guinea MICS were collected within five months of the end of the Ebola epidemic in West Africa, and represent a snapshot of life immediately after the epidemic.

Ebola continues to be a threat in Sub-Saharan Africa, and since the end of the epidemic in West Africa, there have been three further epidemics of Ebola in Africa, all in the Democratic Republic of the Congo, and with cases also seen in Uganda. As cases of COVID-19 continue to increase worldwide, this study is useful in assessing the possible disruptions to malaria management in Sub-Saharan African settings. Africa, generally, has not been hit as badly as other regions, however, it is imperative to consider the wide-reaching, and long-term effects it could have on malaria management and mosquito net distribution programs. This study lays the groundwork for further research into mosquito net distribution, possession, during epidemics and pandemics.

Table 4.1. Study sample characteristics: households with at least one child under the age of five years (n = 14,756)

	2012	2016	2018
Total number of households with at least one child under the age of 5	4,614	4,866	5,276
% Households in each region			
Conakry	16%	16%	13%
Boké	11%	13%	10%
Faranah	9%	8%	9%
Kankan	15%	16%	15%
Kindia	15%	13%	16%
Labé	10%	9%	11%
Mamou	7%	8%	9%
N'Zérékoré	17%	17%	16%
% Households in urban areas	29%	34%	31%
Mean number of people per household	7.44 (±3.73)	6.96 (±3.56)	7.11 (±3.43)
Mean number of children under 5 in household	1.84 (±1.01)	1.57 (±0.82)	1.82 (±1.03)
% Households with female head	15%	16%	15%
Mean age of head of household	46.75 (±14.46)	44.33 (±13.41)	46.61 (±14.10)
% Head of household with secondary/higher education	18%	23%	21%
% Household in possession of at least one net	56%	86%	63%

Table 4.2. Range of number and incidence per 100,000 population of Ebola cases in Guinea by region, December 2013 – March 31, 2016

Region	Crude range of cases	Range of cases per 100k population
Conakry	501-4,000	30.04-239.83
Boké	48-220	4.44-20.34
Faranah	48-220	5.09-23.34
Kankan	149-720	7.50-36.25
Kindia	345-1,700	22.13-109.03
Labé	2-10	0.20-1.00
Mamou	12-40	1.64-5.46
N'Zérékoré	751-5,220	45.14-313.78

Table 4.3. Unadjusted and adjusted prevalence ratios (95% CI) of mosquito net possession in Guinea in 2016 and 2016 cohorts compared to baseline (2012), stratified by region (n = 14,756)

	PR	aPR	aPR Conakry	aPR Boké	aPR Faranah	aPR Kankan	aPR Kindia	aPR Labé	aPR Mamou	aPR N'Zérékoré
2016 cohort (ref = 2012)	1.53 (1.49-1.58)	1.54 (1.50-1.58)	1.72 (1.56-1.90)	1.77 (1.65-1.91)	1.31 (1.24-1.39	1.28 (1.19-1.37)	1.71 (1.57-1.87)	1.35 (1.26-1.44)	1.49 (1.37-1.62)	1.74 (1.61-1.88)
2018 cohort (ref = 2012)	1.11 (1.08-1.15)	1.12 (1.08-1.15)	1.12 (1.01-1.25)	1.34 (1.23-1.45)	1.04 (0.98-1.10)	0.90 (0.83-0.98)	1.42 (1.30-1.55)	1.02 (0.95-1.09)	1.00 (0.92-1.09)	1.11 (1.02-1.20)
Urban/rural residence (ref = rural)		0.88 (0.86-0.90)		0.94 (0.88-1.00)	1.03 (0.97-1.09)	0.94 (0.87-1.02)	0.85 (0.79-0.92)	1.12 (1.03-1.27)	1.15 (1.01-1.25)	0.94 (0.87-1.02)

