THE ECONOMICS OF EBOLA VIRUS DISEASE

By

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Ebola virus disease (EVD) continues to threaten public health globally, disproportionately more so in the low- and middle-income countries (LMICs) of Africa. The enormous burdens of EVD have led to extensive research into prevention and control and triggered significant investments from the global community. There still exists a gap in terms of resource generation and management for addressing this disease, as well as a consequent urgent need for evidence-based economic decision making.

Objectives: The work reported in this thesis aimed to synthesize evidence on EVD economic evaluations and to conduct economic evaluations of an EVD vaccine in LMICs. This thesis is built around three studies: (1) a scoping review to identify, characterize, and evaluate published studies involving the economic evaluation of EVD; (2) an economic evaluation using a dynamic transmission model of EVD to assess the cost-effectiveness analysis of an EVD vaccine and vaccination program in a hypothetical population of 1000 using data from an EVD outbreak in selected countries in Africa; and (3) a comparative economic evaluation to examine value-based pricing of an EVD vaccine in Central and West African countries with prior EVD outbreaks. We used a dynamic transmission model to evaluate the cost-effectiveness and a value-based price (VBP) of an EVD vaccine

Methods: From eligible studies retrieved using multiple databases, we summarized the impact and economics of EVD, assessed economic studies to date, identified unanswered questions for further exploration, and made recommendations for future EVD economic studies with a special focus on LMICs. Using a modified SEIR (Susceptible, Exposed, Infectious, Recovered, with Death added [SEIR-D]) model that accounted for death and epidemiological data from an EVD outbreak in selected countries (Democratic Republic of Congo, Liberia, Sierra Leone, Uganda), we modeled the transmission of EVD in a hypothetical population of 1000. With our model, we estimated the cost-effectiveness of an EVD vaccine and an EVD vaccination intervention. Based on the cost-effectiveness metrics and using willingness-to-pay thresholds equal to varying percentages of the Gross Domestic Product (GDP) per capita, we demonstrated how a VBP is calculated using an adaptation of the "QALY-capped" approach.

Results: Twenty-six studies were retrieved which focused on the cost/burden of EVD, willingness-to-pay for EVD vaccine, cost of preparedness of EVD treatment centers, and funding for EVD. The impact of EVD was estimated to be substantial in terms of human and fiscal loss. Vaccinating the population at risk to the herd immunity threshold was estimated to avert about 99% of infections, deaths, and disability adjusted life years (DALYs). Although vaccination resulted in incremental costs in the countries evaluated, it was found to be cost-effective in all cases given resultant decrements in outcomes that offset the accumulated costs.

Cost-effectiveness was determined to be directly proportional to transmission rate – being more cost-effective in settings with higher transmission rates. The VBP for the vaccine is directly proportional to both cost-effectiveness and GDP per capita- with higher cost-effectiveness and higher GDP per capita resulting in higher price ceilings compared to lower cost-effectiveness and lower GDP.

Conclusions: The severe impact of EVD puts pressure on governments and the international community for better resource utilization and re-allocation. From the payer perspective, vaccination against EVD is cost-effective. Despite the concerns with the "QALY-cap" approach, we illustrated that it is an easily comprehensible method for determining the VBP of a vaccine using a cost-effectiveness analysis. There is an urgent need for territory-specific evidence-based

economic plans and economic evaluation of mitigations to enhance resource allocation for EVD prevention and treatment.

CHAPTER 1

INTRODUCTION

1.1 Problem Statement

According to the World Health Organization (WHO), in the last 45 years, ebola virus disease (EVD) outbreaks have occurred about 40 times, majority of which have been in Africa. EVD outbreaks have resulted in about 15,000 deaths as of 2021, with an average case fatality rate ranging from 25% to 90%.[1] Ebola virus disease is a severe, often fatal, zoonotic hemorrhagic infection caused by several species of the *Ebolavirus*, the most popular of which is *Zaire ebolavirus* (EBOV).[2] Contact with body fluids from infected patients results in human to human transmissions and patients are not considered infectious until they develop symptoms, typically after an incubation period of 1-21 days after infection.[3]Subsequent to EVD infection, persons may experience a variety of symptoms including fever, nausea, vomiting, diarrhea and bleeding. EVD often affects multiple organs leading to gastrointestinal injury and bleeding; hepatic damage; renal failure; and ultimately death.[2]

Ebola virus disease outbreaks have caused considerable harm to people, communities, and countries. A comprehensive economic and social evaluation estimated the impact of the 2014 outbreak in West Africa, in which approximately 29000 people were suspected to be infected, to be $53.2 billion.[4] Coupled with this, these outbreaks have mainly occurred in low- and middle-income countries (LMICs) of Africa where resources are scarce and competing needs abound. Further, the outbreaks have inflicted various degrees of financial and other economic effects, with substantial impact on most systems in affected nations, including healthcare, transportation, tourism, among others.[4] Though geographically centered in sub-Saharan Africa, EVD remains a public health issue of global concern.[2]

Efforts are continuously being made towards containing outbreaks and spread, developing, and testing efficacious and effective vaccines and treatments, educating communities, putting in place infrastructure and processes – all aiming at complete eradication of EVD.[1] While the present management is focused on supportive care and infection control, several other therapies have been developed for EVD treatment and vaccines for prevention. During the 2018-2020 outbreaks in the Democratic Republic of Congo, the first-ever multi-drug clinical trial for EVD treatment was conducted to evaluate the safety and effectiveness of azithromycin, a combination of sunitinib and erlotinib, a combination of atorvastatin and irbesartan, and intravenous fluids in the management of EVD. Again, *Inmazeb* and *Ebanga,* two monoclonal antibodies have been approved for treating EBOV infections. While the Ervebo vaccine has been approved by the US Food and Drug Administration and prequalified by WHO for protection against EBOV, the Zadbeno-Mvabea vaccine has been granted marketing authorization by the European Medicines Agency for individuals a year and older.[1]

The frequency of EVD outbreaks and the resulting financial and human resource burdens in lower-and-middle-income settings demand that efforts be made towards prevention and rapid mitigation. To facilitate these efforts and to help prioritize and manage available resources for EVD, it is imperative that the economics of the disease, its management, as well as its prevention be well-understood and incorporated into decision-making. While economic evaluations of interventions are comparatively more common in higher income settings, there is an increasing need for these evaluations in LMICs.[6] Pitt and colleagues found that while economic evaluations in HICs correlate with disease burdens in their settings, those in LMICs address health areas that account for lower proportions of their disease burdens.[6] This is a challenge in such settings and could potentially limit efficiency and effectiveness of these evaluations while impeding also, the use of resources where they are most needed. Given the magnitude of EVD in LMICs, there is no doubt how important economic evaluations of interventions are in such settings.

The main purpose of this study is to synthesize the research on EVD economic evaluations qualitatively by means of a scoping review and to perform some economic evaluations of an EVD vaccine in LMICs.

1.2 Research objectives

The objectives of this study are three-fold:

1. To identify, characterize, and review published studies involving the economic evaluation of EVD.
2. To develop and use a dynamic transmission model (DTM) to determine the cost-effectiveness of an EVD vaccine and a vaccination program at large in hypothetical population of 1000 using data from an EVD outbreak in Democratic Republic of Congo.
3. To determine a value-based price of a vaccine using a cost-effectiveness analysis of a vaccination program targeted at herd immunity threshold and to compare the price across selected countries.

These objectives will be addressed in three manuscripts prepared for submission to peer reviewed journals. Objective 1, presented as Chapter 2 of this thesis, is addressed in a manuscript *"The Economics of Ebola Virus Disease Vaccination and Treatment: Background, Scoping Review, and Recommendations for Analysis"* which has been submitted to *The Lancet Global Health.* In this manuscript, the impact of EVD especially in LMICs and present interventions for EVD are discussed. A scoping review of studies evaluating the economics of EVD is also performed with identification of gaps and recommendations for future research.

In Chapter 3, Objective 2 was handled as a manuscript "*Economic evaluation using dynamic transition modeling of ebola virus vaccination in lower-and-middle-income countries*" currently under review at the *Journal of Medical Economics*. This involved the use of a dynamic transmission model for a cost-effectiveness analysis of an EVD vaccine in terms of infections, deaths and disability averted life years (DALYs) averted. Finally, Objective 3 is presented as a technical note *"Value-based pricing of a vaccine in resource constrained based on cost-effectiveness analysis – a technical note"* that describes the calculation of a value-based price (VBP) for a vaccine package using a cost-effectiveness analysis (CEA) of a vaccination program. In this technical note, which will be submitted for publication as well, we explore the steps involved in estimating the highest level at which a vaccine package can be priced, when the objective is to attain herd immunity, using cost-effectiveness analyses of the vaccine package in selected affected countries. We compare the prices across these countries and discuss important considerations for such comparison.

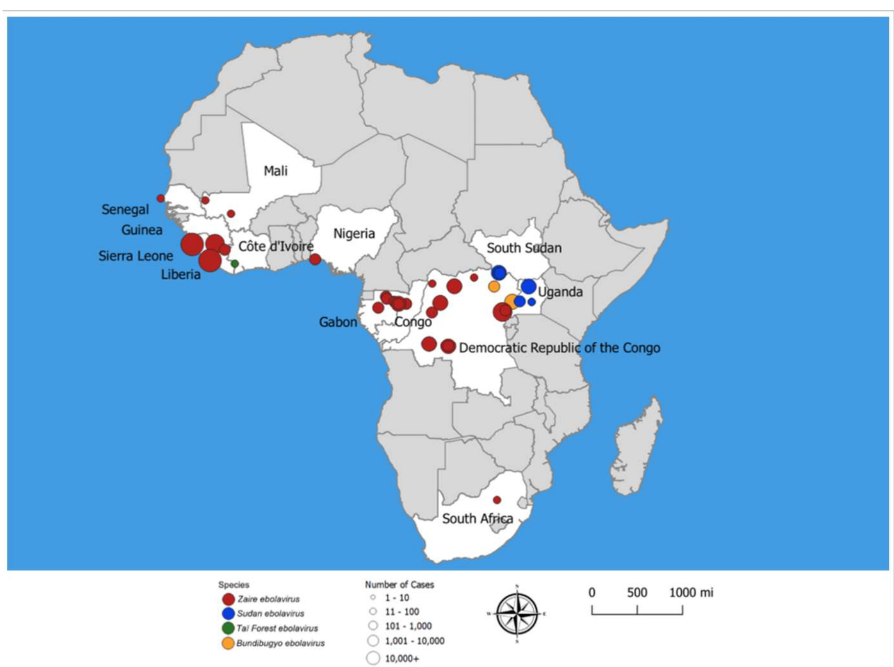

Figure 1.1 Ebola Virus Outbreaks by Species and Size, Since 1976[5]

CHAPTER 2

ARTICLE 1

The Economics of Ebola Virus Disease Vaccination and Treatment: Background, Scoping Review, and Recommendations for Analysis

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2.1 Abstract

Ebola virus disease (EVD) continues to be a major public health threat globally, particularly in the low- and middle-income countries (LMICs) of Africa. The social and economic burdens of EVD are substantial and have triggered extensive research into prevention and control. Some studies have evaluated the economics of EVD; however, several issues remain to be addressed especially for LMICs. In this review, we summarize the impact and economics of EVD, assess economic studies to date, identify unanswered questions for further exploration, and recommend critical areas for future EVD economic studies with a special focus on LMICs. The severe impact of EVD puts pressure on governments and the international community for better resource utilization and re-allocation. There is an urgent need for territory-specific evidence-based economic plans and economic evaluation of mitigations to enhance resource allocation for EVD prevention and treatment.

2.2 Introduction

Ebola virus disease (EVD), a severe viral infection with a mean case fatality of 50% (range 25% to 90%), has plagued the world since the virus was isolated in 1976.[7] The first two outbreaks occurred simultaneously in Nzara, Sudan, where the index case was traced to a rural cotton factory, and the northern part of the Democratic Republic of Congo (DRC) (formerly Zaire), where a male patient being treated for malaria presented with mysterious symptoms. In DRC, the disease, initially thought to be yellow fever, typhoid or malaria, occurred at the Yambuku Mission Hospital (YMH), run by Belgian nuns, in a village near the 240-km-long Ebola River. Within a week, several of his contacts, some staff of YMH, as well as those who received treatment at YMH suffered similar symptoms, all of whom died from the disease. One of the nuns at YMH who had contracted the disease was persuaded by Dr Jean-Jacques Muyembe-Tamfum, a Belgian-trained virologist physician and member of a team of researchers studying the strange disease, to be taken to Kinshasa so blood samples could be taken and analyzed for the culprit organism. The blood specimens were sent to the Institute of Tropical Medicine in Antwerp, where the virus was found to be morphologically similar to but immunologically distinct from the Marburg virus which had earlier been isolated.[8] The virus was named Ebola virus after the River.[7,9] In these first outbreaks of what is now known as ebola virus disease (EVD), 284 and 318 cases associated with case fatalities of 53% and 88%, respectively, were reported in Sudan and DRC. After the emergence of EVD and prior to 2014, about 2345 cases of EVD were confirmed with about 1546 resultant deaths.[3]

The largest EVD outbreak occurred between March 2014 and June 2016 and affected over 28,000 people in Guinea, Liberia and Sierra Leone, with a few isolated cases in DRC, Nigeria, Mali, Senegal, United States, United Kingdom and Italy.[10] DRC is the last country to have experienced an EVD epidemic: the 2018–2020 outbreak, thought to be the world's second deadliest, affected about 3470 people, with a case fatality rate of 66%. Although on the 25th of June 2020, the government of DRC together with the World Health Organization (WHO) announced the end of the outbreak in the eastern part of the country,[11] a new epidemic is currently ongoing in its western Équateur province.[12,13] This outbreak is compounded by an outbreak of measles that has been ongoing for the past year in DRC, as well as the current COVID-19 pandemic.[14]

The ebola virus is primarily transmitted from person to person through direct physical contact with blood and other body fluids such as urine, sweat, feces, saliva, semen and breast milk. Percutaneous injury resulting in broken skin and exposure to the mucosal membranes in the eyes, nose or mouth are the most likely media of viral entry into the human body. Infection with the virus may also occur indirectly by contact with previously contaminated surfaces and objects.[15–17] Studies also found that direct exposure to the remains of an infected person without appropriate personal protective equipment, as well as contact with infected bats, rodents and primates could lead to transmission of EVD.[15,17]

The considerable harm caused to people, communities, and countries, coupled with the fact that EVD outbreaks have mainly occurred in low- and middle-income countries (LMICs) of Africa where resources are scarce and competing needs abound, calls for epidemiological and clinical evidence to support decisions concerning EVD. Countries in which outbreaks have erupted have suffered various degrees of financial and other economic effects and have depended largely on global funds for fighting EVD. Though geographically centered in sub-Saharan Africa, EVD remains a public health issue of global concern. Efforts are continuously being made towards containing outbreaks and spread, developing, and testing efficacious and effective vaccines and treatments, educating communities, putting in place infrastructure and processes – all aiming at complete eradication of EVD.

To facilitate these efforts and to help prioritize and manage available resources for EVD, it is imperative that the economics of the disease, its management, as well as its prevention be well-understood and incorporated into decision-making. We aim to review here several studies examining various aspects of the economics of EVD. These studies have focused on the economic and social impacts of EVD, the cost of preparedness for EVD response, the costs of managing EVD and funding mechanisms. Although much has been learned about the impact, cost and economics of EVD since its emergence, most of the knowledge has accrued during and after the 2004 outbreaks. We also identify several areas of needed economic analysis, including EVD and viral disease specific methods and analytics, that will enhance informed resource planning and allocation. While the focus of this paper is on EVD, as this disease will continue to be a threat, several of the issues translate to the current COVID-19 pandemic while aiming to provide a broader foundation to examine the economics of viral disease outbreaks and epidemics. As such, this paper aims to call attention to the impact and economics of EVD, identify domains that can be further explored in research, and make recommendations for future EVD economic studies.

First, we lay the context by discussing the impact of EVD on the affected countries. We describe how EVD has impacted the lives of individuals and the 'blow' dealt to the economies of these nations. We focus on low- and middle-income countries of Africa where the virus caused the most economic disruptions and highlight how the various sectors in these countries were impacted by the outbreaks. We present evidence on the costs of prevention, treatment, and containment of EVD. We show the role that donor organizations and countries have made in raising funds for EVD response and shed light on the deficit in funds required for tackling EVD globally.

Second, we examine how EVD patients are being managed. With several treatments and vaccines at various stages of clinical trials, treatment of EVD has been evidence-based and targeted at relieving symptoms and providing supportive care. We appraise current treatments and vaccines that are undergoing clinical trials, consider their future use in EVD prevention and treatment, and assess the economics thereof.

In a third section, we review economic evaluation studies of EVD, combining an appraisal of the research to date with an assessment of areas in need of economic analysis. We also point out gaps that are critical to a more comprehensive evaluation of the macro- and microeconomics of EVD. We conclude by recommending areas for further studies to enhance the knowledge base while fostering better decision-making for EVD mitigation amidst limited resources for several competing priorities.

2.3 Impact of EVD

The social and economic effect of EVD cannot be overemphasized. In addition to the enormous human cost, EVD has impacted economies, health, agriculture, travel, commerce, and tourism, among others, in countries so far affected. The impact extends beyond the countries experiencing outbreaks and reaches to other countries that have trade and commerce relationships, as well as donor institutions and governments. While the World Bank estimated the overall impact of the Ebola crisis on Guinea, Liberia, and Sierra Leone between 2014 and 2016 at $2.8 billion due to declining revenues, increasing Ebola-related and health expenditures, and exacerbation of fiscal deficit,[18] Huber *et al.* estimated the comprehensive economic and social burden resulting from EVD in the 2014 outbreak to be $53.2 billion.[19]

EVD has led to significant loss of workforce, livelihood, and household income, with marked decline in gross domestic product (GDP) in the affected countries, the majority of which belong to the low-income bracket. In addition to these losses, EVD also threatened human capital development and the growth of the private sector.[20] The cumulative effect of these is stagnated and decreased economic development that has resulted in deficiencies in all other sectors, decline in standard of living, and decreased economic productivity across these countries.[21]

The already struggling healthcare systems of the affected countries were further weakened by the pressures of the epidemic.[21] Healthcare professionals, who had the responsibility of managing patients, were among those at the highest risk. In 2014, 881 healthcare workers were infected in West Africa. This resulted in reductions in the healthcare workforce through death and due to others leaving the work force out of fear of contracting the disease. The delivery of other health services also saw considerable reductions. Services such as family planning and pre- and post-natal services were relegated to the background as healthcare workers and healthcare funds were diverted for the management of EVD. Increases in HIV/AIDS, tuberculosis, malaria, and other untreated medically related deaths were recorded in most of the affected countries.[20]

The effect of the epidemic on the lives of children was considerable. The US Centers for Disease Control and Prevention (CDC) estimated that more than 17000 children lost either one or both of their parents to the disease. The loss of a “bread-winner” may curtail ambitions these children may have had and puts additional financial and emotional stress on other members of the family and on society. Following the outbreak, school closures led to the loss of weeks of education and there was a decline in the coverage of childhood vaccinations in the afflicted countries.[20,22]

The disease also resulted in decreased cross-border trade due to the restrictions imposed on movements of people, goods, and services.[21] These restrictions further resulted in loss of revenue from tourism and increased costs of running ports of entry due to increased screening at airports, seaports, and land borders. As a result of reductions in movements and transportation, the demand for fuel declined and resulted in lower fuel tax revenues to the respective governments. The cost of doing business, both locally and internationally, also rose as a result of the epidemic.[22]

According to the Food and Agriculture Organization (FAO) of the United Nations, agricultural activity declined in the affected countries.[23] The drop in production volumes of staple crops was compounded by the loss of traders to market the available crops. Food prices increased while declines in exports resulted in high levels of waste.[19,20,23] According to the FAO, about 520,000 persons faced various levels of food insecurity during the 2014 Outbreak in West Africa.[23]

2.4 Management of EVD

There is presently no treatment for EVD, limiting patient management to supportive care and symptomatic treatment.[10] Lamontagne *et al.* developed evidence-based guidelines for the delivery of comprehensive supportive care to patients on admission: oral rehydration, parenteral administration of fluids, systematic monitoring and charting of vital signs and volume status, serum biochemistry, analgesic therapy, and antibiotics, where necessary.[24]

A range of potential treatments including blood products, immune therapies and drug therapies have been investigated with several currently under investigation. Table 1 outlines vaccines and treatments that have been in clinical trials and are registered with Clinicaltrials.gov. The first-ever multi-drug clinical trial for EVD treatment is currently underway in DRC. This study aims to determine whether azithromycin, a combination of sunitinib and erlotinib, a combination of atorvastatin and irbesartan, and intravenous fluids are effective in treating EVD.[25] In a study to assess the efficacy and safety of some promising therapies, MAb114 and REGN-EB3 were found superior to Zmapp in reducing mortality from EVD.[26] Convalescent plasma has emerged as a possible therapy for patients who develop EVD.[27] While Griesven *et al.* found a decrease in case fatality rate by 20% among study participants in Guinea, they found no significant association between the transfusion of convalescent plasma and improved survival in EVD patients.[28] The US FDA has approved Inmazeb, a mixture of atoltivimab, maftivimab, and odesivimab-ebgn,[29] and Ebanga (Ansuvimab-zykl), a human monoclonal antibody,[30] both of which were evaluated for efficacy and safety in the Pamoja Tulinde Maisha (PALM) trial conducted in DRC.

