Mathematical Modelling of the Ebola Virus Disease

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by

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As the candidate's supervisors, we have approved this dissertation for submission

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Professor Faraimunashe Chirove Signature ..... Date: 17/02/2024.....

Abstract

Despite the numerous modelling efforts to advise public health physicians to understand the dynamics of the Ebola virus disease (EVD) and control its spread, the disease continued to spread in Africa. In the current thesis, we systematically review previous EVD models. Further, we develop novel mathematical models to explore two important problems during the 2018-2020 Kivu outbreak: the impact of geographically targeted vaccinations (GTVs) and the interplay between the attacks on Ebola treatment centres (ETCs) and the spread of EVD. In our systematic review, we identify many limitations in the modelling literature and provide brief suggestions for future work. Our modelling findings underscore the importance of considering GTVs in areas with high infections. In particular, we find that implementing GTVs in regions with high infections so that the total vaccinations are increased by 60% decreases the cumulative cases by 15%. On the other hand, we need to increase the vaccinations to more than 1000% to achieve the 15% decrease in EVD cases if we implement GTVs in areas with low infections. On the impact of the attacks on ETCs, we find that due to the attacks on ETCs, the cumulative cases increased by more than 17% during the 2018-2020 Kivu outbreak. We also find that when 10% of the hospitalised individuals flee the attacks on ETCs after spending only three days under treatment, the cumulative cases increased by more than 30% even if these individuals all returned to the ETCs three days later. On the other hand, if only half of these individuals returned to ETCs for treatment, the cumulative cases increase by approximately 50%. Further, when these patients spend one more day in the community, after which they all return to ETCs, the cumulative cases rise by an additional 10%. Global sensitivity analysis also confirmed these findings. To conclude, our literature systematic review is used to identify many critical factors which were overlooked in previous EVD models. Our modelling findings show that the attacks on ETCs can be destructive to the efforts of EVD response teams. Hence, it is important for decision-makers to tackle the reasons for community distrust and address the roots of the hostility towards ETCs. We also find that GTVs can be used to contain the spread of

EVD when ring vaccinations, contact tracing and antiviral treatments cannot successfully control the spread of EVD.

Declaration I - Plagiarism

I, Suliman Jamiel M. Abdalla, declare that

1. The research reported in this dissertation, except where otherwise indicated, is my original research.
2. This dissertation has not been submitted for any degree or examination at any other university.
3. This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
4. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
   (a) Their words have been re-written but the general information attributed to them has been referenced.
   (b) Where their exact words have been used, then their writing has been placed in italics and inside quotation marks, and referenced.
5. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the references sections.

Signed: 

Suliman Jamiel M. Abdalla

Declaration II - Publications

The following publication and submissions have been produced from this work.

1. Suliman Jamiel M. Abdalla, Faraimunashe Chirove, and Keshlan S. Govinder. A systematic review of mathematical models of the Ebola virus disease. *International Journal of Modelling and Simulation*, 42(5), 2022.
2. Suliman Jamiel M. Abdalla, Keshlan S. Govinder, and Faraimunashe Chirove. The impact of geographically-targeted vaccinations during the 2018-2020 Kivu Ebola outbreak. *Applied Mathematical Modelling,* Submitted.
3. Suliman Jamiel M. Abdalla, Keshlan S. Govinder, and Faraimunashe Chirove. The impact of attacks on Ebola treatment centres during the 2018-2020 Kivu outbreak. *Studies in Applied Mathematics,* Submitted.

The author's contributions in each of the papers are as follows:
$1^{st} Author$: Literature review, design and implementation of models, edition of papers.
$2^{nd} and\ 3^{rd} Authors$: Providing advice, discussing issues on models and simulations, proof-reading manuscripts.