Figure 4.1. Andersen's model of healthcare utilization: mosquito net possession

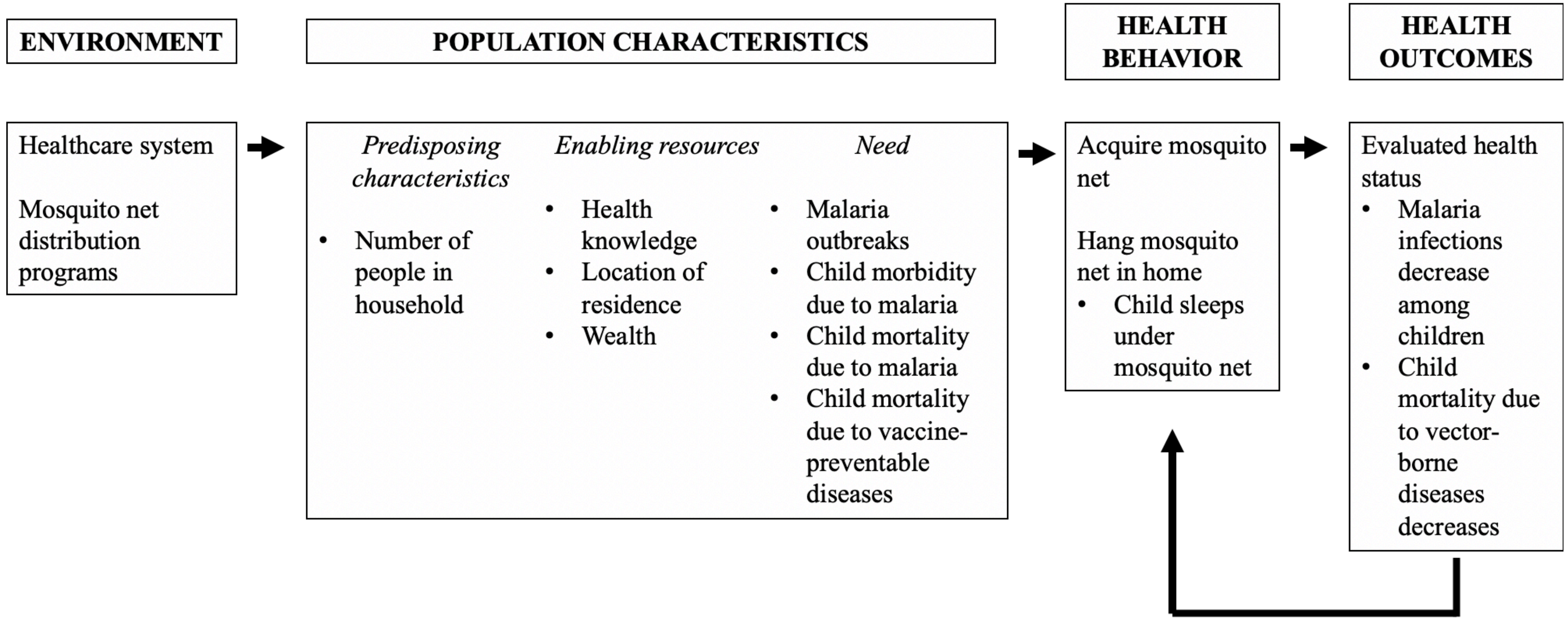


Figure 4.2. Plot of range of incidence per 100,000 population of Ebola cases in Guinea by region, December 2013 – March 31, 2016

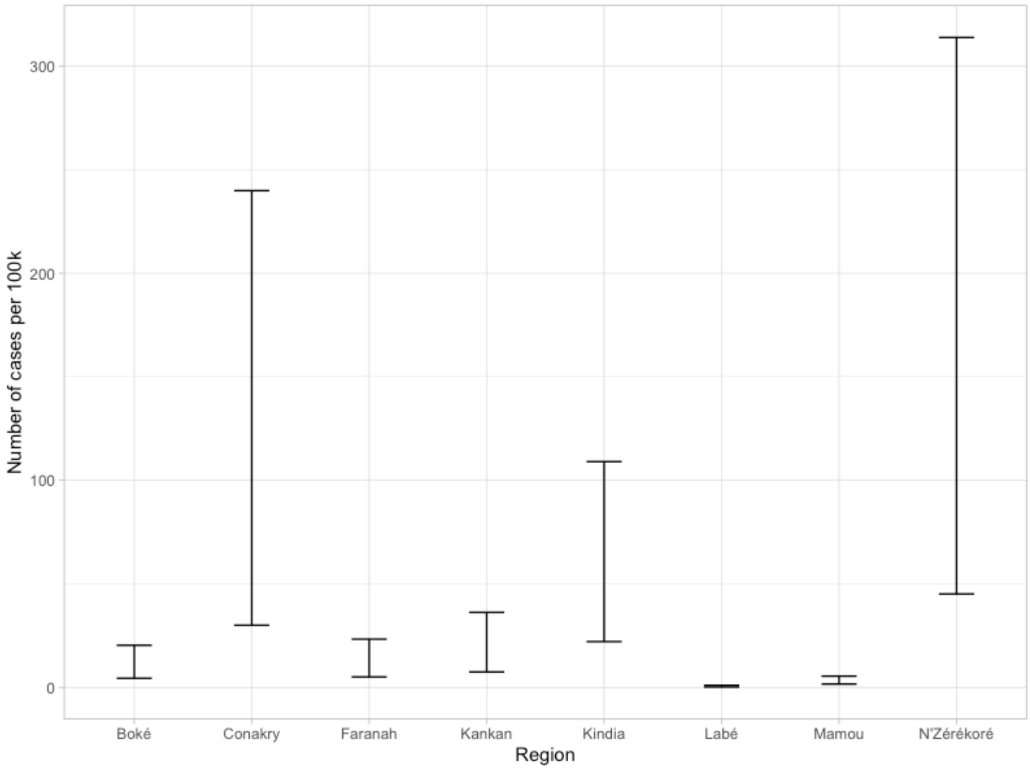
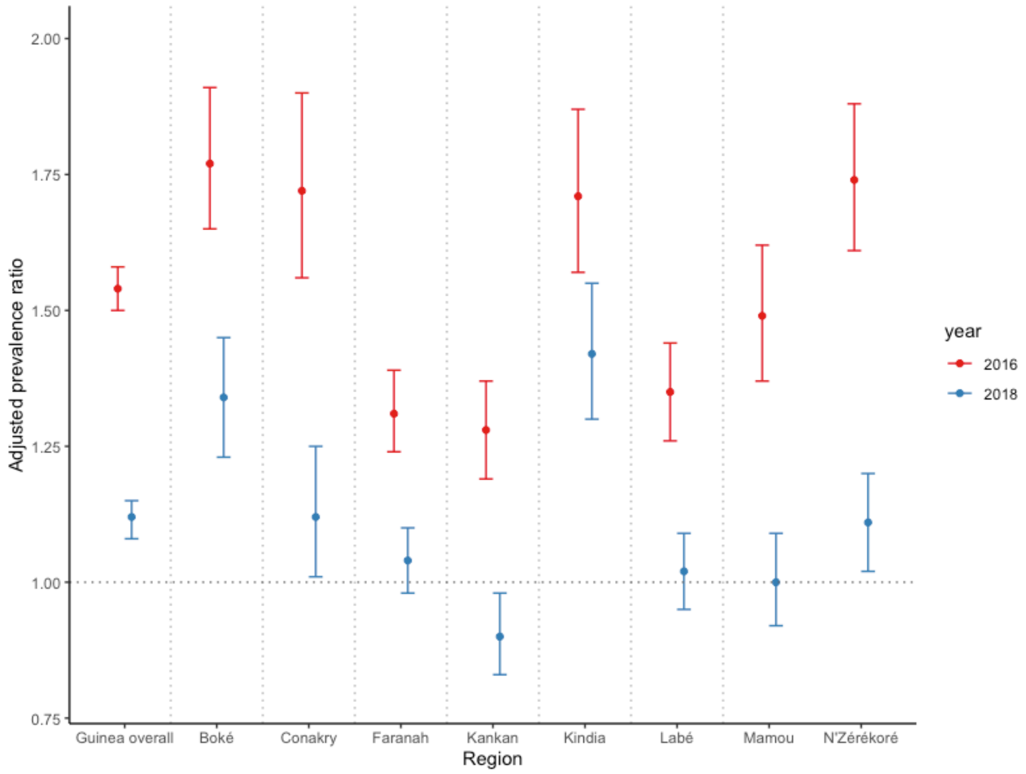