In 2015, the recombinant, replication-competent vesicular stomatitis virus-based vaccine r-VSV-ZEBOV was found to be protective against EVD in a trial in Guinea. This vaccine is being used in the DRC presently for ring vaccination against EVD and has helped to contain the spread of EVD.[11,31] In December 2019, the US Food and Drug Administration approved the use of the r-VSV-ZEBOV (Ervebo) vaccine for the prevention of EVD in patients 18 years and older,[32] following earlier approvals by the WHO and the European Medicines Agency. It was already being used as post-exposure vaccination among contacts of patients and for ring-vaccination of frontline health workers managing EVD patients under an expanded-access compassionate use protocol. After ten or more days of Ervebo vaccination, efficacy was estimated to be about 97.5% among about 90000 exposed individuals. Other vaccines being investigated include, *inter alia*, VRC-EBODNA012-00-VP, an Ebola DNA plasmid vaccine;[33] EBOVAC3DRC, a heterologous vaccine regimen with Ad26.ZEBOV and MVA-BN-Filo(28); and Ad5-EBOV, a recombinant human type 5 adenovirus vector-based Ebola vaccine.[35] Table 1 presents clinical trial records of EVD vaccines and treatments.

2.5 Economics of EVD: Scoping review

2.5.1 Search strategy and criteria

A published literature search was conducted in PubMed/Medline, Embase, Google scholar and Scopus using key words including “ebola virus disease”, “cost”, “cost analysis”, “economic evaluation”, and other related terms. All articles published on the subject were included since EVD dates to 1976, after which some research may have been made until present. Our search yielded 26 studies that reported some form of economic evaluation (Table 2).

2.5.2 Cost/Burden of Illness

Eight studies aimed to estimate the costs of EVD cases and of the 2014 outbreak as a whole.[21,22,36-40] Three studies assessed the direct and indirect costs; typically, the costs of medications, laboratory examinations, and personal protective equipment; personnel costs; and productivity losses.[36–38] Five studies also estimated the costs of EVD deaths, non-EVD deaths, long term EVD sequelae, social factors, direct economic losses, and the decline in economic activities in the affected countries.[19,21,22,39,40] Of the above studies, 6 focused mainly on the 2014 EVD outbreak and were mainly conducted in Liberia, Sierra Leone, Guinea, and Nigeria. Ebola virus disease was found to have resulted in extensive loss of gross domestic product of about $32.6 billion.[41] Huber *et al*., in their systematic review of EVD, pooled together existing estimates, determined areas that had not been covered, and estimated the comprehensive cost of the 2014 EVD outbreak to be $53.2 billion. The greatest cost factor was the cost attributed to death from non-EVD causes.[19] In a study to estimate the cost of a single case of EVD, Bartsch *et al*. reported a wide range between about $500 and $18000 depending on the severity and the outcome.[38] Similar to findings by Huber *et al.*, Bartsch and his colleagues, as well as Kirigia *et* *al.,* also found mortality to be the highest component of the cost incurred, together with the resultant loss of productivity.[36]

2.5.3 Willingness-to-pay for Ebola Virus Vaccine

Four willingness-to-pay studies among various populations have attempted to assess the trade-offs that people in the general population are willing to make with regards to their personal wealth versus their perceived risk of disease and possible death.[42–46] These willingness-to-pay analyses, conducted in Nigeria, Guinea, Indonesia and Sierra Leone, surveyed participants' readiness to be vaccinated against EVD and how much they were prepared to pay for the vaccine if it was not to be given for free. The prevailing preference was for vaccination against Ebola virus to be provided free of charge by participants' respective governments. The proportion of people ready to be vaccinated declined if vaccination was not free.[42–46] The proportions of participants willing to pay were low and was associated with international travel, monthly income, and the perceived efficacy of the vaccine.[44,45] A need to increase awareness and knowledge of EVD and the possible effects of the vaccine, as well as advocacy for governments to absorb the cost of vaccination, were considered critical to improved vaccine acceptability and uptake.[42,46]

2.5.4 Cost of Preparedness of EVD Treatment Centers

Eleven studies have described efforts to assess preparedness activities and associated costs of setting up efficient EVD treatment centers in anticipation of possible EVD cases. The issues of interest were costs of construction and modification of facilities, the direct supply costs, compensated work hours, training of healthcare staff, as well as laboratory costs.[47-55] Hospital preparedness was found to require extraordinary resources which needed to be diverted from existing infection prevention and control activities.[47-49] Costs of preparedness varied widely across different settings depending on the cost elements included.

Notably, construction and modification accounted for a huge part of the cost of preparedness in most cases.[50,56] A study of the cost of setting up an EVD treatment center, conducted in all US children's general hospitals found that the financial impact of preparedness activities exceeded $360 million.[52] Kellerborg and colleagues, in their evaluation of the costs and health effects of early response to EVD, determined that such responses are cost-effective, and that such investments in healthcare systems are needed, and provide value for money.[53]

2.5.5 Funding for EVD

Two reports reviewed EVD-related funding, including research funding, funding in support of various interventions, and funding for public health surveillance and modeling. Several public and philanthropic sources contributed to funding for research, outbreak, containment, and management of EVD.[57–60]

A systematic review by Fitchett *et al*. estimated total EVD research funding from 1997 to 2015 at $1.035 billion, 42% of which had been awarded during the 2014 outbreak. These funds were raised from several public, private, and philanthropic funders including the NIH, European Commission, CDC, Gates Foundation, public and private universities, and biopharmaceutical companies. Ebola research funds have supported clinical trials, product development, surveillance, modeling, and other innovative steps such as bioinformatics and operational research to find solutions to the disease.[57]

In an issue brief, Boddie evaluated US federal funding in support of research and development for EVD. Funding totaling $1.1 billion for the development of EVD countermeasures (drugs, vaccines, and diagnostics) was mainly supported by the NIH and US Department of Defense.

Boddie also highlighted the 2015 Consolidated and Further Continuing Appropriation Act, which set aside $5.4 billion in emergency funding to help the US in their EVD response.[58]

According to a report by the United Nations Special Envoy on Ebola, of the $8.9 billion pledged by individuals, organizations, and governments towards containing, preventing, and treating the disease, $5.9 billion had been disbursed as of October 2015.[61] In addition, affected countries invested considerably in healthcare and disease management plans during the epidemic.[19]

The World Health Organization Ebola Response Fund reported receipt of over $459 million in contributions from over 60 donors during the 2014-2016 outbreak, including countries, private organizations, not-for-profit organizations, and the United Nations.[18] In its bid to offer relief from the current EVD outbreak in DRC, the World Bank announced a $300 million emergency fund toward EVD management[59] while the Vaccine Alliance (Gavi) offered over $9 million to fund vaccination in the DRC.[60]

In spite of having received donations of about $276 million from August 2018 to present for the mitigation of EVD, WHO Ebola Response Funding reported a need of an additional $28.5 million to ensure continuity of EVD response activities and to avoid cashflow shortages.[62]

2.6 Observations from Published Literature and Challenges Facing EVD Economic Evaluations

In Table 3, we summarize several observations on the economics of EVD from our scoping review. These concern EVD cost estimates, regional generalizability, long-term burden, vaccine pricing, and gaps in funding.

We elaborate on this in Table 4, in which we outline several methodological and technical challenges that need to be addressed to further economic evaluations of EVD and support informed decision-making on the allocation of available but constrained resources to improve

EVD outcomes. As Briggs *et al.* point out, health economic evaluation aims to appraise the return on investment for health services and programs to direct resources to maximize health gains.[63] The enormous burden of EVD requires that economic evaluations be conducted to better understand the resources required to battle its impact and to appropriately allocate these resources for addressing critical needs, especially in LMICs.

As with other infectious diseases, economic evaluation of EVD is inherently complex. Although, in itself, an infection prevented or treated in one person is a direct outcome of an intervention, it further limits the spread of EVD.[64] The unique characteristic of a vaccine to protect susceptible, non-vaccinated individuals when vaccination programs are implemented needs to be incorporated into an economic model that aims to assess the effect of such an intervention.[65] Of particular importance is dynamic transition modeling, a mathematical approach to economic evaluation that represent the study population with multiple birth cohorts and allow for the effect of an intervention on one participant to affect others. This methodology is best suited for economic modeling of EVD since it takes into account herd immunity as well as other indirect effects of healthcare programs.[65,66] Dynamic models show how the risk of infection to susceptible individuals who are uninfected is reduced if an intervention reduces infectiousness in the population.[66] This is possible because dynamic models are more reflective of infectious diseases, expressing infection rate as a function of the number of persons infected in the population.[63]

2.7 Recommendations for EVD Economic Evaluations

Fully comprehending the burden of EVD and appropriately estimating the value of potential healthcare programs and services for the prevention and control of EVD, will require foundational research and technical development. The overarching objective is to provide harmonized approaches to enable rigorous, epidemiologically justified, and regionally relevant economic evaluations of EVD prevention and control.

Table 5 presents various areas of foundational research to support this objective, followed by additional specific recommendations for EVD prevention (vaccines) and control (therapeutics). It identifies several economic models and analytics that need to be adapted, refined, or developed; presents definitions and describes general methodologies for each; and offers a rationale for each. Importantly, these methods need to be developed with international and interdisciplinary representation; preferably agreed upon by consensus, or at least a significant majority; and be generalizable within and across countries.

2.8 Conclusion – With A Note on Coincident Measles, COVID-19, and EVD outbreaks

Parts of Africa are dealing with a coincidental measles epidemic and COVID-19 pandemic, and, as the current outbreak in the DRC province of Équateur province, a triple threat involving EVD is a reality. The resultant pressure on governments for better resource utilization and re-allocation underscores the need for evidence-based regionally relevant economic plans to handle present, and prevent and respond to future, infectious disease outbreaks. Although these three viral diseases differ in biology and immunology, their effects on the affected population, varied in magnitude though they may be, are essentially the same: mortality and morbidity, social and societal impacts, and economic implications. Lessons learned from the management of any of these outbreaks are valuable and transferable to others. In the DRC, for instance, public health response to COVID-19 and coincident measles has been guided largely by the experience in combatting EVD. There is evidence that alignment of the responses for these outbreaks has made DRC more responsive and lowers morbidity and mortality.[14] In this same vein, lessons derived from the economics of one outbreak will be invaluable for preparing towards and financing the prevention of and response to future outbreaks. With several decades of experience in dispensing and utilizing funds for a fairly successful global EVD mitigation campaign, capacities built in EVD economics and funds management can be applied to COVID-19 and any other epidemics that may occur in the future.

The burden of EVD globally and particularly in the countries that have been directly affected is enormous epidemiologically, clinically, socially, and economically; putting pressure on governments and the international community for better resource utilization and re-allocation to address both the immediate clinical needs but also the ensuing longer-term social and economic consequences. There is urgent need for territory-specific evidence-based economic plans and economic evaluation of mitigations to enhance resource allocation for EVD prevention and treatment.

Table 2.1 Clinical trial records of EVD vaccines and treatments

Type	Name	Trial Sponsor	Trial status	Dose	Trial number[1]
Vaccine	HPIV3-EbovZ GP	National Institute of Allergy and Infectious Diseases (NIAID)	Phase I	Intended for intranasal administration; two doses required	NCT02564575
	rVSV-ZEBOV	Merck Sharp & Dohme, Public Health Agency of Canada, NewLink Genetics	Phase III (completed)	Single dose vaccine	**NCT02503202**
	Ad26.ZEBOV	Janssen Vaccines & Prevention B.V.	Phase III	Booster vaccine needed	NCT02661464

[1] Trial numbers were extracted from the ClinicalTrials.gov database [66]

Type	Name	Trial Sponsor	Trial status	Dose	Trial number[1]
	AD5-EBOV	Jiangsu Province CDC	Phase II	Booster vaccine needed	NCT02575456
	ChAd3.EBO-Z	Glaxo Smith Kline	Phase II	Booster vaccine needed	NCT02485301
	MVA-BN-Filo	Janssen Vaccines & Prevention B.V.	Phase III	Booster vaccine needed	NCT02598388
	VRC-EBOAdc069-00-vp (MVA-EbolaZ)	University of Maryland, Baltimore	Phase I	Booster vaccine needed	NCT02368119
	VRC-EBOADV018-00-VP	NIAID	Phase I (completed)	Booster vaccine needed	NCT00374309
	INO-4201, -4202, and -4212	Inovio Pharmaceuticals	Phase I	Booster vaccine required	NCT02464670

Type	Name	Trial Sponsor	Trial status	Dose	Trial number[1]
	VRC-EBODNA012-00-VP VRC-EBODNA023-00-VP VRC-EBODNA025-00-VP	NIAID	Phase I	Booster vaccine required	NCT00072605
	rVSVN4CT1-EBOVGP1	Auro Vaccines LLC	Phase I	Double dose vaccine	NCT02718469
	cAd3-EBO S	NIAID	Phase I		NCT04041570
	VSV-ZEBOV	University of Oxford	Phase I	Single dose vaccine	NCT02296983

Type	Name	Trial Sponsor	Trial status	Dose	Trial number[1]
Treatment	Convalescent plasma	Clinical Research Management, Inc.	Phase I/II	Double dose administration	NCT02333578
	INTERCEPT Plasma	Cerus Corporation	Phase I	Single dose	NCT02295501
	Remdesivir	NAIAD	Phase II/III	Multiple doses	NCT03719586
	Zmapp	NAIAD	Phase II/III	Single dose	NCT03719586
	MAP-114	NAIAD	Phase II/III	Single dose	NCT03719586
	REGN-EB3	NAIAD	Phase II/III	Triple dose	NCT03719586
	Favipiravir	Beijing Institute of Pharmacology and Toxicology	Phase II	Multiple dose	NCT02662855
	Azithromycin	Clinical Research Management, Inc.	Phase I/II	Multiple doses	NCT02380625
	Sunitinib and Erlotinib	Clinical Research Management, Inc.	Phase I/II	Multiple doses	NCT02380625

Type	**Name**	**Trial Sponsor**	**Trial status**	**Dose**	**Trial number**[1]
	Atorvastatin and Irbesartan	Clinical Research Management, Inc.	Phase I/II	Multiple doses	NCT02380625
	REGN3470-3471-3479	Regeneron Pharmaceuticals			NCT03576690
	Brincidofovir	Chimerix	Phase II	Multiple doses	NCT02271347

Table 2.2 EVD economic evaluations

First Author, Year, Country/Region	**Objective**	**Perspective**	**Method**	**Results**
I. Burden of disease				
Kirigia, 2005, West Africa[36]	To estimate the future productivity losses associated with EVD deaths in the West African region, in order to encourage increased investments in national systems.	Societal	Cost-of-illness method to calculate future non-health gross domestic product losses associated with EVD deaths and discounted at 3%.	The discounted non-health gross domestic product loss (NHGDPLoss) due to the 11,234 deaths associated with EVD was estimated to be INT$155,663,244. The average NHGDPLoss per EVD death was estimated to be INT$17,473 for Guinea, INT$ 11283 for Liberia, INT$ 25,126 for Mali, INT$47,364 for

First Author, Year, Country/Region	Objective	Perspective	Method	Results
				Nigeria and INT$14,633 for Sierra Leone.
Elmahdawy, 2017, West Africa[37]	To examine the response to an EVD outbreak in West Africa, identify direct and indirect treatment costs, present key economic challenges and learned lessons, and highlight policy recommendations to further assist	Public health system	Discussion	EVD poses a challenge, in terms of significant medical and economic implications, to Africa where the health system is weak.

First Author, Year, Country/Region	**Objective**	**Perspective**	**Method**	**Results**
	an already stretched health system in Africa.			
Huber, 2018, West Africa[19]	To review all currently available estimates, identify social components missed by these estimates and generate a comprehensive cost of the 2014 EVD outbreak.	Societal	Systematic review	The economic burden of EVD was estimated to range from $2.8 to $32.6 billion in GDP losses. A comprehensive economic and social burden was estimated at 53.19 billion, with the most significant component ($18.8 billion) resulting from deaths from non-ebola causes.

First Author, Year, Country/Region	**Objective**	**Perspective**	**Method**	**Results**
Bartsch, 2015, Guinea, Liberia, Sierra Leone[38]	To develop a computational model that estimates the costs of different types of ebola cases for the countries where major outbreaks are occurring	Societal and health care provider	Monte Carlo Simulation model to determine the direct medical costs and productivity losses of ebola cases	"The total societal cost of an EVD case with full recovery ranges from \$480 to \$912, while that of an EVD case not surviving ranges from \$5929 to \$18 929, varying by age and country. Therefore, as of 10 December 2014, the estimated total societal costs of all reported EVD cases in these three countries range from \$82 to potentially over \$356 million".

First Author, Year, Country/Region	Objective	Perspective	Method	Results
Zacharowski, 2015, Germany[39]	To describe the costs of managing an Ebola patient.	Healthcare institution	Cost analysis	The overall costs (direct and indirect) of patient transfer, treatment, and management of exceeded €1 million, a high proportion of which was composed of health and safety measures for personnel. These costs could be considered a high price to pay for treatment and care of one EVD patient.
Olugasa, 2015, Nigeria[16]	To determine the social and preventive cost implications of EVD	Societal	Descriptive cross-sectional study that used questionnaires and key informant interviews.	Respondents declared a total cost of approximately N5,019,379.80 only. The mean

First Author, Year, Country/Region	Objective	Perspective	Method	Results
	among selected public institutions in Lagos, Nigeria.			expenditure on these institutions translated to an approximate N1, 027,094,756.10 on all related institutions (hospitals, hotels and schools) in Lagos state during the study period.
Bowles, 2016, Liberia[40]	To provide evidence on the extent to which economic activity declined and jobs disappeared in Liberia during the outbreak.	Societal	Panel data set of registered firms surveyed by business-development non-profit organization (Building Markets) and comparison of change in economic activity	Decrease in economic activity and jobs during the Ebola outbreak, with a worse decline in Monrovia. Persistence of this decline will require an economic recovery that rebuilds

First Author, Year, Country/Region	Objective	Perspective	Method	Results
			during the outbreak, across regions of the country.	and supports the healthcare system for Liberia to regain its footing.
Kum, 2019, Sierra Leone[21]	To investigate the effect of Ebola outbreak on government capital expenditure of the Sierra Leonean government.	Government	World Bank Data Repository, International Monetary Fund an Endogenous Growth Model of Public Expenditure, which assumes that Gross National Income (GNI) growth is determined by forces governing the production process rather than by forces outside it.	EVD impacted negatively on government capital expenditure in Sierra Leone.