Signed:

Suliman Jamiel M. Abdalla

Date: July 2023

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This thesis is dedicated, with prayers and gratitude, to my parents. My late father, ***Sheikh Jamiel Mohamed****: Even though he had no formal schooling, he loved learning and encouraged his children's progress in education. My mother, Zeinab Ali Jamie, had been my father's right hand. She showed my father and us (her children) unconditional love and support. To them both, I would like to dedicate this achievement.*

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Chapter 1

Introduction

1.1 The interplay between mathematics and epidemiology

Bernoulli proposed the first mathematical model in epidemiology in his work on smallpox [40]. He studied the impact of immunisation against smallpox. He determined how life expectancy would increase if smallpox were eliminated as a reason for death. Hamer [13] explained why the spread of infection should depend on the number of susceptible and infected individuals. He proposed the mass action law for describing a new infection rate, the basic idea for formulating compartmental models. Sir R. A. Ross won the Nobel Prize in medicine for his work on Malaria modelling [13]. It was previously believed that as long as mosquitoes were present in the population, Malaria could not be eliminated. Ross discovered that Malaria is transmitted by the Anopheles mosquito and developed a programme for controlling it at the population level. He introduced a simple compartment model and showed that reducing the Anopheles mosquito below a critical level would be enough to eliminate Malaria. Field trials supported these findings.

Kermack and McKendrick introduced a threshold quantity, which was later denoted by $\mathcal{R}_0$ [13]. This quantity is called the basic reproduction number [13]. It is defined as the average number of infected cases produced by a single infected person in a fully susceptible population during his/her infectious period. In an epidemic situation, in which the period is short enough to neglect demographic effects, and all infected individuals recover with complete immunity against reinfection, the threshold $\mathcal{R}_0 = 1$ is the dividing line between the infection dying out and the onset of an epidemic. In a situation that includes a flow of new susceptible individuals, either through demographic effects or recovery without complete immunity against reinfection, the threshold $\mathcal{R}_0 = 1$ is the dividing line between an approach to a disease-free equilibrium and an approach to an endemic equilibrium, where the disease is always present. Nevertheless, the concept of backward bifurcation presents a complex perspective to this framework [101]. It indicates that, under certain conditions, a stable endemic equilibrium can coexist with a disease-free equilibrium even when $\mathcal{R}_0 < 1$.

This phenomenon suggests that simply achieving $\mathcal{R}_0 < 1$ may not guarantee the elimination of the disease, challenging the conventional threshold-based approach to disease control. Factors such as population heterogeneity, partial immunity, and complex transmission dynamics contribute to backward bifurcation, necessitating more comprehensive strategies for disease eradication [101].

1.2 The epidemiology of Ebola virus disease

Ebola virus is part of the Filoviridae family (Filovirus) [26]. The Ebola virus consists of five strains: Zaire Ebola virus (EBOV), Sudan Ebola virus (SUDV), Taï forest or Côte d'Ivoire Ebola virus (TAFV), Bundibugyo Ebola virus (BDBV) and Reston Ebola virus (RESTV). All these strains except RESTV can infect humans and non-human primates, with different pathogenicity, causing Ebola virus disease (EVD) [143]. EBOV is the most lethal. It was associated with the 2014-2016 EVD epidemic in West Africa, causing an infection of more than $28,000$ cases and deaths of more than $11,000$ [179]. EBOV was discovered after a new fatal viral hemorrhagic fever occurred in a village in Zaire (the Democratic Republic of Congo) in 1976 [180] and in Nazara, South Sudan [161]. The new virus associated with the outbreaks was named Ebola after a river near the Zaire village [113].

EVD is a disease that can be transmitted from animals to humans [156]. It regularly affects and kills non-human primates, such as apes, gorillas, monkeys, and chimpanzees [10]. Additionally, fruit bats from the Pteropodidae family are often considered to be carriers of the Ebola virus [93, 113]. Typically, the initial person infected in an EVD outbreak, referred to as the index case, contracts the disease through the consumption of hunted meat of an infected animal or by direct contact with infected fruit bats [29]. EVD can be transmitted from animals (live or dead) such as antelope, porcupines, non-human primates, and fruit bats to humans through contact with infected animals' blood, organs, or bodily fluids [23]. The Ebola virus can remain in the body cavity and blood of deceased non-human primates for up to seven days. It can also remain up to five days in the dry blood of humans and non-human primates [126, 51]. In some situations, the virus can remain in the fomites of an infected person for more than 30 days [160]. Human-to-human infection occurs through contact with bodily fluids or contaminated fomites of infected individuals [94, 54, 115]. Further, deceased individuals have the highest infection

rate [94]. Social practices such as washing EVD deceased individuals before burial and touching them contribute to the dispersal of EVD [41]. The hospitalisation context can cause further spread of EVD if proper safety protocols are not practiced [121]. Ebola virus can spread from humans to the environment again by inappropriate hygienic and sanitary conditions [11, 10]. EVD is also transmitted sexually [180]. According to WHO, EVD male survivors should practice safe sex for a year from the onset of EVD symptoms or until their semen tested negative twice for EBOV [180].