Figure 4.3. Plot of adjusted prevalence ratios of mosquito net possession in Guinea in 2016 and 2016 cohorts compared to baseline (2012), overall and stratified by region



Chapter 5: Urban migration and HIV testing in Guinea before and after the 2014-2016 Ebola epidemic: a mediation analysis

Abstract

The 2014-2016 Ebola epidemic in West Africa had wide-reaching and long-lasting effects on all aspects of life in Guinea, Sierra Leone, and Liberia. With the loss of economic opportunity in rural areas and an unprecedented need for medical care, urban areas saw a large influx of people arriving from the countryside. Living in an urban area is associated with a greater likelihood of ever having been tested for HIV. This study quantified how much of the association between exposure to the Ebola epidemic and HIV testing could be explained by differences in urban/rural residence rates among adults in Guinea by testing urban/rural residence as a mediator in the association between cohort and HIV testing. This study used data from the 2012 and 2018 Guinea DHS. The two time periods serve as a proxies for exposure to the Ebola epidemic of 2014-2016. The study sample comprised all adults (women 15-49 and men 15-59) who participated in the surveys (N = 27,809). Of the estimated 4.59% (95% CI = 4%-6%) increase in the log-likelihood of ever having been tested for HIV due to being in the 2018 cohort, an estimated 0.269% of the effect (95% CI = 0.04%-1%) was as a result of differences in urban/rural residence. The increase in log-likelihood of having ever been tested for HIV due to being in the 2018 cohort that was not attributable to differences in urban/rural residence was 4.32% (95% CI = 3%-5%). This approach taken in this study approximates temporal mediation analysis, and can lay the groundwork for future prospective mediation studies.

5.1 Background

The 2014-2016 Ebola epidemic in West Africa resulted in more than 28,000 cases, and 11,000 deaths across Guinea, Sierra Leone, and Libera, the three countries most affected by the epidemic. Many aspects of day to day life changed during this time. All three countries suffered economically due to agricultural loss, and children missed up to 39 weeks of school.[14,16] In addition to socioeconomic effects, the Ebola epidemic changed healthcare delivery and access across the three countries. Guinea, Sierra Leone, and Liberia lost an estimated 1.5%, 6.9%, and 8.1% of their healthcare workers to Ebola, respectively.[15] There were also an estimated 10,600 additional deaths across the three countries due to untreated medical conditions, such as malaria, tuberculosis, and HIV/AIDS, due to the a decrease in healthcare facility visits for routine medical care.[31,49]