First Author, Year, Country/Region	Objective	Perspective	Method	Results
II. Willingness to pay for vaccine				
Painter, 2018, West Africa[42]	To examine factors associated with willingness to pay for an ebola vaccine among US national sample during the recent ebola outbreak	Societal	National survey measuring willingness to pay.	Among 1447 participants, 40.3% would not pay for an ebola vaccine, 59.7% would pay at least $1.
Ughasoro, 2015, Nigeria[43]	To determine the public acceptability and willingness to pay for an EVV	Societal	Community based cross-sectional qualitative and quantitative study. Questionnaires used to collect information on respondents' knowledge of ebola, and their	Among those who accepted to be vaccinated, most would only accept after observing the outcome on others who received the vaccine. More than 87.5% were willing to pay for

First Author, Year, Country/Region	**Objective**	**Perspective**	**Method**	**Results**
			acceptability and willingness to pay for a hypothetical vaccine.	the vaccine although 55.2% thought it should be free.
Kpanake, 2018, Guinea[44]	To map the different personal positions of Guinean people regarding vaccination against Ebola	Societal	Using vignettes depicting situations in which getting vaccinated will be possible.	Attitude toward vaccination depends on costs, neighbor's attitude, risk and mistrust of cheap vaccines.
Mudatsir, 2019, Indonesia[45]	To determine the WTP for a hypothetical EVV in Indonesia	Societal	Cross sectional study of interviews in 5 cities in Aceh were participants were interviewed about socio-demographics, knowledge	288 participants out of 311 were willing to pay a mean of $2.08 for the vaccine. Proportion of participants willing to pay was high but the

First Author, Year, Country/Region	Objective	Perspective	Method	Results
			about Ebola, and WTP for a hypothetical vaccine.	amount they were ready to pay was low.
Huo, 2016, Sierra Leone[46]	To understand the Ebola vaccine-related knowledge and attitude of the general population	Societal	Survey on knowledge and attitudes towards the vaccine.	Most participants (72.5%) were willing to take the vaccine if it was for free. If it was not free, only 26.6% were willing to pay for it. Monthly salary, monthly average income of family members and their interaction were found to be associated with charged vaccination uptake willingness.
III. Cost of preparedness				

First Author, Year, Country/Region	Objective	Perspective	Method	Results
Yacisin, 2015, USA[47]	To describe preparedness activities that include planning and practice in effectively monitoring the health of workers involved in Ebola patient care	Local health department	Cost analysis	In New York City, the public health response to one Ebola case cost $4,300,000 in Department of Health and Mental Hygiene funds. This cost included the direct costs of the local public health response and also the indirect costs of increasing citywide preparedness after identifying the one case.

First Author, Year, Country/Region	Objective	Perspective	Method	Results
Simonsen, 2017, USA[48]	To analyze the attributable costs of EVD preparedness during the peak outbreak period at a freestanding children's hospital using an ETF member survey	Health care provider	Cost analysis	Overall, Ebola preparedness annualized expenditures totaled $181,350.
Herstein, 2016, USA[49]	To directly survey the Ebola treatment centers (ETCs) to determine the costs incurred to prepare their facilities to manage and treat EVD patients	Societal	Use of electronic surveys	45 ETCs reported total costs incurred to cumulatively to $53,909,701 (mean of $1,197,993/ETC) to establish the ETCs. The costliest activity

First Author, Year, Country/Region	Objective	Perspective	Method	Results
				was facility construction and modifications.
Morgan, 2015, USA[50]	To examine costs and challenges associated with hospital ebola preparation by means of a survey of Society of Healthcare Epidemiology of America members	Health care provider	Electronic survey of infection prevention experts.	Hospital Ebola preparations required extraordinary resources, diverted from routine infection prevention activities.
Ripper, 2015, USA[56]	To describe the necessary components for building and maintaining an Ebola extended treatment area	Health care provider	Cost analysis	Costs of implementation of the hospital Ebola extended treatment area was $688,000;

First Author, Year, Country/Region	Objective	Perspective	Method	Results
	and to present the predictable costs of implementation, maintenance and care of a university hospital's Ebola extended treatment area			Costs of maintenance was \$19,875 per month. Costs of care for a patient in the treatment area was \$87,500 per 100 patient care hours. The total cost of implementation and maintenance of Ebola extended treatment areas with 100 patient care hours was \$767,000.
Abraham, 2015, USA[68]	To determine the overall cost of EVD preparedness in one county hospital ED.	No clearly defined- Cost to county?	Cost-analysis: Retrospective review of all emergency department expenditures associated with complying	Total emergency department expenditure was \$44,026. The costs of registered nurse management and registered

First Author, Year, Country/Region	Objective	Perspective	Method	Results
			with the CDC recommendations for EVD for a large, urban, academic, county emergency department with annual census of greater than 170000 patients.	nurse personal protective equipment training time were $4,716 and $5,005, respectively. Total PPE costs totaled to $28,098 while containment equipment amounted to $840.
Smit, 2017, USA[52]	To assess resource allocation and costs associated with US hospitals preparing for the possible spread of the	Health care provider	Cross-sectional study using surveys sent to stratified national probability sample of US hospitals. Surveys assessed EVD preparation supply costs and overtime staff hours.	Supply and overtime labor costs totaled $80,461. The cost of preparedness of acute-care hospitals in the US was estimated at $361,108,968.

First Author, Year, Country/Region	Objective	Perspective	Method	Results
	2014-2015 EVD epidemic in the US			
Kellerborg, 2020, Sierra Leone[53]	To estimate the costs and health effects of earlier interventions in Sierra Leone	Societal	Deterministic and a stochastic compartment model describing the EVD outbreak was estimated using a variety of data sources. Costs and Disability-Adjusted Life Years were used to estimate and compare scenarios of earlier interventions.	Investigators found that four weeks prior to their study, interventions would have averted 10,257 cases and 8835 deaths, implying 456 thousand DALYs and million $US saved. The greatest losses occurred outside the healthcare sector.

First Author, Year, Country/Region	Objective	Perspective	Method	Results
Suijkerbuijk, 2017, Netherlands[54]	To present the total costs associated with EVD preparedness and response in healthcare in the Netherlands	Health care provider	Activity based costing methods using interviews with key professionals in EVD preparedness and response in the organizations involved. A time-recording system was used to estimate the cost of staff time spent in preparedness and response activities.	Estimated total cost averaged €12.6 million (€ 6.7 million to 22.5million).
McCullough, 2019, USA[49]	To estimate direct costs of mounting emergency preparedness and	Public health department	A cost analysis was performed from the perspective of the public health department using	Total cost for measles-, Super Bowl-, and Ebola-related activities from January 22,

First Author, Year, Country/Region	**Objective**	**Perspective**	**Method**	**Results**
	response activities to 3 major public health events, simultaneously.		real-time activity diaries and retrospective time and activity self-reporting, wage and fringe benefit data, and financial records to track costs.	2015, through March 4, 2015, was $224 484, majority of which was for personnel ($203 743) and the costliest response to measles ($122 626 in personnel costs).
Herstein, 2020, USA[69]	To determine whether additional costs have been incurred since a previous assessment of cost of establishing ebola treatment centers (ETCs) in 2015, as well as to	Health care provider	Electronic survey of representatives of 56 ETCs.	An average additional $225,000 has been spent per ETC. Even with the increased cost since the initial assessments (nearly $1.8 million compared with $1.2 million in 2015), there are still gaps in reimbursement from

First Author, Year, Country/Region	Objective	Perspective	Method	Results
	assess hospitals' sustainability plans for maintaining capabilities after federal funding ceases.			federal and state funding have also increased.
IV. Funding				
Fitchett, 2016, USA[57]	To document data on research funding for emerging infections (EBOLA)	Funding organizations	Systematic review using data directly from funding organizations.	Funding for Ebola and Marburg virus research totaled $1.035 billion.

First Author, Year, Country/Region	Objective	Perspective	Method	Results
Boddie, 2015, USA[58]	To discuss resources dedicated by the federal government for developing medical countermeasures to be used in the event that Ebola is used as a bioweapon against USA	Federal government	Discussion	As of December 1, 2014, \$25.6 million of the \$750 million in funding had been expended by DoD for Ebola countermeasures research and development.

Table 2.3 Issues in the economics of EVD

Inconsistent EVD cost estimates	The estimated costs across the various studies examined varied widely. This is attributable to the absence of standardized methods, perspectives, outcome metrics, and types of analyses.
Generalizability to Africa	Most cost-of-preparedness studies were conducted in high-income countries (HIC) and do not accurately reflect the situation in low- and middle-income countries (LMIC), especially in the regions of Africa that have been most impacted by the virus.
Unknown long-term burden	Even though the indirect burden of the disease has been discussed in some research findings, the long-term effects of these have not been extensively deliberated. The long-term burden on affected countries and the effect it would have on the reorganization of their economies remain poorly understood
Vaccine pricing	With the introduction of the EVD vaccine, there is a need to have better insights in and transparency of the pricing of the vaccine, and the impact that free vaccination will have on the budgets of countries that opt to make this available to its citizens. Such research will inform decisions between mass vaccination or vaccination according to risk. In turn, this will also help in the mobilization of funds for such programs. Economic evaluations

	and cost-effectiveness studies in particular are needed to adopt pan-African and national vaccination policies in EVD-endemic regions
Gaps in funding	In spite of the significant funds invested in EVD, large gaps remain in financial support towards fighting the disease. There are calls for global commitment to funding in support of managing the disease, along with research and development, as well as global financing mechanisms towards other pandemics that may arise in the future

Table 2.4 Methodological and technical challenges

Healthcare financing	Health system constraints in the form of human resource shortages for clinical and supportive personnel, and financial limitations for managing healthcare systems, as well as adequately managing data, pose a significant threat to the conduct of health economic research affecting the accurate collection of cost data for such studies.
Methodology	Much of the health economic armamentarium was developed for use in HICs, and high-resource healthcare systems, to manage acute and chronic diseases, and where medications and other treatments are highly accessible
Clinical patient data	Accessible and retrievable (electronic) health records are scare in LMICs, limiting the clinical information that can be used.[70]
Perspective	From whose viewpoint is the evaluation being conducted? In LMICs, the societal perspective is preferred as most of health care is financed either by governments or through out-of-pocket means.[70] With little enrollment in insurance or healthcare management organizations, the payer perspective is of limited relevance in LMICs.[71]
Outcome measures	The choice of these measures is critical since they quantify the usefulness of the healthcare program being assessed. While generic and composite measures such as the

	quality-adjusted life year (QALY) are widely used in HIC evaluations, they may not be practical in LMICs where the disability-adjusted life years (DALY) and clinically relevant outcomes, such as number of deaths averted, may be more reflective of the intended outcome. HIC measures of health may be too narrow in LMICs to reflect the entire picture, eliminate some critical dimensions of the effects of the intervention being assessed, and thus may underestimate or undervalue the intervention.[70]
Benchmark levels or thresholds	Benchmarks for determining cost-effectiveness in LMICs need to be chosen deliberately to reflect the income group of the population being assessed. Setting these levels too high and out of proportion may portray all interventions as "cost-effective" and impair educated priority setting.[65] The levels used in HICs do not account for the HICs-to-LMICs inequities in health and wealth. For LMICs, country- or income group-specific thresholds should be set to account for these differences and to align cost-effectiveness thresholds with affordability.[72]
Infectious disease modeling	As with other infectious diseases, economic evaluation of EVD is inherently complex. Although, in itself, an infection prevented or treated in one person is a direct outcome of an intervention, it further limits the spread of EVD.[74] The unique characteristic of a

	vaccine to protect susceptible, non-vaccinated individuals when vaccination programs are implemented needs to be incorporated into an economic model that aims to assess the effect of such an intervention.[65] Dynamic transition models, a mathematical modeling approach to economic evaluation that represent the study population with multiple birth cohorts and allow for the effect of an intervention on one participant to affect others, are best suited for economic modeling of EVD since they take into account herd immunity as well as other indirect effects of healthcare programs.[65,66]

Table 2.5 Economic models and methods for EVD prevention and control

Economic models and analytics	Definition and general methodology	Rationale
EVD-specific cost models		
Cost-of-illness minimum dataset	A cost of illness (COI) evaluates the economic burden an illness imposes on society as a whole with respect to the consumption of health care resources and production losses and is estimated by identifying and assigning monetary value to the cost-generating components.[67] The foundation for standardizing COI methods lies in the development of a harmonized minimum dataset (MDS) for the conduct of such analyses. This "template-like" MDS should contain information on disease definition and epidemiology, direct and indirect costs adequately disaggregated, all relevant data sources, unit costs of	COI gives information about how much society is spending on a particular disease, and consequently how much would be saved with disease eradication. In a COI analysis, different cost components, along with the magnitude of contribution of each sector in society are identified. The resulting information can highlight existing inefficiencies and potential savings and help to determine research and funding priorities.[74,75]

	all cost components, discount rates, and estimates of resource consumption; all expressed in local currencies but with parity parameters to enable comparisons between countries and regions. Once the MDS has been detailed, optional submodules can be added.	Methods for COI, thus, need to be standardized so as to ensure that the burden of diseases is accurately costed.
Cost of sequelae minimum dataset	Studies have found some EVD-related sequelae that persist for more than a year after hospital discharge, the most common of which are headache, myalgia, joint pain, ocular complications and abdominal pains.[76–78] An MDS for costing EVD-related sequelae must include the epidemiology of EVD and EVD-related complications, health care utilization data, and direct and indirect costs of screening and managing sequelae.	Costing the EVD-related sequelae helps to elucidate the incremental economic burden these complications present and to plan for their financial management. This assessment also helps provide a more wholesome assessment of the cost implications of EVD over the long term.

Cost-of-distribution model	A cost-of-distribution model develops a comprehensive "template-like" plan of authorization and distribution channels, along with required logistics for vaccine or therapeutics distribution under consideration of regional and local logistics and infrastructure.[73] Such a model needs to account for approval of the vaccine or therapeutic within the particular national market, demographics, distribution systems, modes of population or patient access, dose of vaccines and therapeutics thus number of either required, type of vaccine or therapeutic procurement (government-, private sector- or donor-purchased), as well as cold chain requirements for storage and maintenance. Optional submodules may be needed to address local or regional needs. As high vaccine effectiveness and	A well-developed cost-of-distribution model will ensure widespread access to vaccines and therapeutics and extensive coverage of the population that needs the vaccine or medicine.[79] This is particularly important in resource-constrained countries where scarcity may result in limited access to vaccines and therapeutics if an adequate distribution model is not available. In accessing the cost-of-distribution, the appropriate vaccine strategies and well-designed treatment protocols need to be considered to optimize both outcomes and costs.

	uptake are important for successful vaccination programs, so are effective treatment protocols to disease management. Vaccination programs and treatment protocols aim to reduce infections by achieving high immunity and recovery levels in the target population. These strategies consider the health system, funding and means of monitoring successes, in addition to the logistics.[80] Mathematical models can help make inferences about the spread of infections, the extent of vaccination and treatment coverage and the appropriate strategy required for cost-effective infection prevention and control programs to be financed and implemented logistically.[80]	
EVD-specific economic analytics		

Dynamic transition modeling (DTM)	Dynamic models show how the risk of infection to susceptible individuals who are uninfected is reduced if an intervention reduces infectiousness in the population.[60] This is possible because dynamic models are more reflective of infectious diseases, expressing infection rate as a function of the number of persons infected in the population.[63]	Dynamic transition models reflect the extent to which continuing infection in the population is dependent on the presence of herd immunity. DTM gives a better economic evaluation of infectious diseases as it accounts for the indirect benefits of the intervention.
Expected value of information (VOI) analysis	Decisions based on economic evaluation using existing information will be uncertain and may thus be a “wrong” decision, resulting in costs with respect to forgone health benefits and resources.[81] VOI analysis estimates the value of collecting more information on key parameters that influence a decision, in terms of health costs and outcomes. This ensures reduction in the uncertainty of parameters and increase the chances of making right decisions.[82]	VOI analysis are important for providing information on the consequences of wrongly adopting an intervention. This is important in the management of infectious diseases where the probability of infectious is a direct function of how many people are infected and where there may be indirect benefits of the interventions. Analyzing addition information when dealing with

		infectious disease interventions may be worth the cost for generating dependable evidence for decision making.
Actuarial analysis	This involves the use of epidemiological and statistical methods, as well as information about expenditure on given programs from populations in past or present periods, to estimate future spending in such programs for comparable populations.[83] In actuarial analysis, financial uncertainty as a result of a program is estimated and solutions are subsequently formulated to mitigate these financial challenges, particularly within health insurance settings.	For infectious disease interventions, there remain substantial uncertainties where the financial impact is concerned. While governments may contemplate the uptake of these programs as part of their health provision and insurance companies may consider their coverage in benefit plans, a well-conducted actuarial analysis will prove valuable in given evidence to support such decision making.
	EVD Macroeconomics	
Economic impact model (standardized, comparative)	Economic impact analysis of diseases, a complement to the epidemiological assessment of	There are substantial heterogeneities in the methods for the conduct of such analyses,

	disease burden, addresses questions related to the micro-economic effects (related to households, firms, etc.) and macro-economic effects (aggregated effects on country's gross domestic project and future economic potential) that a disease may have. Economic impact modeling takes on a wide approach account for both direct and indirect (social welfare) costs, as well as other susceptible economic components such as consumption of good and services within a jurisdiction. An impactful economic impact model needs to be clear and consistent about which domains of economic welfare need to be captured.[84] An economic impact analysis that is comparative in nature must also be explicit in terms of comparators and the approach	with many conceptual shortfalls.[84] A defined conceptual framework within which the economic impact of infectious diseases can be estimated appropriately, coherently and consistently is important to enhance the understanding of the rather multi-faceted impact of such diseases in populations.