The incubation period is the period from when an individual becomes infected to the initial appearance of symptoms and signs of the infection [6, 79]. This period ranges from 2 to 21 days for EVD [180], and people are not infectious when asymptomatic. EVD symptoms start with influenza and malaria-like symptoms of headache, fever, muscle pain and sore throat. However, they develop into diarrhoea, vomiting, rash and severe weakness. The final stage is kidney and liver damage and internal and external bleeding [113, 25, 127]. The average EVD case fatality rate is 0.5, but case fatality rates of up to 0.9 have also been recorded in past outbreaks [10, 180].

EVD treatment usually entailed relieving EVD symptoms, oral and intravenous rehydration, and curing other diseases that a patient may have [94]. Now the following steps are followed to interrupt the viral transmission chain [10, 127, 113]:

- Minimising the danger of animals to humans transmission by avoiding contact with fruit bats, monkeys and other non-human primates and avoiding eating their raw meat,
- Reducing the danger of human-to-human infection that results from close contact with EVD-symptomatic individuals, especially with the bodily fluids of these people. If close contact must be made with symptomatic people, for example, taking care of EVD-ill persons at home or hospital, gloves and protective equipment must be worn. Further, hands must be washed properly after caring for and visiting patients,
- Raising public awareness of EVD risks and protective measures,
- Contact tracing of EVD contacts,
- Placing suspected cases in quarantine for three weeks (maximum incubation period),

- Practising prompt and safe burial for EVD deceased individuals,
- Vaccinations,
- Experimental antiviral treatments.

Despite these control efforts, the disease still spreads in many parts of Africa. We hope to study the dynamics of this disease in order to mitigate its effects.

The objectives of this thesis are to:

1. identify crucial gaps in the modelling literature and improve prospective models by addressing current models' constraints;
2. quantify and study important epidemiological issues on the spread and control of EVD using novel mathematical models.

The deadliest outbreaks in recent history were the 2014-2016 West African outbreak (2014 WA EVD) and the 2018-2020 Kivu outbreak in the Democratic Republic of Congo. We discuss these outbreaks to motivate the problems that the current study explores.

1.3 The 2014-2016 EVD outbreak

One of history's most devastating EVD epidemics occurred between 2014 and 2016 in West Africa. The index case (primary incidence) was an 18-month-old boy living in Meliandou village in Guéckédou prefecture in Guinea who died after becoming infected by EBOV [178]. The origin of the infection is uncertain, but it is likely to have originated from an animal, possibly a bat [162]. Although the outbreak may have started from animals, secondary transmissions have occurred from humans to humans [59]. Figure 1.1 depict how the 2014 WA progressed over two years in Sierra Leone, Liberia and Guinea. Despite the lessons learnt from the modelling efforts of the 2014-2016 WA EVD, the disease continued to spread on a large scale in Africa. Thus, it is vital to systematically review mathematical models of EVD, identify gaps, and improve prospective models by addressing current models' constraints.

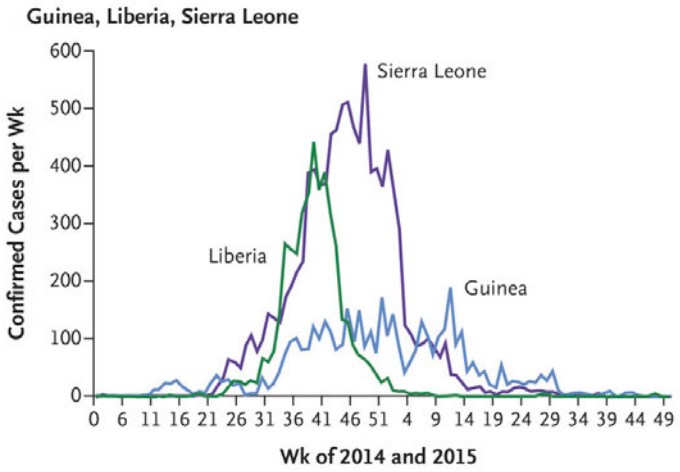


Figure 1.1: The number of EVD cases reported every week (Wk) during the years 2014 and 2015. This figure was adapted from [162].