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) laid out ambitious targets to help end the AIDS epidemic. The 90-90-90 treatment targets aimed for 90% of people living with HIV globally to be diagnosed, 90% of those diagnosed to be on treatment, and 90% of those on treatment to be virally suppressed by 2020.[105] Globally, there has been much progress in HIV testing and treatment. At the end of 2019, 81% of those living with HIV knew their HIV status, and 67% were on treatment.[106] Guinea, however, falls short of these targets. Although the prevalence of HIV in Guinea is low – around 1.4% – it is estimated that only 57% of those living with HIV in Guinea know their status.[107] Prevalence is not constant across demographic groups either, and it is estimated that 1.8% of women between the ages of 15 and 49 are infected with HIV, as opposed to 0.9% of men in the same age group.[107] While there is little data on HIV testing rates and trends in Guinea, studies set in other Sub-Saharan African settings show that men and adolescents are less likely to get tested for HIV than other demographic groups.[108–112]

HIV testing is the first stage in the HIV cascade of care. The HIV treatment cascade, also referred to as the HIV treatment continuum, refers to the framework in which a person living with HIV moves through stages of HIV care to achieve viral suppression. The World Health Organization defines four steps within the cascade: HIV testing, enrollment in care, antiretroviral treatment (ART) initiation, and viral load suppression via retention in care.[113] In order to analyze HIV testing in Guinea, it is important to consider factors that are associated with HIV testing.

If and how someone moves through the HIV treatment cascade depends on their surroundings and the resources available to them. Studies that examine differences in HIV testing rates among urban and rural populations have found that those living in urban areas are more likely to have been tested for HIV in Sub-Saharan African settings. In a study on home-based testing and counseling among adolescents and adults in an urban informal settlement and a rural setting, it was found that at baseline, over 40% of those living in the urban area had already been tested for HIV, compared to less than 30% among those living in the rural setting.[42] A study that compared four repeated cross-sectional nationally representative household-based HIV surveys in South African consistently found that those in rural areas had a lower odds of ever having been tested for HIV than those in urban areas.[43] A study on uptake of HIV testing among pregnant women across 16 Sub-Saharan African countries found that those who lived in urban settings had a higher odds of having been tested for HIV than those living in rural settings.[44] Two studies on HIV testing in Ethiopia both found that pre-marital women and women generally living in urban areas had a higher odds of ever having been tested for HIV.[40,41] This has also been found in studies set outside Sub-Saharan Africa, for example, in China, the United States, and the United Kingdom.[114–116]

Studies paint a complex picture of HIV testing, treatment, and care during the Ebola epidemic in West Africa. Studies in Sierra Leone and Liberia found that while HIV testing decreased during the Ebola epidemic, ART initiation rates increased among those who tested positive for HIV.[36,37] When looking at the longer term trends of HIV testing in Liberia, it was found that less-affected counties saw a large increase in testing rates from pre-Ebola figures, while medium and highly affected counties lagged behind their pre-Ebola testing rates.[37] A study among pregnant women in Guinea found a significant reduction in the number of antenatal visits and HIV tests performed, as well as a reduction in the number of women who were newly diagnosed with HIV initiating ART from 2013 to 2014 in Ebola-affected prefectures. They did not examine the same trend in prefectures that were not affected by Ebola.[38] A study of members of the Sierra Leone Armed Forces living with HIV found that there was an increased rate of defaulting on ART and an increased number of days without ART during the Ebola epidemic compared to the pre-Ebola baseline, but that these both stabilized as cases of Ebola decreased.[39]

Additionally, there is evidence that migration from rural to urban areas occurred during the Ebola epidemic. Between 2010 and 2015, it is estimated that the urban population grew in Guinea by 2.2%, while in Sierra Leone and Liberia, it grew by

1.7% and 1.9%, respectively.[45] An analysis of population movement during the Ebola epidemic cited fear of disease, stigmatization of illness, and the need for healthcare as some of the main drivers of migration from rural to urban areas during this time. The report also found that there was more movement across the three Ebola-affected countries during the epidemic than in pre-epidemic periods.[45] Results from a cell-phone survey conducted by the World Bank in Sierra Leone, on the other hand, concluded that the majority of migration was economic in nature. They also found that the Western Urban area of Sierra Leone, which includes Freetown, received the largest number of migrants compared to other areas.[46]

Although many studies have linked urban/rural residence to HIV outcomes, none, to our knowledge, have studied the intersection of urban/rural residence and HIV testing in the context of the Ebola epidemic. Additionally, although there is research to suggest a disruption of HIV services during the Ebola epidemic, several studies found that rates of testing and adherence to treatment improved as cases of Ebola declined, but there have not been any follow-up studies to examine the longer-term effects of the epidemic. This study aims to fill the research gap by analyzing data collected in 2012 and 2018, and estimating differences in HIV testing, as well as how much of this change can be attributed to changes in urban/rural residence.