	(prevalence-based or incidence-based) that would be useful for addressing the underlying questions.	
Return on investment analysis (ROI)	This is a form of cost analysis that gives an indication of financial implications of an intervention from the perspective of a given payer.[83] ROI is estimated as the ratio of net benefits to costs and often incorporates data on the cost of infections avoided, economic and productivity benefits as well as societal benefits derived from the program.[85,86] The chosen perspective for an ROI is critical to the process as an analysis from a perspective other than the intended payer may not fully reflect the estimated returns and may render an intervention valuable where it may actually not be to the payer, and vice versa.	ROI analyses are instrumental in determining what is considered a "wise" use of resources in health care especially where there are several competing needs.[85] In decision making for the adoption or otherwise of an infectious disease intervention, appropriate assessment of the ROI remains a valuable tool and standards for the uniform conduct of such analyses would be important for decision making across various infectious disease and resource settings.
Costing and pricing		

Cost minimization analysis (CMA)	In some instances, interventions are considered equivalent where outcomes are concerned. In such circumstances, the option with the lowest cost is said to represent greater value for money.[63] For CMA, the assumption of equivalent outcomes or effects means that an MDS may not necessarily include data on outcomes, while still incorporating data on costs - both direct and indirect expressed in disaggregated form, the perspective of the study, discount rates, as well as other inputs characteristic of economic evaluations.	Different interventions for infectious diseases may have outcomes that are equivalent. This may be particularly true for vaccines for which the ultimate outcome is the prevention of infections. CMAs hold an important place in the evaluation of infectious disease interventions, one that must be harmonized across disease types and populations to be effective.
Budget impact model	A budget impact model (BIM) is an economic model intended to estimate the short-to-medium term financial consequences of introducing new technology in a specific setting. [87] A typical BIM covers a period of 3 to 5 years. A "template-like"	BIM is important for budget planning and forecasting particularly where there is competition for limited resources.[87] In addressing EVD in LMICs, BIM is critical to ensure for predicting how the trajectory

	BIM for EVD needs to be constructed from the payer perspective and should account for the natural history of the disease, as well as the evidence regarding the vaccine.[88] Factors such as the population size, patient eligibility, units of analysis, market share and uptake of the vaccine need to be incorporated into this model. One or more appropriate comparators also needs to be chosen to help clarify how the condition changes with the introduction of the vaccine or therapeutic. An important element for BIM is transparency in the assumptions used for modeling.	of spending on EVD will change and also inform what manner of vaccination program needs to be adopted to effectively manage EVD.[88]
Independent outcomes-based contracting	Outcomes-based pricing is a type of value-based pricing that rewards a drug manufacturer based on outcomes generated from the intervention but guarantees a payback if stipulated outcomes are not	In order to prevent payers from spending large resources on expensive medications that may not be effective outside of clinical trials, outcomes-based contracting may

	achieved.[83] In this equivalent of a rebate approach, the payer is responsible for analyzing all relevant data and determining if the outcome thresholds are met. This introduces a system in which effectiveness is rewarded and innovation is encouraged.[90]	offer the opportunity for the use of these new drugs in selected populations with a guarantee of paybacks should acceptable outcomes not be met. This is particularly important where comparators may not exist. In decision making about interventions for infectious diseases (particularly emerging infectious diseases), this approach to pricing interventions offers valuable benefits. The use of independent platforms that incorporate stakeholder interests, and promotes transparency, information sharing, and inclusivity potentially provides an unbiased means of assuring access to and enhanced intervention coverage.[89]

Classical pharmacoeconomic methods		
Cost-effectiveness analysis (CEA)	CEA compares interventions in terms of the costs in monetary units and outcomes in quantitative non-monetary units, e.g., reduced mortality or morbidity.[63] CEA has better appeal among doctors since the estimation of outcomes in natural units are easier to interpret. Basic rules related to identification of cost-effective options are typically applied in cost-effectiveness analyses and these involve the calculation of incremental cost-effectiveness ratios and the use of cost-effectiveness planes. A good cost-effectiveness analysis incorporates a clear objective, alternatives being compared, a definition of any constraint in terms of health care budget, definition of outcome(s) being	Economic evaluation of infectious disease interventions that apply CEA need to be well-structured and evidence based. Model inputs need to be obtained from appropriate sources and the model correctly structured to incorporate all the distinct epidemiological characteristics of the disease in question. To better enhance the use of the results of a CEA for infectious diseases, the conduct and communication of such analyses need to be formalized and synchronized across all infectious disease types.

	assessed, costs of interventions, study perspective, as well as other optional study inputs.[57]	
Cost utility analysis (CUA)	CUA, like CEA, compares interventions in terms of costs and outcomes. However, in CUA, outcomes are quantified in utilities, usually from the patients' perspective, and measured in more generic metrics such as the QALY. This allows for comparison across different interventions.[63,91] The choice of a suitable generic measure is of particular importance.	CUAs are instrumental for evaluating interventions for infectious diseases, particularly in LMICs. Issues with choice of outcome metrics are, however, worth considering.
Cost benefit analysis (CBA)	CBA compares costs and benefits, both of which are quantified in common monetary units. This type of analysis aims to value a range of outcomes of an intervention or policy change, subsequently comparing it to resource costs as a form of test of the compensation.[63] As with other forms of economic evaluations, an MDS for CBA should	A CBA evaluates the value of the consequences of interventions being assessed in terms of the monetary remittance to be paid for avoiding a cost or assessing this benefit. In LMICs, a streamlined approach to CBAs would be an

	include the comparators of interest, perspectives, outcomes, cost inputs, as well as a choice between marginal or actual costs. Time horizon for this analysis, as well as the discount rate to be applied are also critical to the conduct of a CBA.[63]	important addition to the "toolbox" for economic evaluations.
Technical development		
Outcomes – standardized natural units and generic units	Outcomes quantify the usefulness of the healthcare program being assessed. Natural units such as deaths averted, as well as more generic options such as quality-adjusted life years may be used. While one-dimensional metrics may not be easily combined or compared across individual studies, more generic outcomes may be challenging for interpretation and may not reflect outcomes of value to patients or the population under study.[83] There is a need to develop standardized outcomes measures that reflect	Choosing the right outcomes, which have been standardized for specific diseases and specific settings, ensure that the impact of diseases is adequately estimated and also help to appropriately assess the impact of interventions.

	intended outcomes especially for infectious diseases in LMICs.	
Utility weights	Utility weights, defined as the strength of preference for a given health state, are used to account for quality adjustments of survival for different health states in estimating quality adjusted health states. While much research has gone into the determination of such utility weights in high-income countries, this has not been the case for LMICs.[92] It is of note that the use of weights derived from preferences of people from different cultures or societies and the variances in how these weights are derived can significantly impact the resulting economic evaluations. The concept of multi-criteria decision analysis (MCDA) has been proposed for use in LMICs.[92] MCDA involves the use of several	In LMICs where there are scarce resources and high disease burden, there is an marked need for population-specific utility weights conducting health care economic evaluations. MCDA may be an appropriate approach to economic evaluations in LMICs since it provides a structure in which decision-making is transparent and consistent and where all relevant stakeholders are involved in the decision-making process.[94,95] MCDA has the potential to improve decision-making in LMICs by providing a systematic setting which can lend itself useful in the complex,

	criteria, which are evaluated and combined, and subsequently used to rank competing alternatives. MCDA requires explicit weighting of these criteria and the trade-offs between them for all alternatives under consideration.[93]	LMICs setting that are marked by complexities due to limited evidence, fragile capacities and the influence of multiple policy makers and international donors.[94]
Sensitivity analysis	Estimates of variables used in any cost evaluation (costs and outcomes) are often ridden with uncertainties, an element that could cause potential variations in evaluation results. Sensitivity analysis aims to determine the possible variations in these estimates and to assess the confidence level associated with conclusions drawn from the evaluation. Sensitivity analysis involves varying the values of input parameters and altering initial structural assumptions of the economic analysis and	To determine the robustness of the findings of an economic evaluation, it is important that an efficient sensitivity analysis that is able to vary the key parameters of the evaluation be conducted. This also helps to assess the need or otherwise for the collection of addition information before a decision is taken. In economic evaluations, the value of sensitivity analysis cannot be underestimated and a standard approach for this analysis under varies conditions of

	can be conducted in several ways depending on the type of economic evaluation being conducted.[96]	economic evaluation will be enhance its usefulness in economic analyses.
Evidence synthesis	Simultaneously considering the findings of multiple studies may provide more wholesome information for decision making compared to interpreting the findings of these studies individually. Shemilt *et al.* identified systematic reviews, along with other summaries of published evidence and decision modeling as two broad approaches to evidence synthesis for policy information.[97] There are several variants of these methods. Information needs, search strategies and resource selection need to be well specified for evidence synthesis to be conducted effectively.	Economic evaluation must reflect pertinent evidence, and this is important for infectious disease evaluations in which there may be several estimates of parameters from multiple trials. With the emergence of infectious diseases comes the proliferation of several trials in a bit to promptly halt their spread. Transparent and efficient evidence synthetic methods with associated interpretation would foster evaluations, the findings of which would support infectious disease decision making.

CHAPTER 3

ARTICLE 2

Economic evaluation using dynamic transition modeling of ebola virus vaccination in lower-and-middle-income countries

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3.1 Abstract

Background

With increasing occurrence of infectious diseases in lower-and-middle-income countries (LMICs), emergency preparedness is essential for rapid response and mitigation. Economic evaluations of mitigation technologies and strategies have been recommended for inclusion in emergency preparedness plans. We aimed to perform an economic evaluation using dynamic transition modeling of ebola virus disease (EVD) vaccination in a hypothetical community of 1000 persons in the Democratic Republic of Congo (DRC).

Method

Using a modified SEIR (Susceptible, Exposed, Infectious, Recovered, with Death added [SEIR-D]) model that accounted for death and epidemiological data from an EVD outbreak in the DRC, we modeled the transmission of EVD in a hypothetical population of 1000. With our model, we estimated the cost-effectiveness of an EVD vaccine and an EVD vaccination intervention.

Results

The results showed vaccinating 50% of the population at risk prevented 670 cases, 538 deaths and 22022 disability adjusted life years (DALYs). The vaccine was found to be cost-effective with an incremental cost-effectiveness ratio (ICER) of $95.63 per DALY averted. We also determined the minimum required vaccination coverage for cost-effectiveness to be 40%. Sensitivity analysis showed our model to be fairly robust, assuring relatively consistent results

even with variations in such input parameters as cost of screening, as well as transmission, infection, incubation and case fatality rates.

Conclusion

EVD vaccination in our hypothetical population was found to be cost-effective from the payer perspective. Our model presents an efficient and reliable approach for conducting economic evaluations of infectious disease interventions as part of an emergency preparedness plan.

Keywords: Dynamic modeling, emergency preparedness, ebola virus disease, vaccination, cost-effectiveness

3.2 Introduction

Despite the availability of measures to prevent them, a wide range of hazards continue to afflict public health the world over; necessitating timely and effective response and mitigation.[98] It is in this light that emergency preparedness – “the knowledge, and capacities and organizational systems developed by governments, response and recovery organizations, communities and individuals to effectively anticipate, respond to and recover from the impacts of likely, imminent, emerging or current emergencies” – emerged.[99] In fact, countries are requested to develop and maintain a process in which action, funding, partnerships and commitments exist at all levels to minimize the risks posed by such emergencies and to attenuate their impact.[98] The immense global consequences of the coronavirus disease (COVID-19), along with other outbreaks such as *inter alia*, ebola virus disease (EVD) and measles, spotlight the emergency prospects of infectious diseases. Emergency preparedness aimed at establishing systems and plans for early detection and effective response are, thus, critical for managing infectious disease outbreaks.[99] By virtue of their demographic, geographic, epidemiologic, and socio-economic characteristics, low-and-middle-income countries (LMICs) are more vulnerable to infectious disease outbreaks.[101,102] While all countries are struggling with increasing trends in various communicable and non-communicable disease, the burden is disproportionately higher in LMICs where diseases such as HIV/AIDS, malaria, tuberculosis, EVD, among others, persist with high mortality rates.[100] A complicating factor in the case of infectious diseases in LMICs is that there are often multiple simultaneous outbreaks for health systems to surveille, respond to, and contain using limited resources. With several priorities competing for these constrained resources, it is important that effective preparedness plans be in place for efficient infectious disease prevention and management. Research examining emergency preparedness in low-resource settings is, however, minimal.[103] Studies that have examined various forms of emergency preparedness in these settings have evaluated the resources available in the event of natural disaster, proximity to healthcare services in the event of a health crisis, and preparedness for infectious disease outbreaks, specifically of COVID-19.[103-105] These studies, though diverse in scope, all conclude that there are limited resources available to locals and health professions in the occurrence of an emergency situation, which inevitably leads to poorer outcomes for those affected and places greater burdens on already strained healthcare systems. [103-106]

Reacting to an ongoing outbreak, rather than preparing for it, places yet another strain on the healthcare system that results in increased costs to manage the outbreak that might have been better used in preparing for it. To respond rapidly to outbreaks, several components must be incorporated into an effective plan, most of which are usually lacking in LMICs and pose threats to the development and implementation of such plans. Sustainable resources are required for developing capacities such as surveillance, diagnostics, training, equipment and supplies, human and logistic resources, etc., with all readiness actions closely tied to sufficient contingency financing.[100] A pertussis outbreak in Ethiopia highlighted the lack of important infrastructure to properly investigate and manage outbreaks in low-resource settings.[107] In addition to finances, there is the need for structured and reliable evidence to inform public health decision making in the development of a preparedness plan. [100] Furthermore, reflections on the Ebola outbreak suggest that community engagement and relative socio-political stability, as well as emphasis on the cultural practices that underlie disease transmission and the latent health of at-risk populations contributing to the increasing burden of the infectious disease are essential toward ending the outbreak.[108] An emergency preparedness plan, therefore, ought to rely on a systematic evidence-based approach that considers all contingencies for informing decision-making and efficient implementation.

Miglietta and colleagues propound that health technology assessment (HTA) provides reliable evidence and is valuable for developing emergency preparedness plans.[100] In their perspective on emergency preparedness, they propose how HTA domains can address different components of a preparedness plan and ultimately be used for populating the plan, allowing stakeholders to put together a systematic and robust tool for timely emergency management. According to their recommendations, the costs and economic evaluation domain of HTA is instrumental for addressing resource utilization for case finding and management, as well as assessing the cost-effectiveness of different health technologies intended for use in outbreak situations. This approach offers evidence in support of choices related to prevention, diagnosis, treatment, and response options.[100] Especially in the case of insufficiently understood diseases, such decisions need to be made rapidly and as best as possible to ensure maximum impact. The lack of cost benefit evidence justifying inclusion of EVD vaccination into routine vaccination[109] speaks particularly to this issue. Given no consensus on the most cost-effective vaccination approach for EVD, Bausch put forward a vaccination strategy that combines various existing approaches such as widespread routine vaccination of healthcare workers and those at high risk, population-based vaccination campaigns during outbreaks, targeted vaccination of sex partners of male survivors and a possible expansion of the target population after outbreak is declared over.[109] While such a strategy may be useful over a long period, it may be limited by time, which is critical especially for highly contagious and fatal infectious diseases. In this case an emergency preparedness plan can facilitate a quick decision on the most appropriate choice and help distribute resources towards other priority areas.

The frequency of infectious disease outbreaks in low-resource settings and the financial and human resource burdens that these outbreaks bring present an opportunity to identify mechanisms that encourage surveillance and support preparedness efforts within the limitations that are often present in LMICs. There is a lack of literature on ways to support emergency preparedness, particularly for infectious disease outbreaks, in a way that leads to empowerment of local leadership and healthcare systems to build capacity that leads to a more informed response when an outbreak occurs. We aimed to develop a dynamic transmission model (DTM) to determine the cost-effectiveness of (a) an EVD vaccine and (b) a vaccination program at large in hypothetical population of 1000.

3.3 Methods

3.3.1 Overview

We used a dynamic compartmental model to estimate the cost-effectiveness of vaccinating a proportion of the population compared to a base scenario of no vaccination for a hypothetical population of 1000. We used the size of 1000 to reflect the relatively small proportion of the entire population who are mostly at risk of the infection during a given outbreak; while also providing a base count from which multiples can be estimated as needed for larger populations. The population size of 1000 also recognizes that, in the case EVD, outbreaks often originate in more isolated rural areas.[110] Our choice of model allowed us to account for the force of infection while also incorporating the indirect benefits of vaccination in the form of herd immunity. We based our model on the epidemiological data obtained from an EVD outbreak in the Democratic Republic of Congo (DRC).[111] Given that the mean length of an EVD outbreak is about 10 months,[112] and the uncertainty of waning vaccine effectiveness, along with the possible emergence of new outbreaks and variants, we limited the time horizon to one year.

We considered effectiveness in terms of infections, deaths, and disability adjusted life years averted (DALYs). We based our estimation of DALYs on the median population age of 19.2 years[113] and life expectation of 60.97 years in DRC,[114] accounting for no variations in the ages of patients. The analysis takes a payer perspective with the objective of assisting payer organizations and funders assess potential investments for an emergency preparedness plan and informing donor and payer decision making. For this study, the payer is defined broadly as any organization, government or third party who purchases and pays for the EVD vaccine on behalf of the end user. This perspective is to reflect the dependence on government and donor funding in LMICs where vaccination programs are concerned as several literature have shown.[115-117]

3.3.2 Intervention: Vaccination

With the approval of two vaccines against EVD,[109] and the commencement of vaccination in DRC,[118] we chose vaccination as our intervention of choice. The role of vaccination in our model was two-fold: first, to consider the counterfactual ideal of how vaccination would impact disease transmission in our theoretical population and second, to quantify the economic impact of vaccination by comparing the cost of disease transmission through the population with and without vaccination. Data on vaccine effectiveness was obtained from published literature, while the proportion to be vaccinated was estimated based on the herd immunity threshold using the formula:

$$\text{Herd immunity threshold} = 1 - \frac{1}{R_0}$$

where R_0 is the basic reproductive number.

Given a herd immunity threshold of 45.3%, vaccination coverage proportion for this model was set at 50%.

3.3.3 Dynamic Transmission Modeling

We used the SEIR-D, a modification of the standard SEIR model in which we incorporated death as a final state in our model (Figure 1). Transition probabilities from one state to another were determined by epidemiological parameters obtained from published literature. We converted rates and durations into probabilities and further scaled down all probabilities to daily cycle probabilities. Rates were obtained from durations by taking the inverse of the durations in days while rates were converted into daily probabilities using the formula:

$$p = 1 - e^{-rt}$$ [119]

where *r* is the rate and *t* the duration in days.

The population at risk moves to or through one of the following possible states: susceptible, exposed, infected, recovery or death. We accounted for the infectious nature of the disease with transitions from one state to another being dependent on the number of infected persons in the model at each cycle. To keep the model tractable, we conservatively assumed that individuals moved linearly in this model with infected individuals either recovering or dying. Our model did not allow for re-infection, nor did it account for population changes that were not a direct result of the disease (i.e., births, all-cause mortality, immigration, and emigration). Given that the mean duration of the epidemic was 200 days,[112,120] we allowed the model to run over a period of 1 years or 365 days to populate the states of the model.

Following compartmental modeling concepts,[120] the following modified differential equations, that account for a separate death compartment, were used for modeling:

$$\mathrm{S(t)} = \frac{-\beta S(t) I(t)}{N}$$

$$\mathrm{E(t)} = \frac{\beta S(t) I(t)}{N} - \xi\, \mathrm{E(t)}$$

$$I(t) = \xi E(t) - \gamma I(t)$$

$$R(t) = \delta I(t)$$

$$D(t) = \mu I(t)$$

$$N = S+E+I+R+D$$

$$\gamma = \delta + \mu$$

where N is the population, S is the number of this population susceptible, E is the number exposed, I is the number infected, R is the number who recover from the infection and D is the number who die from the infection. We assumed an initial population size of 1000 with 1 infected patient. Susceptible persons become exposed at a rate of $\beta I/N$ where β is the transmission rate and I/N represents the probability of contact with an infected person. Given an incubation period of $1/\xi$ days in which exposed persons are assumed not infectious and asymptomatic, exposed persons move into the infected compartment at a rate of ξ per day. Infected persons either recover at a rate of δ or die at a rate of μ per day.

3.3.4 Cost-effectiveness Analysis

We estimated the cost per infections averted, cost per death averted, and cost per disability adjusted life year (DALY) averted. Infections and deaths averted were defined as the number of infections and deaths, respectively, that would have happened in the absence of the intervention and was calculated as the number of infections and deaths among the unvaccinated cohort minus the number of infections among the vaccinated cohort.

Using the equation for calculation of DALYs,[121,122] we estimated DALYs as the sum of years of life lost (YLL) and years of life lived with disability (YLDs). We obtained disability weights from the Global Burden of Disease Study 2015 (GDB, 2015). Formulas used for DALYs calculation are given below:

$$\text{DALY} = \text{YLL} + \text{YLD}$$ [121,122]

$$\text{YLL} = ((1\text{-}K)/0.00000001) * (1\text{-}\exp(-0.00000001*\text{YLL\_L}))$$ [121]

$$\text{YLL discounted} = \text{YLL}*\exp(-(0.00000001*s))$$

$$\text{Population YLL discounted} = \text{YLL discounted}*\text{incident deaths}$$

$$\text{YLD} = D*(((1\text{-}K)/0.00000001) * (1\text{-}\exp(-0.00000001*s)))$$ [121]

$$\text{Population YLD} = \text{YLD}*\text{incident cases}$$

where K is the age weighting modulation factor (0 if no age weighting modulation factor is used); YLL_L is the life expectancy at age of death; s the average age at premature death due to disease minus average age at disease onset; and D the disability weight.

Costs of treatment, screening, and vaccination were obtained from published literature. The cost of vaccination comprised the price of the vaccine as well as the composite cost of administration. Given that the vaccine price is unknown, we employed estimations of the total cost of vaccination from the World Health Organization (WHO)[123] and the United Nations Children's Emergency Fund (UNICEF). [124] All costs were converted to 2021 USD using the US Consumer Price Index for Medical Care.[125] With the assumptions that all persons in the model, except those who die, would be screened, all those who are infected will be treated, and a proportion of the susceptible population will be vaccinated for the vaccine model, we obtained total costs of screening of EVD, treating a case of EVD, and vaccinating an individual against EVD. Since we modeled this disease over a one-year period, no discounting was applied for either costs or outcomes.