1.4 The 2018-2020 Kivu outbreak

The second-largest EVD outbreak in history was declared in North Kivu and Ituri provinces in 2018. The outbreak infected 3481 individuals and caused 2299 deaths. It affected more than 18 health zones in North Kivu and around eight health zones in Ituri provinces [167]. However, not all areas had the same EVD spread. Only six health zones in the North Kivu and Ituri provinces - Beni, Butembo, Kalunguta, Katwa, Mabalako, and Mandima - accounted for roughly 81% of infections by 25 August 2019 [68]. As a result, immunisations directed towards high infection locations may be a critical factor in controlling the spread of EVD when other intervention techniques fail to stop the outbreak's spread.

During the 2018-2020 Kivu outbreak, unidentified assailants stormed an Ebola treatment centre (ETC) in Butembo and burned several buildings and vehicles. The centre had 57 patients including 15 confirmed cases. The incident occurred several days after another attack in Katwa's ETC. Ten patients were present at the Katwa centre, four of whom had been diagnosed with EVD. In a previous outbreak, a group of community members attacked an ETC near Monrovia [66]. They looted items including mattresses containing blood and other bodily fluids of infected individuals [66]. Understanding the interplay between the attacks on Ebola treatment centres (ETCs) and the spread of EVD is critical to comprehend how EVD unfolds in conflict and community distrust zones.

1.5 Outline

In Chapter Two, we systematically review previous modelling literature on EVD and determine limitations in these models. A detailed review of each article is presented in an Appendix of this thesis. In Chapter Three, we study the impact of geographically-targeted vaccinations when the spread of EVD cannot be controlled using contact tracing, ring vaccinations and antiviral treatments. The proof of the theorems used in Chapter Three is presented in an Appendix. Chapter four studies the impact of the attacks on Ebola treatment centres during the 2018-2020 Kivu outbreak. In Chapter Five, we summarise the thesis findings and determine routes for future work.

Chapter 2

A Systematic review of mathematical models of the Ebola virus disease

2.1 Introduction

Recently, humanity has confronted an increasingly difficult re-emergence of the Ebola virus disease (EVD) [98, 132]. According to the World Health Organization (WHO) report in 2019, EVD was classified as one of the top ten threats to global health [182]. To date, more than 26 EVD outbreaks are know to have occurred [23]. The most severe was the 2014 West African Ebola outbreak (2014 WA EVD) which caused more than 11000 deaths followed by the 2018-2020 outbreak in the Democratic Republic of Congo (DR Congo) which caused more than 2000 deaths.

EVD is a zoonotic disease [156]. It follows a periodic cycle in non-human primates (apes, gorillas, monkeys and chimpanzees) and eradicates them [10]. Further, fruit bats of the Pteropodidae family are believed to be a reservoir for the Ebola virus [93, 113]. In almost every EVD outbreak, the first infected case was suspected to be due to eating hunted meat of an infected animal or by contact with fruit bats [29]. Human to human infection occurs through contact with bodily fluids or contaminated fomites of infected individuals [94, 54, 115]. The average EVD case fatality rate (CFR) is 0.5, but case fatality rates of up to 0.9 were also recorded in previous outbreaks [10, 180]. As the number of infected persons escalated during the past EVD outbreaks, many questions emerged about the epidemiology of EVD and the efficiency of tools and methods used for controlling the outbreaks. Mathematical models played an important role in assessing the value of different control measures and forecasting the trajectories of the outbreaks.

A mathematical model in the context of biology is defined to be an equation or a set of equations describing a biological phenomenon that quantitatively explain the phenomenon and ideally predicts its dynamics. Mathematical modelling is the process of formulating

and analysing model equations and comparing model prediction with observations. Mathematical modelling of EVD has been effectively utilised to plan strategies for probable geographic spread, handle disease outbreaks in real-time, assess the impact of therapeutic and non-therapeutic control measures, and assist in the formulation of policy decisions [186].