The aim of this study is to estimate how much of the association between exposure to the Ebola epidemic and ever having been tested for HIV can by attributed to changes in urban/rural residence by analyzing urban/rural residence as a mediator. This study will use data from the 2012 Guinea DHS and the 2018 Guinea DHS. The two time periods serve as a proxies for being unexposed or exposed to the Ebola epidemic of 2014-2016. Those in the 2012 cohort are considered "unexposed," while those in the 2018 cohort are considered "exposed."

This study aims to answer the following questions: how much of the association between cohort and HIV testing can be attributed to changes in urban/rural residence among adults ages 15 and older in Guinea? We hypothesized that the association between cohort and HIV testing can partly be explained by differences in urban/rural residence among adults, and that the likelihood of ever having been tested for HIV would be higher for those in the 2018 cohort versus the 2012 cohort.

5.2 Methods

This study utilizes Andersen's model of healthcare utilization as a theoretical basis for analyzing the process and factors that lead adults in Guinea to receive an HIV test.[55] Other studies have applied Andersen's model to HIV testing, as well as to other HIV outcomes, such as retention in care.[117–119] The most recent iteration of the Andersen model, developed in 1995, is made up of four elements: environmental factors, population characteristics, health behavior, and outcomes. The environmental factors explain the environmental context of the healthcare problem, in this case, how HIV testing is conducted within the Guinean healthcare system. Population characteristics are made up of predisposing characteristics, including demographics; enabling resources, including factors that enable HIV testing; and need, including the fact that a relatively low proportion of those living with HIV know their status. The health behavior of interest is receiving an HIV test. The outcome is an increase in the proportion of people living with HIV who know their status. Figure 5.1 illustrates how Andersen's model is applied to this study.

This is a cross-sectional study using data from two DHS datasets. DHS surveys are nationally representative household surveys that asks questions on a wide range of demographic and health topics, and are completed approximately every five years to allow for comparisons over time. This study used data from the 2012 and 2018 Guinea DHS surveys.[62,63]

The study sample comprised all adults in the 2012 and 2018 Guinea DHS datasets. Adults are defined as females aged 15-49, and males aged 15-59 years of age. There were 9,142 women and 3,782 men surveyed in the 2012 Guinea DHS, and 10,874 women and 4,117 men surveyed in the 2018 Guinea DHS.

The outcome variable was having ever been tested for HIV during the participant's lifetime. All participants of the 2012 and 2018 Guinea DHS surveys of all age groups were asked, "Have you ever been tested for HIV?" or "Have you ever been tested for the AIDS virus?" This variable is a binary variable coded as "yes" or "no." The independent variable for this study is cohort. Study participants were categorized into one of two cohorts according to whether they participated in the 2012 Guinea DHS or the 2018 Guinea DHS. This is a binary variable that indicates when data on the individual were collected.

This study analyzed how much of the association between cohort and ever having ever been tested for HIV is explained by differences in urban/rural residence. For both the 2012 and the 2018 Guinea DHS, this variable is the setting of the *de facto* residence of the household. This is a binary variable to indicate whether the household is in a rural or urban setting. This variable is coded according to whether the cluster or sample point is defined as urban or rural, and is not the survey participant's classification.

This study considered participant age and sex as confounders. Age is a continuous variable in both the 2012 and 2018 Guinea DHS datasets that indicates the age in years of the participant. Participant age is calculated from the variables for month of birth and year of birth and to month and year of interview. Participant sex is a binary variable indicating the sex of the study participant. As data for males and females are provided separately, the variable for sex was created to indicate whether the participant comes from the male or female dataset.

To assess for confounding, we ran a model with the independent variable, dependent variable, and each potential confounder. The effect of the independent variable on the dependent variable was compared in both models, and if there was a 10% or greater change in effect size, measured by the prevalence ratio, the variable was treated as a confounder. Variables were also considered confounders if there was strong evidence in the literature to suggest it. We also tested for effect modification between cohort and of urban/rural residence using interaction terms (urban/rural*cohort). Effect modification was tested using a likelihood ratio test.

Two models were constructed: an log-binomial model with urban/rural residence as the dependent variable, cohort as the independent variable, and age and sex as confounders; and a log-binomial model with ever having been tested for HIV as the dependent variable, urban/rural*cohort as the interaction term, and age and sex as confounders. Results from the likelihood ratio test for effect modification informed whether we would use an interaction term (urban/rural*cohort) in the second model. Survey weights were applied to the models.