Incremental cost-effectiveness ratios (ICER) for all outcomes of interest were calculated using the formula:

$$\text{ICER} = \frac{Total\ cost\ of\ outbreak\ with\ vaccination - Total\ cost\ of\ outbreak\ without\ vaccination}{Total\ outcomes\ with\ vaccination - Total\ outcomes\ without\ vaccination}$$

Using the WHO-CHOICE recommendations for cost-effectiveness,[126] we considered the intervention highly cost-effective if the ICER per DALY averted was less than 1*gross domestic product (GDP) of the country and cost-effective if the ICER per DALY averted was less than 3* GDP.

3.3.5 Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of our model. In one-way sensitivity analyses, we varied model input parameters individually from low to high values, with all other variables fixed. Parameter ranges were based on 95% CIs, in the absence of which parameters were varied by +/- 10% of their point estimates. Results for these one-way analyses were presented in line plots showing how the ICER per DALY averted changes with varying parameters as well as compiled in a tornado plot.

In two-way sensitivity analyses, we assessed the effects of linearly increasing vaccination coverage in the population and the other parameters (one at a time) on the ICER per DALY averted. The results of these analyses were presented in heat maps.

We conducted probabilistic sensitivity analyses (PSA) using simultaneous random sampling from estimated probability distributions for uncertain parameters. A total of 1000 Monte Carlo simulations were run, allowing for quantification of combined uncertainties. The results were visually presented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEAC) over a range of different willingness to pay (WTP) thresholds. Where available, ranges for the input parameters were based on 95% CIs or standard errors (or computed from standard deviations) and where these were not reported, varied by +/- 10% of the point estimates. We used gamma distribution for the cost parameters, beta distribution for utility and probability parameters, and lognormal distribution for the vaccination proportion parameter. The baseline values, ranges, and distributions of model parameters are presented in Table 1.

3.4 Results

3.4.1 Health Outcomes

From our analysis, vaccinating 50% of the 1000 people susceptible to EVD infections will prevent an estimated 670 infections (or 99.3% of expected infections without vaccination) and 538 (or 99.1% of expected deaths without vaccination) deaths, while also averting a total of 22022 DALYs (or 99.2% of expected DALYs without vaccination), corresponding to 22.022 DALYs per person)(Table 2).

Figure 2 shows the dynamics of the movement of the 1000 persons within each of the 5 SEIR-D compartments without (panel A) and with vaccination (panel B). Without vaccination, the Susceptible population is projected to decline from the initial 999 to about 300 at 200 days, at which time it reaches asymptote. Simultaneously, the population projected to Die due to EVD increases rapidly from zero, crossing the Susceptible curve at 149 days, and reaching asymptote at 535 Deaths at 215 days. Of the population of 1000 subjects, only 135 are projected to have Recovered from infection at the end of the outbreak. At that time, in descending order, the population of 1000 either have Died (54.3%), remain Susceptible (32.3%), or have recovered (13.5%).

Conversely, with vaccination of 50% of the population, 499 persons are no longer susceptible. The entire population appears to reach asymptote by day 50, with 5 (0.5%) persons becoming infected over the period, 4 of whom die (0.4%).

3.4.2 Base Case Cost-effectiveness Analysis

The results of the base case analysis are presented in Table 3. The vaccination program resulted in increased total costs while decreasing infections, deaths, and DALYs. While a total cost of $4,723,258.42 was expected from not vaccinating in the population, vaccinating 50% of the population cost a total of $6,804,616.21. As indicated by the ICERs, preventing each additional infection, death or DALY was estimated to cost $3,100.64, $3,869.0, and $94.51, respectively.

3.4.3 One-way sensitivity analyses

In these analyses, the ICER of DALYs averted was found to be a function of vaccine efficacy, vaccination coverage, vaccine cost, screening cost, treatment cost, and population size, (Figure 3, panels A through F). The ICER per DALY averted declined steadily from vaccine efficacy of 20% to 40% and decreased sharply to 80% after which it remained constant over increasing vaccine efficacy. Similarly, ICER declined rapidly from a vaccination coverage of 20%, reaching its lowest value at a coverage rate of 45% which coincides with the herd immunity threshold, and rising marginally at higher rates of vaccine/vaccination coverage (Panel B). With increasing costs of vaccination (Panel C) and screening (Panel D), ICER per DALY averted increased linearly, while it decreased with increasing cost of treatment (Panel E). The ICER per DALY averted also declined gradually with increasing population size (Panel F).

Figure 4 presents a tornado diagram showing the results of the one-way sensitivity analysis for the cost-effectiveness analysis in terms of DALYs averted. The center line represents the baseline ICER of $95.62 per DALY averted. Results of our model were most sensitive to the cost of screening for EVD and the transmission rate; with the infectious and case fatality rates exerting a modest influence. The cost of vaccination, proportion of vaccination coverage, and vaccine efficacy had minor influence on the results of our model.

3.4.4 Two-way sensitivity analyses

The heat maps in Figure 5 depict the ICER for DALYs averted as a function of vaccine coverage under various scenarios of vaccination cost, vaccine efficacy, screening cost, population size, and treatment cost. Dark green indicates the highest cost-effective scenarios, dark red the least cost-effective scenarios, and yellow modestly cost-effective scenarios, with variations in these colors' shades reflection areas of relative upward or downward transitions in cost-effectiveness.

Panel A shows changes in cost-effectiveness with simultaneous change in vaccine efficacy and vaccination coverage. Vaccinating 20% or less of the population and vaccine efficacies of 20% and below results in the least favorable ICERs per DALY averted. As both coverage and efficacy increase, ICERs increase to highest cost-effectiveness with coverage of 100% and efficacy of 40% or coverage of at least 40% and efficacy of 100%. Vaccinating the entire population at risk using a vaccine with efficacy beyond 60%, just like vaccinating more than 60% of the population at risk with a fully efficacious vaccine results in slightly decreased cost-effectiveness.

Considering the cost of vaccination (panel A), a cost of zero (unsurprisingly) yields the best ICER at vaccine coverage of 45-50%. At costs of $50 and, slightly less so, of $100 the increase in ICER is marginal. Unless the cost is zero and coverage is at least 40%, the ICER estimates are highly cost-effective though with a slight diminishing return at vaccination rates exceeding 50%. Higher vaccine costs and higher vaccination coverage are less cost-effective. Vaccination rates less than 20% are least cost-effective. Similar to how ICERs vary with the cost of vaccination, costs of screening at 0 were the most cost-effective scenarios. Irrespective of the vaccination coverage, screening costs above $25 are least cost-effective while there is increasing cost-effectiveness with decreasing cost of screening (Panel C). With varied treatment costs (Panel D) and population size (Panel E), cost-effectiveness is least when coverage is below 40%. The vaccination program approaches more favorable levels of cost-effectiveness with increasing treatment cost of about $80 and population size of 2500 and increases to most favorable as these increase.

3.4.5 Probabilistic sensitivity analysis

The results of the PSA are shown in the ICER planes (Figure 6; northeast quadrant of better outcomes at higher costs only) for the outcomes of infections and deaths (panel A) and DALYs everted (Panel B) and the CEAC (Figure 7). Figure 6 reveals clustering of simulation results in the lower region of the northeast quadrants, an indication of the cost-effectiveness of vaccinating compared to not vaccinating in terms of infections, deaths, and DALYs averted. In terms of the latter, there was no probability of cost-effectiveness below a WTP threshold of $65, beyond which the probability of cost-effectiveness steadily increases. Vaccination demonstrated 100% probability of cost-effectiveness at a WTP threshold of approximately $175 per DALY averted.

3.5 Discussion

While several studies have evaluated the impact of an EVD vaccine, ours assesses the cost-effectiveness of an EVD vaccine in terms of infections, deaths, and DALYs averted. Summarized, we evaluated the cost-effectiveness of an EVD vaccine in a hypothetical town with a population of 1000 using epidemiological data from the DRC. Using a vaccine of 100% effectiveness and assuming coverage of 50%, a vaccination program would be cost-effective from a payer perspective in terms of infections, deaths, and DALYs prevented. In our model, EVD vaccination reduced infections, deaths as well as DALYs by about 99%. At a mere incremental cost of $94.51, EVD vaccination averts 1 DALY, proving to be highly cost-effective per the WHO recommendation. With about 22000 DALYs averted in a population of 1000, this means that, on average, vaccination grants each of the 1000 persons an additional 22 life years free of EVD-related disability – arguably, an unmeasurable human, economic, and societal benefit. Thus, although vaccinating a proportion of the population against EVD requires extra investments, these the additional costs are largely offset by the benefits in terms of prevented infections, deaths, and DALYs. More generally, both our model and the results of our analyses provide stakeholders, policy makers and payers in particular, a readily available and easily interpretable approach to assessing the impact of a vaccine in anticipation of an outbreak and would be instrumental for rapid resource allocation decision-making in such an event.

Extensive sensitivity analyses were conducted given that there were several uncertainties. For example, vaccine coverage is considered an important determinant of cost-effectiveness.[127-129] To assess its effect on our model, sensitivity analyses demonstrated that increasing coverage translates into greater cost-effectiveness critically, the highest cost-effectiveness was observed at a coverage equivalent to the herd immunity threshold of about 45%. This underscores economically that EVD vaccination is not only cost-effective, but also the most cost-effective right at the herd immunity threshold – a double win. Further, this finding is in line with other studies in which cost-effectiveness of vaccines have been seen to be optimized at the coverage level required to attain the herd immunity threshold; that is, the level of coverage at which vaccination confers indirect protection on the population and beyond which scarcely any incremental impacts on cases averted are achieved.[128,130] Conversely, as our findings also show, there is a diminishing return in terms of vaccination outcomes when vaccination beyond the herd immunity threshold.

In the case of EVD, a highly fatal yet rare disease with an infinitesimally low risk of infection at the general population level if outbreaks are geographically contained, our findings provide compelling support for the assertion by Bausch that there is no evidence for including vaccination against EVD into routine vaccination of populations at large, even in endemic regions.[109] In addition to this, our findings reinforce Bausch's recommendation of immediate population-based vaccination as soon as an outbreak occurs.[109] Further, our finding that the vaccine is not cost-effective at coverage levels below 40% is consistent with that of a study that analyzed the impact of vaccination against EVD in Sierra Leone.[131] In this study, Bodine and colleagues concluded that a vaccination coverage of 40% is sufficient to prevent the catastrophic effects of an outbreak. [131]

Of note also, is the inelasticity of vaccination in terms of cost-effectiveness. As the sensitivity analysis showed, variations in the cost of vaccination have minimal effect on the ICER per DALY averted. Even at cost of vaccination as high as $250, the increase in the ICER to $99.40 to avert one DALY is low. Considering the economic impact of an outbreak of ebola, along with the inestimable burden of lives lost, influence on healthcare and the healthcare system, among others, there is a case to be made for vaccination even at high costs of vaccination. Huber *et al.* estimated the 2014 EVD outbreak to have caused loss in GDP ranging from $2.8 to %32.6 billion with a more comprehensive estimate of the economic and social burden pegged at a total of $53.19 billion.[132] In estimating the monetary value of human lives lost through EVD in DRC using the human capital approach, Kirigia and colleagues valued a life lost to EVD at Int$13,801 averagely. [133] The price of vaccination is minuscule compared to the burden in the absence of vaccination. In this light, our findings reinforce calls for timely vaccination in the event of an outbreak.

We see an increase in cost-effectiveness with increasing treatment cost for EVD. While this appears counterintuitive, it reflects the value of vaccination where the prevention of infections is concerned. In the absence of vaccination, more infections are projected to occur resulting in more costs for treating infected persons. With lower treatment costs, the value of the vaccine in terms of how much total costs it averts appears less substantial. As the cost of treatment increases, however, it becomes more apparent how infections averted translate into total costs saved by the vaccination program. This is particularly important for EVD where management also depends on the presenting symptoms[134] and thus varies across disease severity and setting. Another parameter examined in our sensitivity analyses was the size of the population. Since we assumed a hypothetical population, we queried the outcome of our model over a range of population sizes and found that increasing the population size results in lower costs for averting infections, deaths, and DALYs. In part, this reflects the base costs for launching a vaccination program. More importantly, though, this demonstrates the role of economies of scale in achieving cost-effectiveness. Larger populations require more vaccine doses to attain the target vaccination coverage, and this provides payers bargaining leverage for securing favorable vaccine prices and value for money. Our results, thus, buttress the attribution of economies of scale to vaccination programs in developing countries, [135] including in EVD vaccination and similar vaccinations that do not require vaccination at the general population level. Transmission rate is crucial to the cost-effectiveness of a vaccine, and this was evidenced also in in the one-way sensitivity analyses in our model. The force of infection, a measure of the rate at which susceptible individuals in a population contract the disease and a parameter dependent also on the transmission rate of the disease, drives infectious disease outbreaks. [136] Another driver of cost-effectiveness revealed in our analyses is the cost of screening. With the highly fatal nature of EVD and the potential for spread within the population at risk, screening is critical for infection prevention and control.[137,138] In the light of this, our model accounted for daily screening of all persons living in the population during the assessment duration. The impact in our model attributed to the cost of screening could be caused by the cumulative cost of this daily testing routine, which depending on the affected country's protocol, may differ from one population to another.

In terms of the effectiveness, our results align with those from previous studies. Vaccination provides significant benefit in preventing infections and deaths, and ultimately preventing or controlling a potentially catastrophic outbreak [34,42,43].[131,139,140] In their study modeling the daily risk of EVD in the presence and absence of a potential vaccine, Abo and Smith found that even at high transmission rates, a vaccine is effective at controlling an outbreak.[139] The efficacy of a vaccine and the proportion of people in the population receiving the vaccine are critical to the vaccine's effectiveness with higher proportions required to be vaccinated when less efficacious vaccines are used. [131,139] Potluri and colleagues found that benefits of EVD vaccination in terms of cases and deaths prevented increase with greater vaccine coverage, although this happens at a lower incremental rate.[140] Generally, vaccines are cost-effective, and help to ease the burden on the economies of affected communities[135] and our results lend further evidence in support. Note that vaccines against diseases such as influenza,[130] cervical cancer,[129] herpes zoster,[141] malaria,[127] and the recent corona virus (COVID-19)[128] have all been found to be cost-effective.

Our model is parsimonious but robust for conducting an economic evaluation of an infectious disease vaccine for inclusion in an emergency preparedness plan. The use of the DTM approach allowed us to account for the force of infection and the indirect effects of the vaccine.[142] This ensures that decisions made based on this model consider the entire scope of the benefits, expressed in natural as well as generic units, obtained from a vaccination program. Our model assessed both natural outcomes (infections and deaths) and a generic utility-based outcome

(DALYs). While natural outcomes are easier to understand and better appreciated, especially by decision-makers who are not economists, generic outcomes permit comparison of the cost-effectiveness of programs in other disease areas that may be endemic in the same population.[143] This is essential especially for LMICs where various outbreaks may be occurring simultaneously and where limited resources make such decision making even more crucial.

Despite these strengths, our study has some limitations. Like most models, it assumes a rather homogenous target population in its composition and characteristics. We did not consider background births, deaths, immigration, and emigration; in good part because we considered the zoonotic nature of EVD and outbreaks tending to be in often small isolated rural locations. We opted against highly granular models, as the gains in precision would have been offset by our aim to provide a parsimonious and workable model for integration into emergency preparedness Our study was from a payer as opposed to societal perspective, because we aimed to provide evidence mainly to donor organizations who typically pay for vaccines in LMICs. With no data on the waning immunity from EVD vaccination, we could not account for this factor. Using a time horizon of one year, we did not evaluate the benefits of the vaccine on the long-term (beyond one year) complications of EVD. The model did not account for other infection prevention methods that may reduce transmission and infection such as isolation and use of personal protective equipment. Future studies that account for these would be beneficial and help to better understand the effects of EVD vaccinations under various conditions.

3.6 Conclusion

In conclusion, EVD vaccination in our hypothetical population was found to be highly cost-effective from the payer perspective, with extensive sensitivity analyses underscoring our model's robustness and elucidating key determinants of vaccination-related outcomes. For fast response and mitigation of a potential infectious disease outbreak, the model presents an efficient approach for economic evaluations of vaccination programs for EVD and other infectious disease outbreaks as part of an emergency preparedness plan.

Table 3.1 Model input parameters – baseline values, ranges and distributions applied for sensitivity analyses

Variable	Value	Range*	Distribution	Reference
Population size	1000			Model assumption
Initially infected	1			Model assumption
Transmission rate (β)/day	0.330		beta	[111]
Incubation rate (ξ)/ day	0.190		beta	[111]
Infectious rate (γ) / day	0.180		beta	[111]
Recovery rate (δ)/ day	0.030		beta	Calculated
Case fatality rate (200 days)	0.810		beta	[111]
Case fatality rate / day	0.140		beta	Calculated
Basic reproductive number (R_0)	1.830		beta	[111]
Disability weight for EVD	0.133	0.139-0.298	beta	[144]
Vaccine efficacy	100%	79-100%	lognormal	[145]
Vaccine coverage proportion	50%			Assumed based on herd immunity threshold
Cost of vaccine bundle ($)	33.54		gamma	[123, 124]
Cost of vaccination kit ($)	17.26		gamma	[123, 124]
Cost of vaccine storage and management ($)	66.45		gamma	[123, 124]
Cost of screening ($)	18.49		gamma	[146]
Cost of treating a case of EVD	86.72	83.59-90.07	gamma	[147]
Personal cost for treating EVD case	6.16	5.96-6.37	gamma	[147]
Median age in DRC	19.2		Normal	[113]
Life expectancy of DRC	60.97		Normal	[114]

* Variables without published ranges were varied by +/- 10%.

Table 3.2 Infections, deaths and DALYs averted by vaccination in a population of 1000

Outcome	**No vaccination**	**Vaccination**	**Outcomes averted**	**Percentage reduction attributable to vaccination**
Infections	676	5	671	99.26%
Deaths	543	4	539	99.08%
DALYs	22209	187	22022	99.16%

DALY disability adjusted life year

Table 3.3 Results of base case cost-effectiveness analysis.

	Vaccination	**No vaccination**
Total cost	$6,804,616.21	$4,723,258.42
Incremental cost	$2,081,357.80	
Infections	5	676
Infections averted		671
ICER per infection averted		**$3,100.64**
Deaths	4	543
Deaths averted		539
ICER per death averted		**$3,869.05**
DALYs	187.29	22208.80
DALYs averted		22022
ICER per DALY averted		**$94.51**

ICER incremental cost-effectiveness ratio; DALY disability adjusted life year.

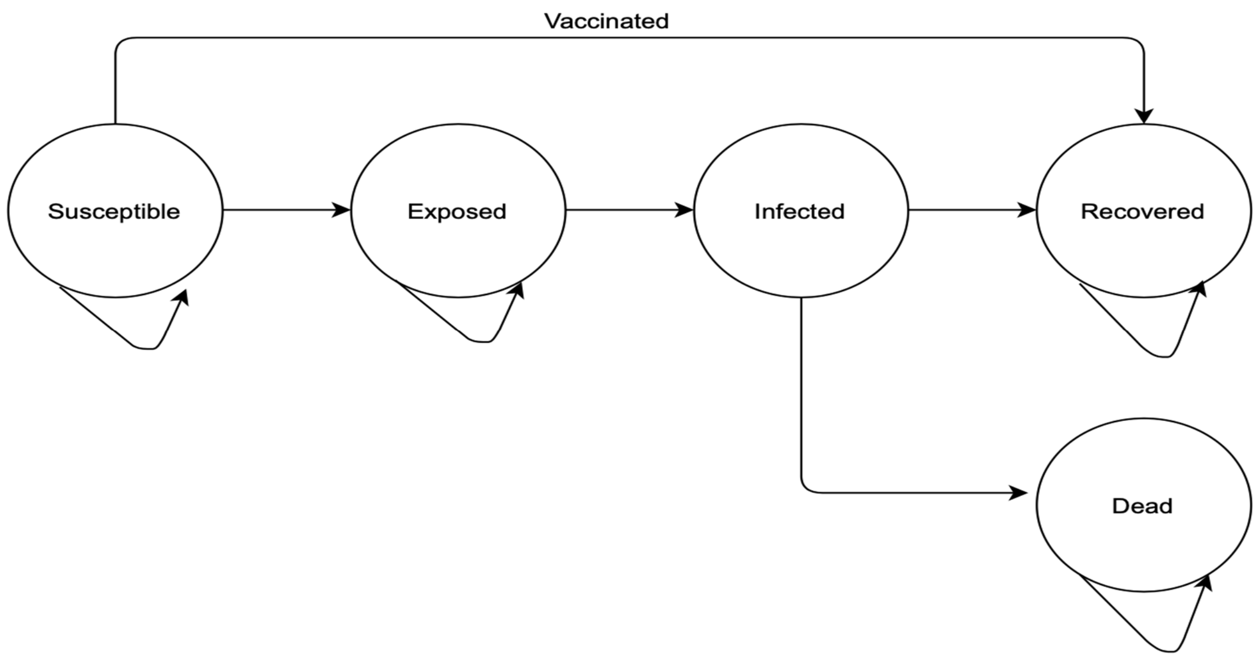


Figure 3.1 Schematic view of the dynamic transmission model.

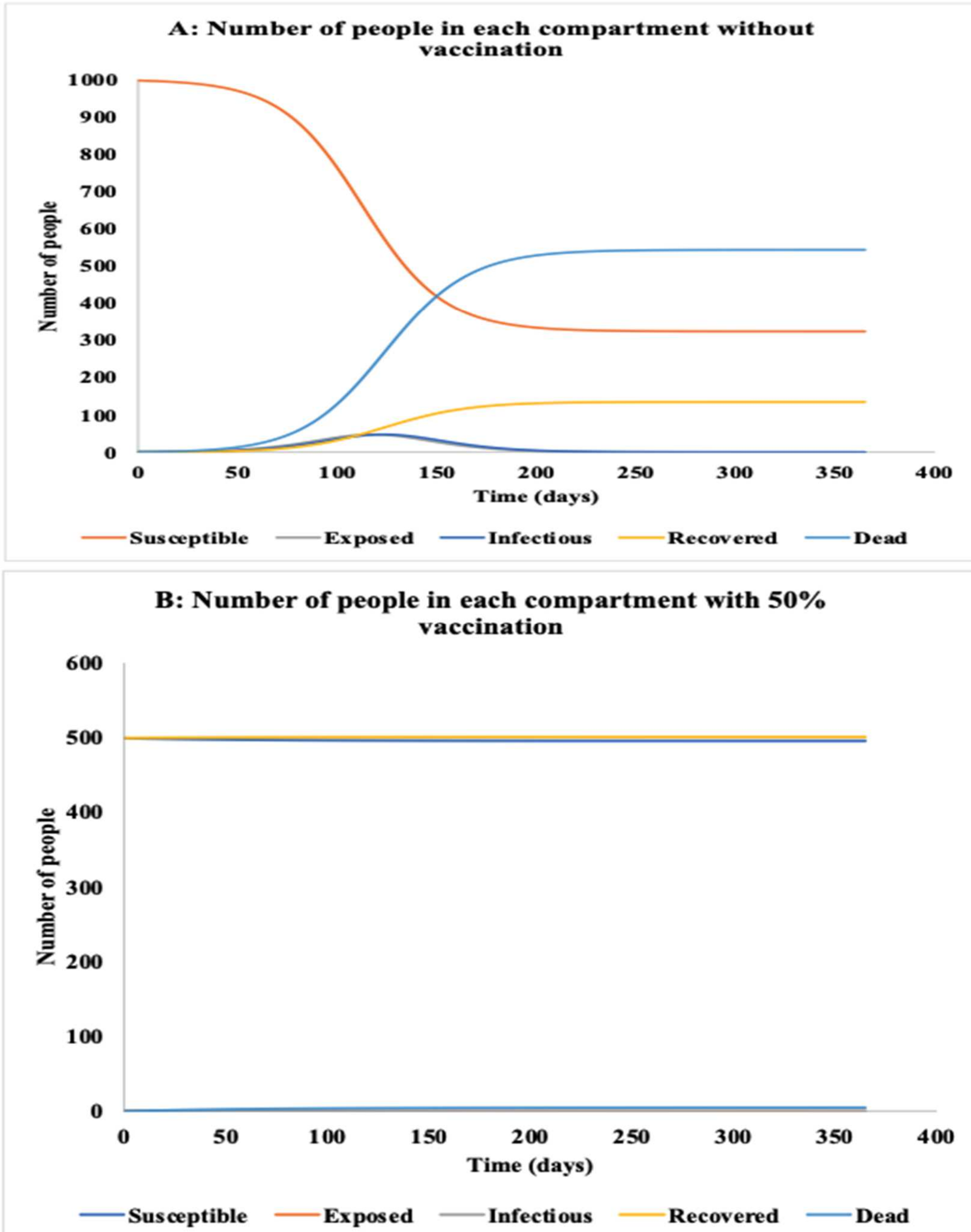


Figure 3.2 Graphical representation of dynamic transmission model without (Panel A) and with vaccination (Panel B). S susceptible; E exposed; I infectious; R recovered; D dead

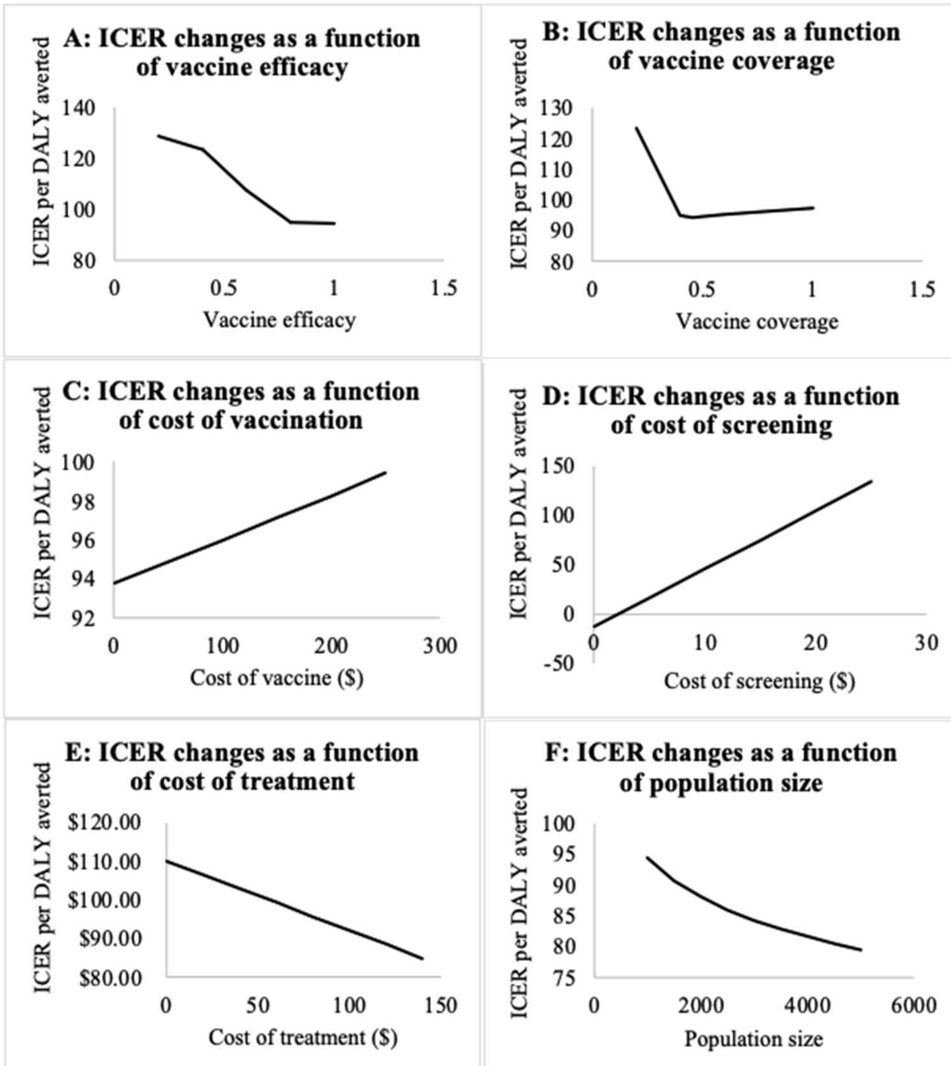


Figure 3.3 Results of one-way sensitivity analyses. ICER incremental cost-effectiveness ratio; DALY disability adjusted life year.

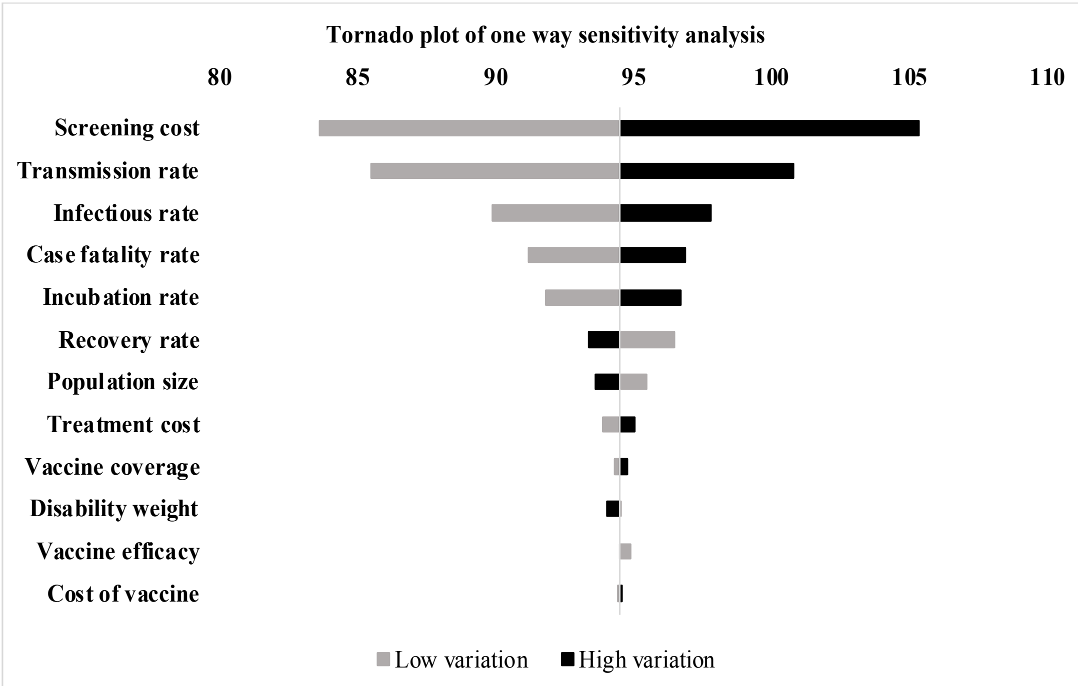


Figure 3.4 Tornado plot showing compiled one-way sensitivity analyses of model parameters.

Middle line represents the base case incremental cost utility ratio (ICER) per disability adjusted life year (DALY) averted ($94.51). Horizonal bars represent the variations in the ICERs as a result of variations in model parameters.

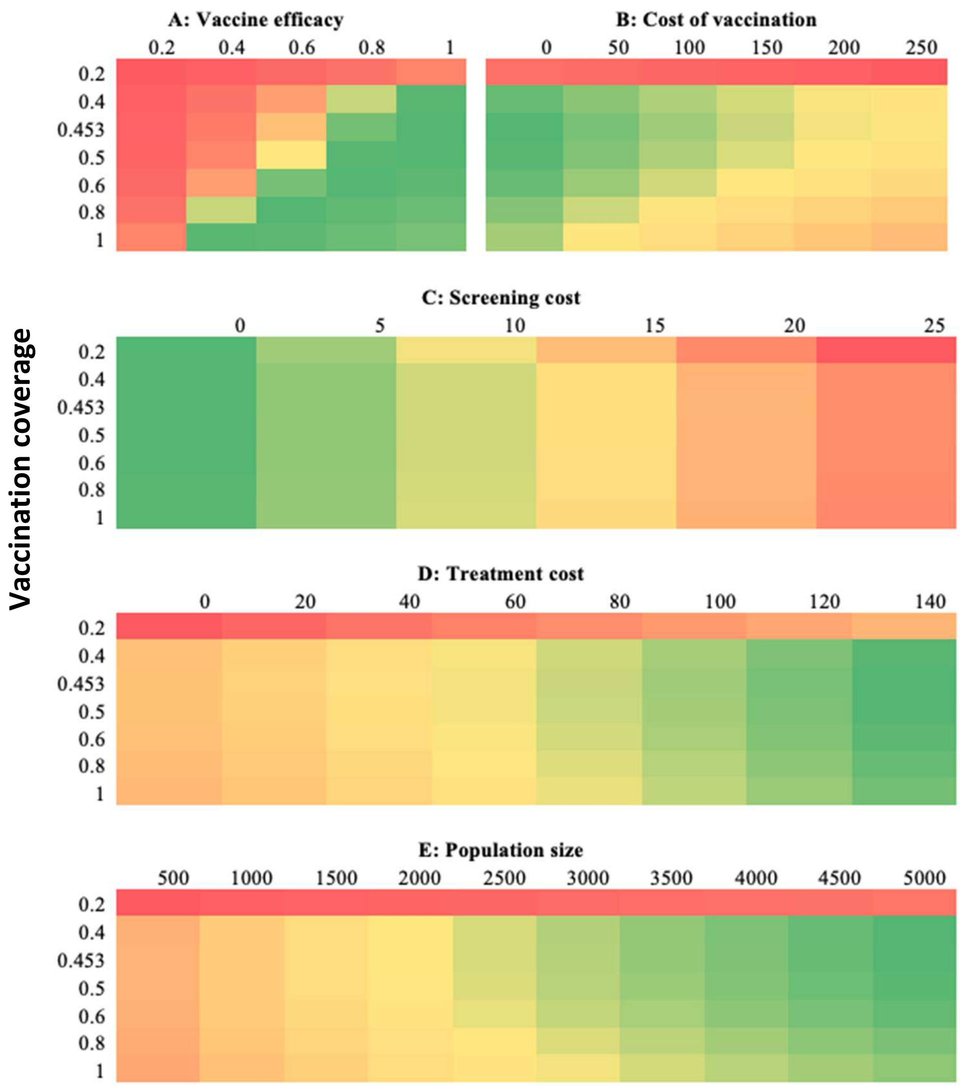
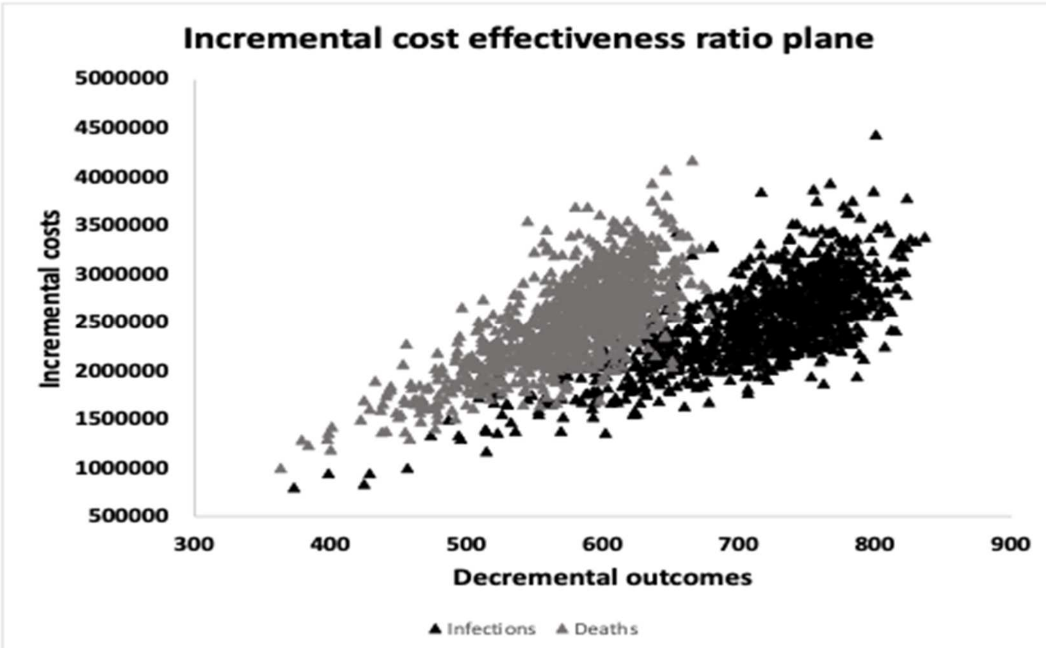


Figure 3.5 Heat maps showing incremental cost-effectiveness ratio (ICER) per disability adjusted life year (DALY) averted from varying vaccination coverage and other parameters. Green areas represent favorable ICERs , red areas represent least favorable ICERs.



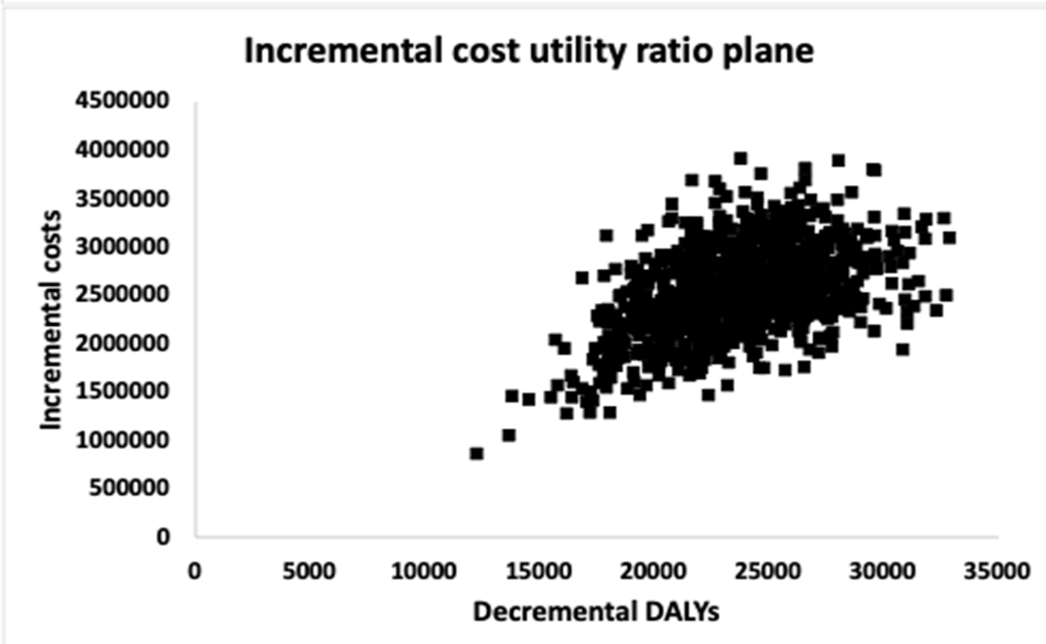


Figure 3.6 Incremental cost-effectiveness ratio (ICER) planes for cost-effectiveness of EVD vaccine.

DALY disability adjusted life year. Upper panel represents iterations of ICERs per infections and deaths averted.

Lower B represents iterations of ICER per DALY averted.