To test whether the association between cohort and having ever been tested for HIV is significantly explained by differences in urban/rural residence, we used Vanderweele's method with a bootstrap approach.[71] Estimates for direct effect, indirect effect, proportion of the effect that was mediated, and confidence intervals for these estimates were generated by bootstrapping using 1,000 repetitions. Survey weights were applied to all analyses. We used R's causal mediation package, *Causal Mediation Analysis* (*mediation*) to calculate estimates.[120] All analyses were conducted using R version 4.0.3.[72]

5.3 Results

There were 27,809 adults aged 15-59 in the sample, 12,835 of whom were part of the 2012 cohort, and 14,974 of whom were part of the 2018 cohort. The 2018 cohort had a statistically higher proportion of females, with 73% of the sample, compared to the 2012 cohort, with 71% of the sample ($p = 0.0006$). The mean ages in the two groups were not statistically different, with the mean age in the 2012 cohort being 29.36 years of age, and the mean age in the 2018 cohort being 29.29 years of age ($p = 0.57$). The proportion of those living in urban areas increase from 37% in the 2012 cohort to 39% in the 2018 cohort ($p = 0.004$), and the proportion of the sample who had ever received an HIV test increased from 12% in the 2012 cohort to 16% in the 2018 cohort ($p < 0.0001$). Table 5.1 outlines the characteristics of the study sample.

The effect of cohort on ever having been tested for HIV was partially mediated via urban/rural residence. The regression coefficient between cohort and urban/rural residence ($\beta = 0.046$) and the regression coefficient between urban/rural residence and ever having been tested for HIV ($\beta = 1.42$) were significant with $p < 0.05$ for both coefficients, as was the regression coefficient between cohort and ever having been tested for HIV, without a term for urban/rural residence ($\beta = 0.33$). The significant effects of cohort on urban/rural residence, and urban/rural residence on ever having been tested for HIV provided evidence of mediation. Table 5.2 details these results.

We tested the significance of the direct and indirect effects using bootstrapping with 1,000 samples. Of the estimated 4.59% (95% CI = 4%-6%) increase in the log-likelihood of ever having been tested for HIV due to being in the 2018 cohort, an estimated 0.269% of the effect (95% CI = 0.04%-1%) was as a result of differences in urban/rural residence. This was the indirect effect. The increase in log-likelihood of having ever been tested for HIV due to being in the 2018 cohort that was not attributable to differences in urban/rural residence was 4.32% (95% CI = 3%-5%). This was the direct effect. The proportion of the causal effect of being in the 2018 cohort versus the 2012 cohort on ever having been tested for HIV that was mediated by urban/rural residence was 5.86% (95% CI = 0.9%-12%). Table 5.3 details these results and Figure 5.3 plots these estimates.

There were 51 missing records for ever having been tested for HIV, the dependent variable. As these records represented less than 0.2% of the data, complete case analysis was used.

5.4 Discussion

The overall findings of this study show that between 2012 and 2018, there was an increase in the proportion of the population that lived in urban areas versus rural areas, indicating migration from the countryside to the cities, and that this migration is associated with a small but significant increase in the likelihood of ever having been tested for HIV. The literature that examined trends in migration during the Ebola epidemic supports this finding. There was also a significant direct effect in the log-likelihood of ever having been tested for HIV among those in the 2018 cohort versus those in the 2012 cohort.

A strength of this study is the use of a large, nationally representative sample, which make findings more generalizable on the country-level. Additionally, with the ongoing COVID-19 pandemic, there is a need for more research that looks at some of the potential ramifications that low-income countries might experience.

A limitation is that, as much as we tried to control for external factors, there are other possible unmeasured social, economic, or political factors that we were not able to consider. An inherent limitation of the cross-sectional study design is temporality. This approach taken in this study approximates temporal mediation analysis, and can lay the groundwork for future prospective mediation studies.

Guinea's GDP grew by 0.1% in 2015, compared to a pre-Ebola forecast of 4% due to low use of services and a reduction in mining, and reports suggest that the loss of economic opportunity in rural areas was one of the main drivers for migration to the cities during the Ebola epidemic.[14,46] Despite evidence that HIV testing declined during the Ebola epidemic, this study suggests that trend was short-lived. It also shows that the increase in the proportion of the population that had ever been tested for HIV increased, at least in part, because of migration to urban areas.

On the one hand, an increase in the proportion of the adult population who had ever been tested for HIV between 2012 and 2018 is a positive development. However, when taking into account that a small portion of this increase can be attributed to migration to urban areas, where healthcare services are more accessible, which itself can be attributed to economic downturn in rural areas, the public health implications for this study become more complex. In addition to location of residence, other enabling factors from Andersen's model are health knowledge, education, and wealth. The main conclusion of this study, therefore, could be that there is a need to improve access to HIV services in rural areas. However, as Guinea's cities continue to grow, as research suggests they will, outreach for HIV testing services could be extended to those who have recently migrated from rural areas.[45]

Table 5.1. Study sample characteristics: all adult survey participants (n = 27,809)

	2012 **n = 12,835**	**2018** **n = 14,974**	***p*-value**
% Female	71%	73%	0.0006
Mean age in years (± SD)	29.36 (±10.51)	29.29 (±10.74)	0.57
% Urban residence	37%	39%	0.004
% Received HIV test	12%	16%	<0.0001

Table 5.2. Beta coefficients of models for mediation analysis: 1) effect of independent variable on dependent variable; 2) effect of independent variable on mediator; and 3) effect of mediator on dependent variable (n = 27,809)