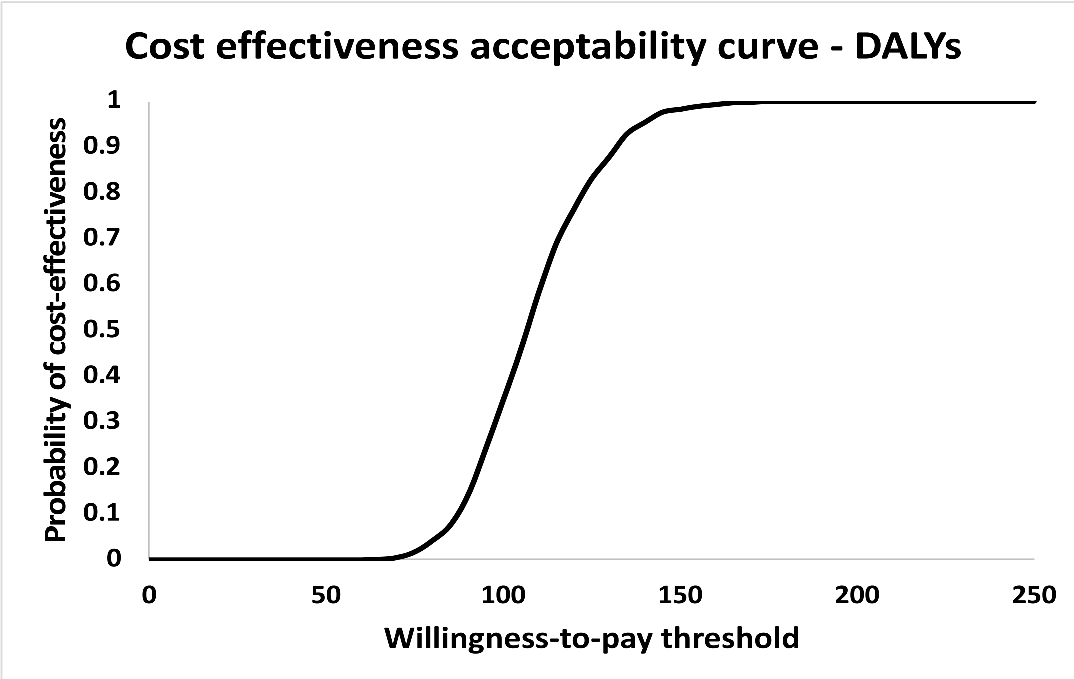


Figure 3.7 Cost-effectiveness ratio acceptability curve for cost-effectiveness of EVD vaccine in terms of DALYs averted. DALY disability adjusted life year.

CHAPTER 4

ARTICLE 3

Value-based pricing of an ebola vaccine in resource-constrained countries based on cost-effectiveness analysis – a technical note.

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4.1 Abstract

Objectives

Pricing, affordability, and access are important deliberations around infectious disease interventions. Determining a fair price that not only incentivizes development but ensures value and access for patients is critical given the increasing global health crisis. Using ebola virus disease (EVD) as exemplar, we aim to elucidate the estimation of a value-based price (VBP) for a vaccine package and to consider how the price compares across selected countries that have experienced EVD outbreaks.

Methods

Using a dynamic transmission model, we assessed the cost-effectiveness of a vaccine package – composed of the vaccine, storage, maintenance, and administration - for vaccination toward herd immunity in 4 countries affected with EVD (Democratic Republic of Congo, Liberia, Sierra Leone, Uganda). Based on the cost-effectiveness metrics and using willingness-to-pay thresholds equal to varying percentages of the Gross Domestic Product (GDP), we demonstrated how a VBP is calculated using an adaptation of the "QALY-capped" approach.

Results

The VBP for the vaccine is directly proportional to both cost-effectiveness and GDP per capita- with higher cost-effectiveness and higher GDP per capita resulting in higher price ceilings compared to lower cost-effectiveness and lower GDP.

Conclusion

Despite the concerns with the "QALY-cap" approach, we illustrated that it is an easily comprehensible method for determining the VBP of a vaccine using a cost-effectiveness analysis. Choice of data, population characteristics, disease dynamics, and others are among factors that need to be considered when comparisons are made across countries.

Keywords

Value-based pricing; pricing; value; cost-effectiveness comparison; ebola virus disease

4.2 Introduction

Infectious diseases continue to afflict public health the world over; with the corona virus (COVID-19), ebola virus disease (EVD), and measles outbreaks erupting in various parts of the world. The public health, economic and other impacts of these outbreaks are immense, and efforts being made to mitigate these are barely able to completely control them.[148] Substantial research, as well as fiscal resources, are invested into control measures for infectious diseases such as treatments and vaccines. While the initial focus of infectious disease interventions, especially in outbreak situations, is centered on efficacy, safety, logistics and access, there is increasing interest in the other aspects of pricing, affordability, and allocation.[149]

There is an ongoing discussion about price, value and rewarding innovation with many proposed methods for pricing pharmaceuticals to balance these elements.[150] Cost-based, competition-based and value-based pricing are used in industrial markets, the latter of which is considered a gold standard.[151] From an economic perspective, value-based pricing is about setting a price of an intervention which reflects its value to the consumer[152] and value represents an opportunity cost sacrificed by an individual to free up resources for use on their next best alternative. [153] VBP takes into account disease burden and health effects that are important to society and works towards efficient use of health system resources, subsequently improving health outcomes.

There are several methods of generating information for calculating value-based prices, many of which are from cost-effectiveness analyses (CEAs). While the use of CEA for VBP calculations is ridden with challenges related to addressing uncertainties, reflecting social values and lifetime gains, as well as including additional elements of value, CEAs are still considered an important methodology for VBP. Pearson and colleagues put forward four basic approaches of calculating VBP using CEA. While the sliding scale for the ICER related to an intervention has the ability of creating rules that help decide whether VBP needs to be done using an alternative approach, a second approach that disallows full credit for cost offsets is easy to imagine in cases where prices exceed a traditional cost-effectiveness threshold. The “QALY-cap” approach credits the intervention with its full value in terms of the health benefits. It is, however, viewed by some as an approach that undervalues interventions that reduce healthcare costs. The “shared saving” approach advocates for sharing the rewards of an intervention between the innovator and the health system.[154]

We describe how a value-based price of a vaccine package, made up of the vaccine, storage, maintenance, and administration, is determined based on a CEA of a vaccination program that targets herd immunity. We apply this to ebola virus disease (EVD) vaccination programs in selected affected countries in Africa and discuss how the value of the program compares in these countries based on their distinct characteristics.

4.3 Application of value-based pricing

Ebola virus disease is a severe, often fatal, hemorrhagic infection caused by several species of the *Ebolavirus*, the most popular of which is *Zaire ebolavirus* (EBOV).[155] The disease is spread by contact with body fluids from infected patients and symptoms are developed typically within an incubation period of 1-21 days.[156] Symptoms range from fever, nausea, vomiting, diarrhea and bleeding, to more extensive multiple organ damage such as gastrointestinal injury and bleeding; hepatic damage; renal failure; and ultimately death.[155] Most EVD outbreaks have occurred in Africa with the countries Democratic Republic of Congo (DRC), Liberia, Sierra Leone, and Uganda being hit the hardest from outbreaks over the years.[157]

Presently, management is focused on supportive care and infection control with other therapies being developed for EVD treatment. A multi-drug clinical trial for EVD treatment was conducted to evaluate the safety and effectiveness of azithromycin, a combination of sunitinib and erlotinib, a combination of atorvastatin and irbesartan, and intravenous fluids in the management of EVD.[158] Two monoclonal antibodies, Inmazeb™ (Regeneron, Tarrytown, NY) and Ebanga ™ (Ridgeback, Miami, FL), have been approved for treating EBOV infections. While the Ervebo® (Merck, Kenilworth, NJ) vaccine has been approved by the US Food and Drug Administration and prequalified by WHO for protection against EBOV, the Zabdeno®-Mvabea® (Janssen Global Services, LLC) vaccine has been granted marketing authorization by the European Medicines Agency for individuals a year and older.[158] EVD vaccines are currently paid for by the International Coordinating Group (ICG) on Vaccine Provision, which includes the World Health Organization (WHO), UNICEF, the International Federation of Red Cross and Red Crescent Societies (IFRC), and Médecins Sans Frontières (MSF), with financial support from Gavi, the Vaccine Alliance.[159] To ensure value for money and return on investments for such payers, it is important that an appropriate price be set for EVD vaccines to reflect their value while also rewarding innovation by manufacturers.

4.4 Method

4.4.1 Cost-effectiveness analysis

Our CEA was based on a dynamic transmission model (DTM) that estimates the cost-effectiveness of vaccinating a proportion of the population compared to a base scenario of no vaccination for a hypothetical population of 1000 in the selected countries; using a recent DTM analysis for the Democratic Republic of Congo as the reference methodology and results to which we then compare the new estimates for Liberia, Sierra Leone, and Uganda. We used epidemiological data related to the 2014-2016 EVD outbreaks in these four countries. For the purposes of this study, we modeled the disease over a one-year period and determined effectiveness in terms of disability-adjusted life years (DALYs) from the payer perspective. We modeled vaccinating a proportion of the population equivalent to the herd immunity threshold using the formula:

$$\textit{herd immunity threshold} = 1 - \frac{1}{R_0}$$

where R_0 refers to the basic reproductive number.

A modified SEIR model, in which the participants move from susceptible, through exposed, infected, recovered, and dead at various rates was specified (Figure 1). Applying compartmental modeling concepts,[160] we used the following differential equations to move participants from one compartment to another:

$$S(t) = \frac{-\beta S(t)I(t)}{N}$$

$$E(t) = \frac{\beta S(t)I(t)}{N} - \xi E(t)$$

$$I(t) = \xi E(t) - \gamma I(t)$$

$$R(t) = \delta I(t)$$

$$D(t) = \mu I(t)$$

$$N = S+E+I+R+D$$

$$\gamma = \delta + \mu$$

where N is the population, S is the number of this population susceptible, E is the number exposed, I is the number infected, R is the number who recover from the infection and D is the number who die from the infection.

To assess the cost-effectiveness of the program in terms of DALYs averted, we obtained disability weights from the Global Burden of Disease Study 2015[161] and subsequently computed DALYs. Costs of treatment, screening, and vaccination were obtained from published literature.

The cost of the vaccine package comprised the price of the vaccine as well as the composite cost of administration. All costs were converted to 2021 USD using the US Consumer Price Index for Medical Care.[162] Incremental cost-effectiveness ratios (ICERs) were calculated as follows:

$$\text{ICER} = \frac{\textit{Total cost of outbreak with vaccination} - \textit{Total cost of outbreak without vaccination}}{\textit{Total outcomes with vaccination} - \textit{Total outcomes without vaccination}}$$

4.4.2 Value-Based Pricing

To estimate a value-based price for the vaccine package, we adapted the method by Pearson *et al.,* which determined the VBP using a QALY-based price cap.[154] For our analysis, the value of the package was reflected in the estimated DALYs averted and a willingness-to-pay or cost-effectiveness thresholds were set at varying percentages of each country's gross domestic product (GDP) per capita. Following the approach by Pearson and colleagues, we calculated the VBP using the following formula:

*VBP = (Cost-effectiveness threshold*DALYs averted) + Total cost of EVD without vaccination*

A flow chart of the step-by-step calculation of VBP is provided in Figure 2. All analyses were conducted in Microsoft Excel. Input parameters for the model and analyses are provided in Tables 1 and 2.

4.5 Results

In all the included countries, the vaccination resulted in increased total costs while decreasing DALYs. Averting a DALY was estimated to cost $73.43, $94.51, $ 101.63, and $666.49 in Uganda, DRC, Liberia, and Sierra Leone, respectively (Table 2)

The highest prices a vaccine package can assume at willingness-to-pay thresholds equal to percentages of each country's GDP per capita are shown in Table 3 and Figure 3. From the table, the vaccine package can be most highly priced in Uganda, followed by DRC, Liberia and finally least priced in Sierra Leone.

4.6 Discussion

In this technical note, we aimed to describe value-based pricing based on CEA using the case of an EVD vaccine program that targets, in a given population, vaccination to herd immunity. Secondary to this, we describe how this price compares across different countries and the factors that should be considered in generalizing value-based prices across jurisdictions. To enable a degree of comparison between countries, however, not without some controversy, the World Health Organization (WHO) classifies cost-effectiveness of treatments into three levels using a country's GDP per capita as the metric: highly cost-effective if ICER < 1*GDP/capita, cost-effective < 3*GDP/capita and not cost effective >3*GDP/capita. Using this classification, we found the vaccination program to be highly cost-effective in three of the countries assessed, i.e., DRC, Liberia and Uganda (ICER < 1*GDP) and cost-effective in Sierra Leone (ICER = 1.34*GDP).[169] The price ceiling of the vaccine package based on the DALYs averted was determined to be lowest in Sierra Leone where the program was least cost-effective and GDP per capita was lowest, and highest in Uganda where the program was most cost-effective and GDP per capita was highest.

Value-based pricing of the vaccine package is important because it reflects both the clinical and economic benefits of the intervention.[152] The method used to estimate the VBP of the vaccine package is credited with the ability to assign a price based on the full value, in terms of the health benefits, of the therapy being assessed.[154] Arguments have been made for its ability to promote equity in that a more effective product or one that replaces other services is likely to be priced higher and still remain within the willingness-to-pay threshold.[154,170] It is also important to note that this method allows the payer's willingness-to-pay threshold to act as a control on price, within the intervention's cost offsets as well as incremental effectiveness.[170]

The choice of using percentages of a country's GDP per capita as cost-effectiveness thresholds was based on several, yet disparate recommendations, on appropriate cost-effectiveness thresholds especially in LMIC settings. While the WHO recommends cost-effectiveness thresholds between 1 to 3 times GBP,[172] Daroudi *et al*. propound thresholds less than 1*GDP in LMICs.[24] Jit, in assessing global cost-effectiveness thresholds for human papillomavirus vaccine introductions, found that a threshold between 30% to 40% of GDP were optimal in LMICs.[172] Also, in re-evaluating the cost-effectiveness of rotavirus vaccination in 73 Gavi countries, most of which are LMICs, Debellut and colleagues found cost-effectiveness thresholds between 50% and 100% GDP per capita to be optimal.[173] Given no consensus on appropriate thresholds in LMICs, we varied these percentages to give an overview of VBP of the vaccine package for better elucidation. Thresholds that incorporate GDP per capita, a measure of wealth in individual countries, take into account fiscal differences in these countries and attempts to price interventions in proportion to each country's economy.[174] Thus, the price of an intervention in countries with lower GDPs would be lower than in countries with higher GDPs as illustrated by our analysis.

To better understand the findings, it is important to view them in light of each country's characteristics. Briefly, the included countries were similar in terms of median age and general life expectancy. All the countries had relatively young populations, with the median ages ranging from 16 years to about 19 years and general life expectancy from 54 years to 63 years. In terms of GDP per capita, DRC, Liberia and Sierra Leone were within similar ranges of about $500 while Uganda was at $817. Further, it is essential to consider the epidemiology of EVD for the countries assessed. While transmission rate, one of the important drivers of infectious diseases, was lowest in Sierra Leone,[175] it was highest in Uganda. The basic reproductive number, the number of secondary infections expected from one case of an infectious disease, was highest in Uganda resulting in a higher herd immunity threshold and subsequently a higher proportion requiring vaccination, and lowest in Sierra Leone.

From our analyses, we found vaccination programs to be more cost-effective where transmission rates are higher compared to settings with lower transmission rates. This is reflective of the clinical value of vaccination in limiting transmission, since persons who would have been susceptible receive protection against the infection.[175,176] Thus, with higher transmission rates, the effect of a vaccination program is more pronounced: more infections are prevented leading to higher returns in effectiveness and thus greater cost-effectiveness. Given that the R_0 is proportional to the transmission dynamics of a disease,[177] it is understandable that countries with higher transmission rates had a higher R_0, which in turn makes vaccination programs more cost-effective than countries with lower transmission rates. One could think of this as follows: vaccination is essential, but it will be more clinically effective and cost-effective when transmission rates are high and there is more disease to be prevented.

As previously mentioned, VBP based on QALYs averted integrates value in terms of both cost and outcomes.[174,178] In Uganda, the country with the highest GDP per capita in our analyses, and where consequently the program was most cost-effective, the VBP for the vaccine package can be set the highest compared to the other countries where GDP per capita is lower and the program is less cost-effective. On the contrary, in Sierra Leone where GDP per capita was the lowest and the vaccination program the least cost-effective, the VBP was lowest. While this may appear counterintuitive, it reflects lower demand for vaccines in situations where less transmissible diseases break out. This translates into lower cost-effectiveness, lower value of vaccination programs, and lower ceilings for prices for vaccine packages compared to countries where more transmissible diseases break out.

Several considerations need to be made in attempting to compare or generalize the results of such analyses across countries or jurisdictions, and these are even more pronounced in infectious disease evaluations. Infectious diseases are dynamic, with rates changing constantly. Thus, input parameters for modeling are likely to be unknown, often "guesstimated" based on available data or, worse, inaccurately measured.[177,179] Also, given different population characteristics, contact patterns, along with other infectious disease complexities across countries, such comparisons must be conducted and interpreted cautiously.

Types of data are also an important element requiring attention. According to recommendations of the ISPOR Task Force Report on transferability of Economic Evaluations Across Jurisdictions, some parameters may have to be jurisdiction-specific, requiring that they are based on data from the population under study.[180] While it may be more appropriate to conduct economic evaluations using data from populations under study, this may not be feasible in all situations due to unavailability of data. In the absence of relevant data in the country, exchangeability of data should be justified by jurisdictions being sufficiently similar to allow comparability or transferability for the purposes of the economic evaluation. For this, the sources of data need to be as comparable as possible. Clinical trials and epidemiological studies that serve as sources for these studies need to be based on similar participant profiles while the choices between hard clinical outcomes, surrogates, as well as more generic outcomes need to be sufficiently similar to facilitate comparison across countries.[152]

While efforts were made to ensure accuracy and robustness, our analyses have a few limitations while also pointing at direction for future research. Some data required for modeling were unavailable in certain countries, leading to the use of more general data for the analyses. Like most models, ours assumed homogenous target populations across the countries in terms of composition and characteristics. While these may have changed the results of the analyses, they did not affect the methods described and the concepts we wished to introduce. Data permitting, future research should focus on subpopulations to examine the effect of heterogeneity.

4.7 Conclusion

In this technical note, and using vaccination against EVD as exemplar, we demonstrated an approach to estimating the VBP of an intervention based on cost-effectiveness analysis and capped at a predetermined willingness-to-pay threshold. This approach is easily comprehensible and allows for the incorporation of both costs and benefits of the intervention. We also demonstrated the advantage of cost-effectiveness thresholds based on GDP per capita in terms of their reflection of national wealth and subsequent indirect incorporation of affordability within specific countries. Finally, the exercise of comparing cost-effectiveness and VBP prices in the included countries highlighted important considerations for cross-jurisdiction comparisons of economic evaluations of infectious diseases such as disease dynamics, population characteristics, data types and sources.

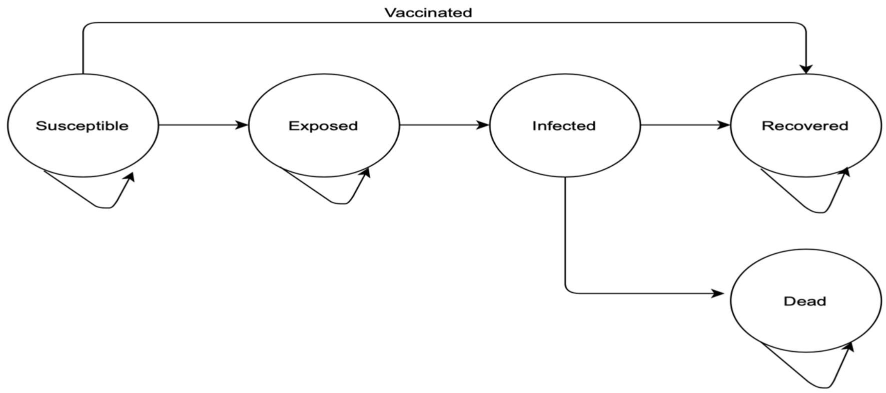

Figure 4.1 Schematic view of the dynamic transmission model.

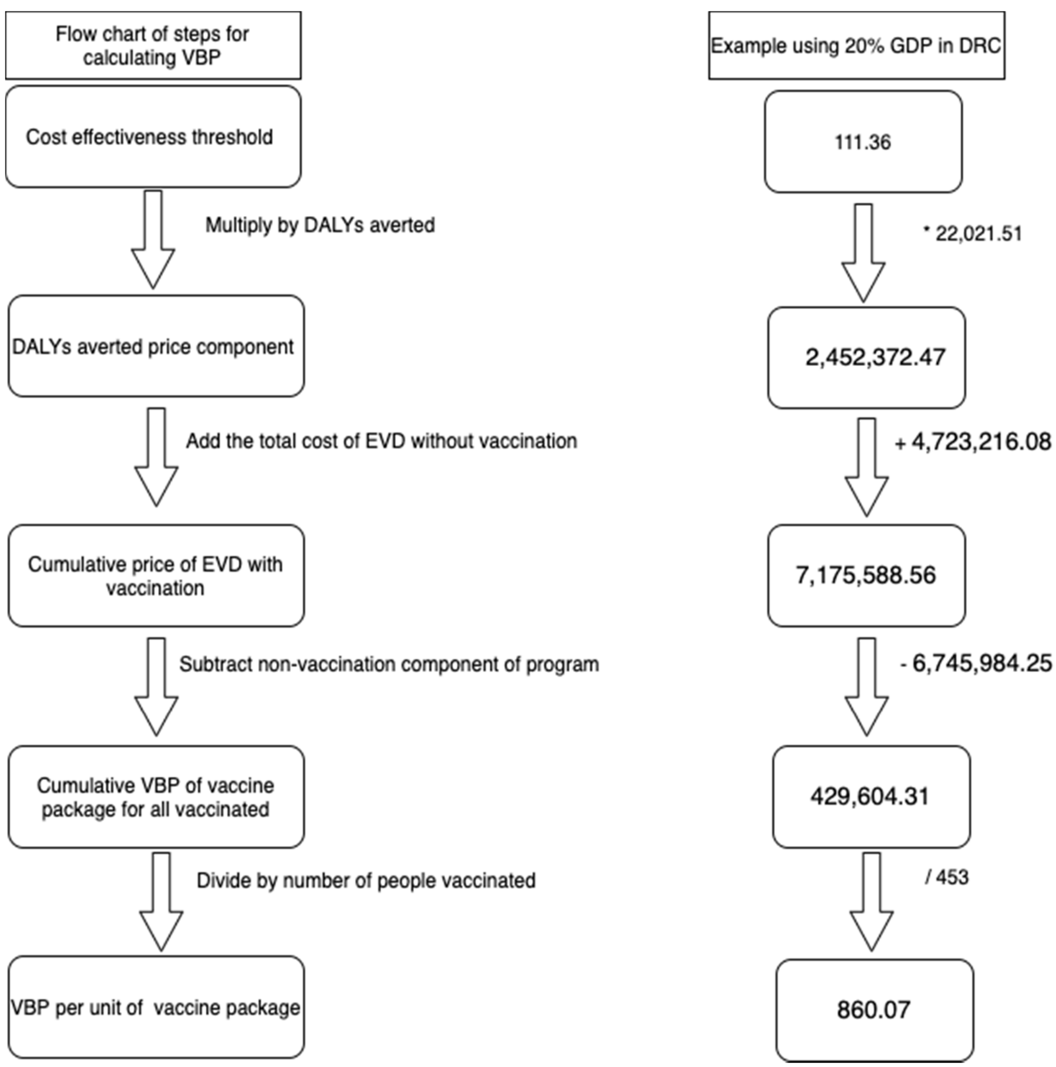

Figure 4.2 Flow chart for calculating VBP

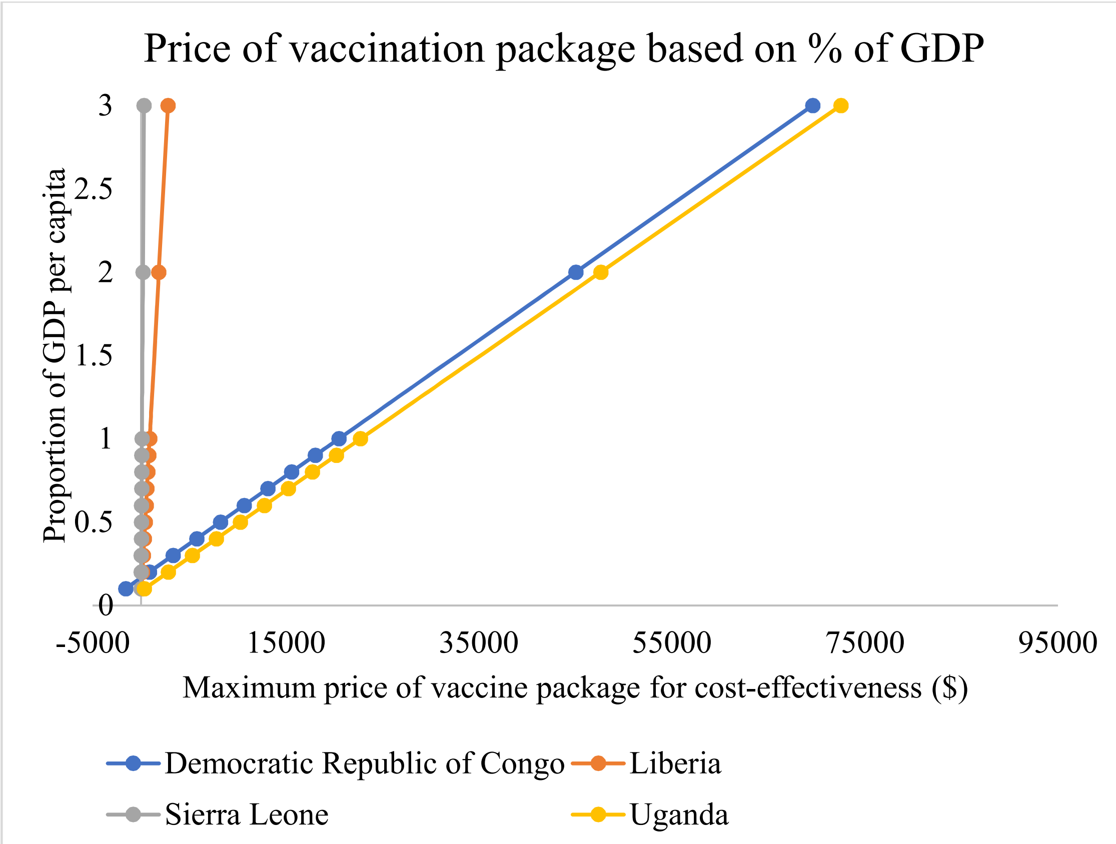

Figure 4.3 Value-based price of vaccine package based on % of GDP per capita across countries ($)

Table 4.1 Country specific inputs for analyses

	DRC[13]	Liberia[16]	Sierra Leone[16]	Uganda[17]
Transmission rate (β)/day	0.33	0.16	0.13	0.50
Incubation rate (ξ)/ day	0.19	0.08	0.1	0.08
Infectious rate (γ) / day	0.18	0.07	0.05	0.1
Case fatality rate	0.14	0.08	0.1	0.12
Basic reproductive number (R_0)	1.83	2.02	1.81	2.7
Median age (years)	19.2	19.4	19.4	16.7
Life expectancy (years)	60.97	64.1	54.7	63.37
GDP per capita ($)	556.80	583.30	484.50	817.00

DRC Democratic Republic of Congo; GDP Gross Domestic Product

Table 4.2 General model inputs for analyses

Variable	Value	Reference
Population size	1000	Assumed
Initially infected	1	Assumed
Disability weight for EVD	0.133	[161]
Vaccine efficacy	100%	[165]
Cost of vaccine bundle ($)	33.54	[166,167]
Cost of vaccination kit ($)	17.26	[166,167]
Cost of vaccine storage and management ($)	66.45	[166,167]
Cost of screening ($)	18.49	[168]
Cost of treating a case of EVD	86.72	[168]
Personal cost for treating EVD case	6.16	[168]

EVD ebola virus disease

Table 4.3 Base – case cost-effectiveness analysis for DRC, Liberia, Sierra Leone, and Uganda

Country	Cost with vax ($)	DALYs with vax	Cost without vax ($)	DALYs without vax	Cost averted ($)	DALYs averted	ICER ($/DALY averted)
DRC	6,804,551	187	4,723,216	22,209	2,081,335	22,022	94.51
Liberia	6,821,783	50	6,738,990	864	82,793	815	101.63
Sierra Leone	6,820,836	42	6,751,731	146	69,105	104	666.49
Uganda	6,818,167	81	5,411,455	19239	1,406,712	19,157	73.43

Vax vaccination; DRC Democratic Republic of Congo; DALY disability adjusted life years; ICER incremental cost-effectiveness ratio

Table 4.4 Value-based price of vaccine package across countries ($)

Cost-effectiveness threshold (%GDP per capita)	DRC	Liberia	Sierra Leone	Uganda
0.1	-1594.76	46.16	-12.17	345.14
0.2	860.07	140.35	-1.08	2833.60
0.3	3314.90	234.55	10.00	5322.06
0.4	5769.72	328.74	21.09	7810.52
0.5	8224.55	422.93	32.18	10298.98
0.6	10679.38	517.12	43.26	12787.44
0.7	13134.21	611.31	54.35	15275.90
0.8	15589.03	705.50	65.44	17764.36
0.9	18043.86	799.69	76.52	20252.82
1	20498.69	893.88	87.61	22741.28
2	45046.96	1835.79	198.48	47625.88
3	69595.23	2777.69	309.35	72510.48

CE cost-effectiveness; GDP gross domestic product; DRC Democratic Republic of Congo. Prices of vaccine package 0 and below represent situations in which any payment for the package will render the program not cost-effective.

Appendices

Appendix A. Value-based pricing of vaccine package – Democratic Republic of Congo ($)

CE threshold (%GDP) GDP = $556.80		DALY averted	Total cost of DALYs averted (DALY averted cost component)	Total cost of not vaccinating (Cost offset price component)	Cumulative "value-based" price of entire vaccination program	Non-vaccination Cost component of vaccination program	Cumulative "value-based' price of vaccination component	Cumulative "value-based' price per person (N of vaccinated =453)
0.1	55.68	22,021.51	1,226,186.24	4,723,216.08	5,949,402.32	6,745,984.25	(796,581.93)	(1,594.76)
0.2	111.36	22,021.51	2,452,372.47	4,723,216.08	7,175,588.56	6,745,984.25	429,604.31	860.07
0.3	167.04	22,021.51	3,678,558.71	4,723,216.08	8,401,774.79	6,745,984.25	1,655,790.55	3,314.90
0.4	222.73	22,021.51	4,904,744.95	4,723,216.08	9,627,961.03	6,745,984.25	2,881,976.78	5,769.72
0.5	278.41	22,021.51	6,130,931.18	4,723,216.08	10,854,147.26	6,745,984.25	4,108,163.02	8,224.55
0.6	334.09	22,021.51	7,357,117.42	4,723,216.08	12,080,333.50	6,745,984.25	5,334,349.26	10,679.38
0.7	389.77	22,021.51	8,583,303.65	4,723,216.08	13,306,519.74	6,745,984.25	6,560,535.49	13,134.21
0.8	445.45	22,021.51	9,809,489.89	4,723,216.08	14,532,705.97	6,745,984.25	7,786,721.73	15,589.03
0.9	501.13	22,021.51	11,035,676.13	4,723,216.08	15,758,892.21	6,745,984.25	9,012,907.96	18,043.86
1	556.81	22,021.51	12,261,862.36	4,723,216.08	16,985,078.45	6,745,984.25	10,239,094.20	20,498.69
2	1113.63	22,021.51	24,523,724.73	4,723,216.08	29,246,940.81	6,745,984.25	22,500,956.56	45,046.96
3	1670.44	22,021.51	36,785,587.09	4,723,216.08	41,508,803.17	6,745,984.25	34,762,818.93	69,595.23

CE Cost-effectiveness; DALY disability adjusted life year; GDP gross domestic product

Appendix B. Value-based pricing of vaccine package – Liberia ($)

CE threshold (%GDP) GDP = $583.30		DALY averted	Total cost of DALYs averted (DALY averted cost component	Total cost of not vaccinating (Cost offset price component)	Cumulative "value-based" price of entire vaccination program	Non-vaccination Cost component of vaccination program	Cumulative "value-based' price of vaccination component	Cumulative "value-based' price per person (N of vaccinated =504)
0.1	58.33	814.62	47514.50	6738990.12	6786504.62	6763217.08	23287.54	46.16
0.2	116.65	814.62	95029.01	6738990.12	6834019.13	6763217.08	70802.05	140.35
0.3	174.98	814.62	142543.51	6738990.12	6881533.63	6763217.08	118316.55	234.55
0.4	233.31	814.62	190058.01	6738990.12	6929048.13	6763217.08	165831.05	328.74
0.5	291.64	814.62	237572.51	6738990.12	6976562.63	6763217.08	213345.55	422.93
0.6	349.96	814.62	285087.02	6738990.12	7024077.14	6763217.08	260860.06	517.12
0.7	408.29	814.62	332601.52	6738990.12	7071591.64	6763217.08	308374.56	611.31
0.8	466.62	814.62	380116.02	6738990.12	7119106.14	6763217.08	355889.06	705.50
0.9	524.94	814.62	427630.52	6738990.12	7166620.64	6763217.08	403403.56	799.69
1	583.27	814.62	475145.03	6738990.12	7214135.15	6763217.08	450918.07	893.88
2	1166.54	814.62	950290.05	6738990.12	7689280.17	6763217.08	926063.09	1835.79
3	1749.81	814.62	1425435.08	6738990.12	8164425.20	6763217.08	1401208.12	2777.69

CE Cost-effectiveness; DALY disability adjusted life year; GDP gross domestic product

Appendix C. Value-based pricing of vaccine package – Sierra Leone ($)

CE threshold (%GDP) **GDP = $484.50**		**DALY averted**	**Total cost of DALYs averted (DALY averted cost component**	**Total cost of not vaccinating (Cost offset price component)**	**Cumulative "value-based" price of entire vaccination program**	**Non-vaccination Cost component of vaccination program**	**Cumulative "value-based' price of vaccination component**	**Cumulative "value-based' price per person** (N of vaccinated =453)
0.1	48.45	103.68	5023.50	6751730.87	6756754.37	6762269.45	-5515.08	-12.17
0.2	96.90	103.68	10047.01	6751730.87	6761777.88	6762269.45	-491.57	-1.08
0.3	145.36	103.68	15070.51	6751730.87	6766801.38	6762269.45	4531.93	10.00
0.4	193.81	103.68	20094.01	6751730.87	6771824.89	6762269.45	9555.44	21.09
0.5	242.26	103.68	25117.52	6751730.87	6776848.39	6762269.45	14578.94	32.18
0.6	290.71	103.68	30141.02	6751730.87	6781871.89	6762269.45	19602.44	43.26
0.7	339.16	103.68	35164.52	6751730.87	6786895.40	6762269.45	24625.95	54.35
0.8	387.62	103.68	40188.03	6751730.87	6791918.90	6762269.45	29649.45	65.44
0.9	436.07	103.68	45211.53	6751730.87	6796942.40	6762269.45	34672.95	76.52
1	484.52	103.68	50235.03	6751730.87	6801965.91	6762269.45	39696.46	87.61
2	969.04	103.68	100470.07	6751730.87	6852200.94	6762269.45	89931.49	198.48
3	1453.56	103.68	150705.10	6751730.87	6902435.97	6762269.45	140166.52	309.35

CE Cost-effectiveness; DALY disability adjusted life year; GDP gross domestic product

Appendix D. Value-based pricing of vaccine package – Uganda ($)

CE threshold (%GDP) GDP = $817.00		DALY averted	Total cost of DALYs averted (DALY averted cost component	Total cost of not vaccinating (Cost offset price component)	Cumulative "value-based" price of entire vaccination program	Non-vaccination Cost component of vaccination program	Cumulative "value-based' price of vaccination component	Cumulative "value-based' price per person (N of vaccinated =629)
0.1	81.70	19157.46	1565241.21	5411454.85	6976696.06	6759600.63	217095.42	345.14
0.2	163.41	19157.46	3130482.42	5411454.85	8541937.27	6759600.63	1782336.64	2833.60
0.3	245.11	19157.46	4695723.64	5411454.85	10107178.49	6759600.63	3347577.85	5322.06
0.4	326.82	19157.46	6260964.85	5411454.85	11672419.70	6759600.63	4912819.06	7810.52
0.5	408.52	19157.46	7826206.06	5411454.85	13237660.91	6759600.63	6478060.27	10298.98
0.6	490.22	19157.46	9391447.27	5411454.85	14802902.12	6759600.63	8043301.49	12787.44
0.7	571.93	19157.46	10956688.48	5411454.85	16368143.33	6759600.63	9608542.70	15275.90
0.8	653.63	19157.46	12521929.69	5411454.85	17933384.54	6759600.63	11173783.91	17764.36
0.9	735.34	19157.46	14087170.91	5411454.85	19498625.76	6759600.63	12739025.12	20252.82
1	817.04	19157.46	15652412.12	5411454.85	21063866.97	6759600.63	14304266.33	22741.28
2	1634.08	19157.46	31304824.23	5411454.85	36716279.08	6759600.63	29956678.45	47625.88
3	2451.12	19157.46	46957236.35	5411454.85	52368691.20	6759600.63	45609090.57	72510.48

CE Cost-effectiveness; DALY disability adjusted life year; GDP gross domestic product

CHAPTER 5

CONCLUSION

The burden of EVD globally and particularly in the countries that have been directly affected is enormous epidemiologically, clinically, socially, and economically. Rightfully so, this has put pressure on governments and the international community for better resource utilization and re-allocation to address both the immediate clinical needs, but also the ensuing longer-term social and economic consequences. There is an urgent need for territory-specific evidence-based economic plans for, as well as economic evaluations of, mitigations to enhance resource allocation for EVD prevention and treatment. Lessons derived from the economics of one outbreak will be invaluable for preparing towards and financing the prevention of and response to future outbreaks. Yet, as we showed in our first paper, there may be more shortcomings and challenges in the economics of infectious diseases especially in low-resourced settings.

In our second paper, we applied a model that was robust for determining the cost-effectiveness of a vaccination program. From the payer perspective, although vaccination against EVD at 50% of population led to increased total costs, gains in outcomes in terms of infections, deaths and DALYs averted were sufficiently high to make the EVD vaccination program cost-effective. Linking this also to our third paper, we demonstrated that for the LMICs evaluated, vaccinating the population to the herd immunity threshold was cost-effective – and sufficiently robust to inform policy. Both papers underscore that disease dynamics as well as the characteristics of the target population play significant roles in the cost-effectiveness of vaccination programs. While our data support vaccinating at herd immunity for infectious diseases at the macro-level, it is important that, at the micro-level, each outbreak be handled with respect to the population at risk: targeting solely vaccination to herd immunity thresholds may not necessarily be cost-effective in all scenarios. It is important that stakeholders conduct tailored economic evaluations and assessments to determine what works best given the particular characteristics of each infectious disease and the affected population.

While a technical note at this time and in need of further validation, our third paper showed that value-based pricing using cost-effectiveness analysis is a feasible and defensible approach of determining the highest price for a vaccination package without threat to its cost-effectiveness. While, arguably, this approach may limit incentives for innovators to commit to tackling more expensive infectious disease outbreaks, we demonstrated that VBP using the "QALY-cap" approach assigns full value to a program based on its health benefits. Capping the cost per QALY at varied percentages of countries' GDP per capita may be an approach that considers pricing not only in terms of the outcomes of the intervention, but also in terms of country-specific economics. Importantly, it may be an empirical approach for taking affordability and access into consideration.

Generalizability of economic evaluations across countries needs to be approached with caution. While countries in similar jurisdictions may have some shared characteristics, it may not be prudent to generalize findings across these countries. In the case of infectious diseases, where disease dynamics may vary within regions of a given country, it is important that country specific parameters be used to evaluate interventions. Additionally, one needs to consider that countries are entities defined by political and administrative boundaries, and that infectious disease outbreaks may have different geographies, including cross-boundary ones. As shown in the CDC's map of EVD outbreak distributions in Africa, for example, outbreaks have varied by species, size and geographical location over the years. Even within the same country, there have been geographic containment in affected regions with diverse outbreak sizes.[5] Various species of the virus affected different countries to different degrees, and it is obvious that disease dynamics in one population cannot be imputed to another without some form of adjustment to account for their differing characteristics.[5] Nonetheless, for economic and international aid purposes, inputs such as prices and cost-effectiveness thresholds may need to be country-specific to best incorporate value, cost-effectiveness, and affordability within these countries. Where certain parameters need to be generalized, it is important that they reflect the attributes of the country in which the evaluation is based and that these assumptions be empirically justified.

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