	Model 1: Effect of cohort on ever having been tested for HIV	**Model 2: Effect of cohort on living in urban area**	**Model 3: Effect of urban/rural residence on having ever been tested for HIV**
Cohort (ref = 2012)	0.33 **	0.046 *	0.56 **
Age	0.010 **	-0.013 **	0.017 **
Sex (ref = male)	0.32 **	-0.13 **	0.38 **
Urban/rural (ref = rural)			1.42 **
Urban/rural*cohort			-0.36 **

** $p < 0.0001$; * $0.0001 \leq p < 0.05$

Table 5.3. Estimates of causal mediation effects of urban/rural residence in the association between cohort and ever having been tested for HIV in Guinea (n = 27,809)

	Estimate	**95% CI**
Average causal mediation effect (2012 cohort)	0.00263	0.0004-0.01
Average causal mediation effect (2018)	0.00275	0.0004-0.01
Average direct effect (2012 cohort)	0.0431	0.03-0.05
Average direct effect (2018 cohort)	0.0433	0.03-0.05
Total effect	0.0459	0.04-0.06
Proportion mediated (2012 cohort)	0.0572	0.009-0.12
Proportion mediated (2018 cohort)	0.0599	0.009-0.12
Average causal mediation effect	0.00269	0.0004-0.01
Average direct effect	0.0432	0.03-0.05
Average proportion mediated	0.0586	0.009-0.12

Figure 5.1. Andersen's model of healthcare utilization: HIV testing

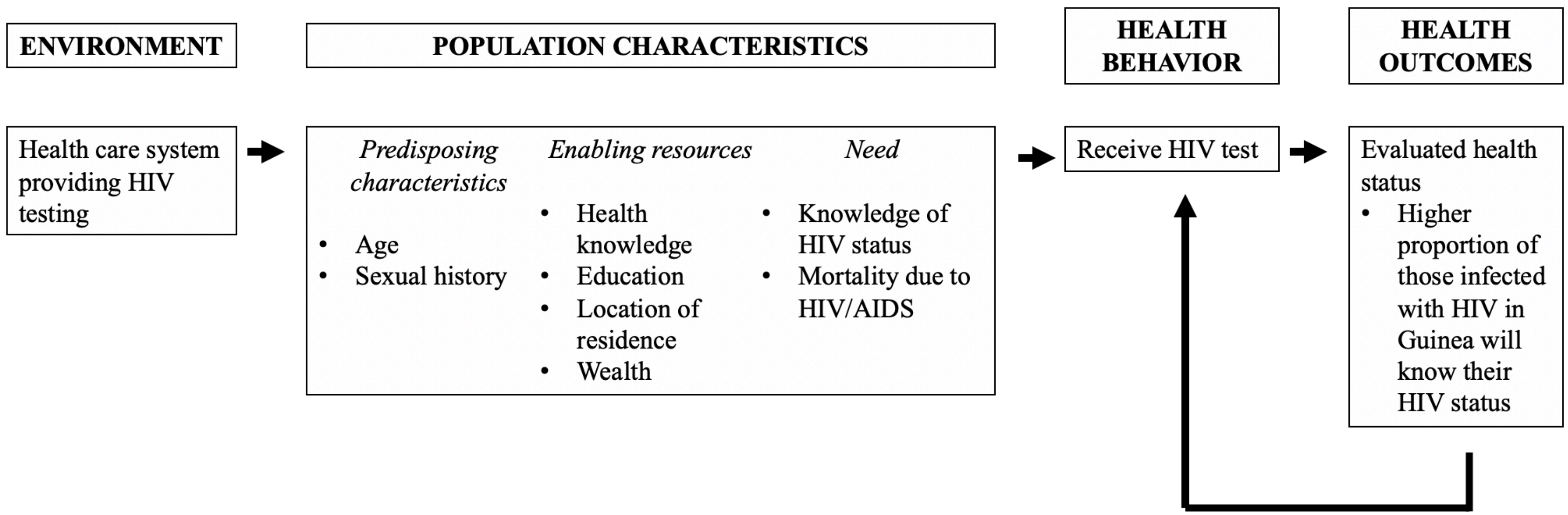


Figure 5.2. Directed acyclic graph of association between cohort, ever having been tested for HIV, and urban/rural residence, controlling for age and sex

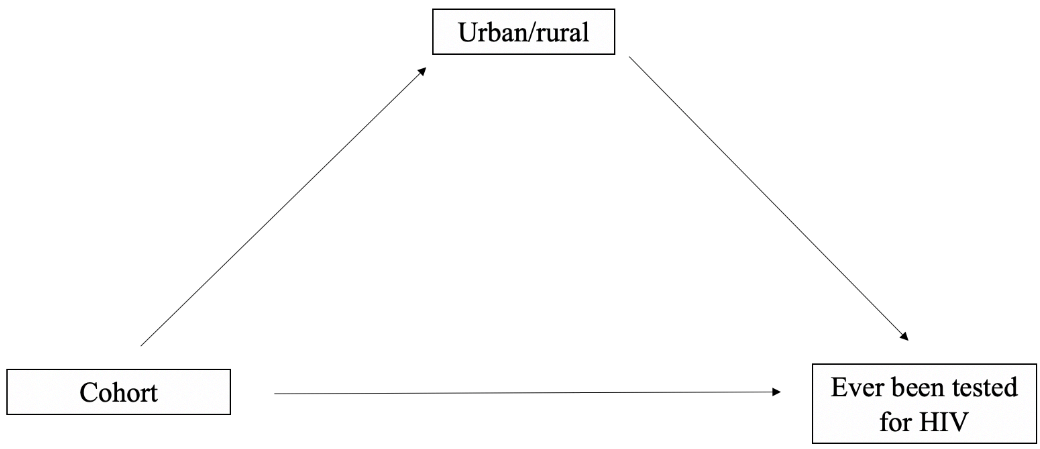
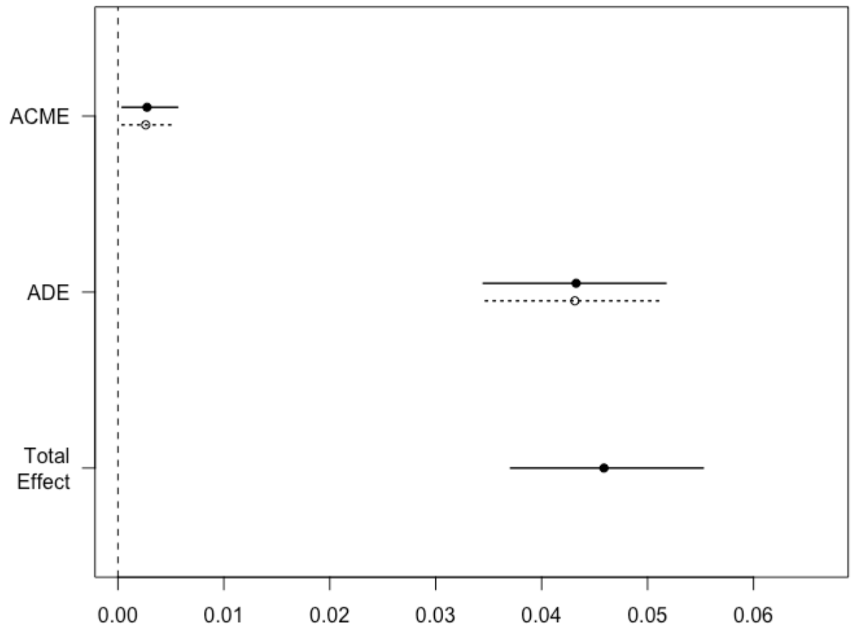


Figure 5.3. Plot of estimates of mediated effect (ACME) of urban/rural residence on association between cohort and ever having been tested for HIV, direct effect (ADE) of cohort on ever having been tested for HIV, and total effect of cohort and urban/rural residence on ever having been tested for HIV (n = 27,809)



Chapter 6: Conclusions & public health significance

This research provides insight into the effects of epidemics on infectious disease prevention and management in Sub-Saharan Africa. There are many ways in which Guinea, as well as Sierra Leone and Liberia, have recovered after the Ebola epidemic. For example, they have developed robust emergency plans that can be implemented for future outbreaks.[121] However, it remains unknown how much progress was lost in the management of measles, malaria, and HIV during the two years that Ebola devastated the region, and it remains unknown whether progress will be lost in these areas of infectious disease management due to the current COVID-19 pandemic.

Examining how measles, malaria, and HIV prevention and management changed over the course of the Ebola epidemic gives a more complete picture of the potential implications for each. We can apply the Andersen model of healthcare utilization to examine how changes in healthcare utilization for prevention of these infectious disease affects health outcomes. A decrease in the proportion of children vaccinated for measles leads to communities becoming more vulnerable to measles outbreaks as immunity on the community level declines. A decline in the possession of mosquito nets in homes leads to more children and other risk groups becoming infected with malaria. Such implications can have devastating effects on already fragile communities. On the other hand, an increase in HIV testing due, in part, to migration from rural to urban areas highlights the need for HIV services beyond the urban centers. Understanding these processes can help governments and public health officials plan for the future.

Ebola continues to be a threat in Sub-Saharan Africa, and since 2016, there have been three further epidemics of Ebola in the region, all in the Democratic Republic of the Congo, and with cases also seen in Uganda. Additionally, as cases of COVID-19 continue to increase worldwide, this study will be useful in assessing the possible disruptions to infectious disease management in Sub-Saharan African settings. As of writing, Guinea has had 19,084 confirmed cases of COVID-19, and 113 deaths.[98] Africa, generally, has not been hit as badly as other regions, however, it is imperative to consider the wide-reaching, and long-term effects it could have on infectious disease prevention.

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