Several studies have surveyed the literature on mathematical modelling of EVD [32, 43, 150, 37, 33, 164, 35, 155, 186, 38]. Chowell and Nishiura [32] reviewed significant epidemiological parameter estimates from historical EVD outbreaks (outbreaks which occurred before the 2014 WA EVD) and conducted a brief comparative review of different historical models and the 2014 WA EVD. Drake et al. [43] reviewed six mathematical modelling articles of outbreaks prior to the 2014 WA EVD. Van Kerkhove et al. [150] created a database of EVD parameter estimates from the past and the 2014 WA EVD. Chretien et al. [37] reviewed 66 studies of mathematical modelling of EVD. They aimed to discuss critical uncertainties addressed by these models, the data used, the public allocation of the data, results, and the performance of these models. Chowell et al. [33] analysed simulation data and reviewed models that accounted for realistic population mixing assumptions. Wong et al. [164] reviewed phenomenological and mechanistic models published from January 2014 to December 2015. They aimed to assess the impact of compartment models and under-reporting in the disease parameter estimates as well as in the disease trajectories. Chowell et al. [35] aimed to provide a viewpoint on some of the difficulties and conclusions learnt from the 2014 WA EVD modelling efforts. Viboud et al. [155] presented findings of an EVD forecasting challenge using synthetic data and conducted a systematic comparison for the performance of eight modelling approaches that participated in the trial. Zitzmann and Kaderali [186] concerned themselves with reviewing the literature on mathematical modelling of viral dynamics. In addition to reviewing six articles of mathematical modelling of the Ebola virus, they also reviewed mathematical models for other viruses, including HIV, Influenza, Hepatitis C, Dengue, and Zika viruses. Dembek et al. [38] reviewed mathematical models for diseases that potentially affect large populations. They presented key findings of some EVD models without discussing the models and their assumptions or approaches.

Most of the articles mentioned above did not review any work published after January 2016. Furthermore, those that have considered such work only focused on either particular

types of models [186], presented only findings for some models [38], or included just a few articles published in 2016 [33, 35, 155]. Additionally, these reviews did not focus on examining models by systematically identifying advantages and limitations or gaps for further research. Thus, there is a gap in the literature for systematically reviewing models published after January 2016.

In light of this, we carried out a systematic review of mathematical models of EVD. The objectives of this review are to present an overview of the mathematical modelling literature on EVD, identify gaps, and improve prospective models by addressing current models' constraints.

To achieve the current study objectives, we focused on reviewing each surveyed model in terms of the proposed problem, the data used, the approach, findings, advantages, and limitations. We chose to survey the modelling approaches because the choice of the method is essential in modelling. For example, phenomenological modelling approaches are generally more useful in providing a general sense of the data when there is not enough information about the disease's natural history parameters or enough data for quantifying modelling that account for the underlying mechanisms by which the disease variables are linked. Mechanistic modelling, on the other hand, is more useful in providing estimates for model parameters and natural history when there is sufficient data.

Models sometimes account for spatial, within-household, and within-host transmissions in their components. Due to its geographical distribution, the 2014 WA EVD become the most devastating EVD outbreak in history. The outbreak is believed to have started with an 18 month old boy living in Meliandou village in Guéckédou prefecture in Guinea and spread regionally and internationally through the mobility of people [178]. Spatial transmission models are used to understand, for example, how the migration of individuals contribute to the dispersal of EVD and how long it could take for the Ebola virus infecting someone in a region to cause subsequent infections in another region. They are also used to understand the impact of spatially-targeted intervention measures. Within-household transmission, on the other hand, was recorded to have created 82% of community transmissions in Guinea and more than 66% of the total transmissions in the country [49]. The reason for the increased proportion of the within-household transmission has resulted from the nature of EVD spread. The disease spreads through close contacts with patients via their bodily fluids and contaminated fomites. Modelling can account for within-household

transmission and be used to assess the impact of household-targeted interventions. Within-host transmission models help in understanding the interaction measurements of the Ebola virus with target cells. This modelling is particularly important since the virus is rated at level four in biosafety measures and hence basic research on the virus is limited [63].

Motivated by the importance of the consideration of spatial, within-household and within-host transmission components in modelling, we group our reviewed studies into five ensembles: spatial, within-and-between-households, within-host, other transmission, and other intervention models.

The rest of the chapter is organised as follows: In Section two, we create a system of identifying the surveyed literature. In particular, we set up the characteristics to be used to select eligible studies. Thereafter, we determine these studies. In Section three, we present an overview of the modelling issues and approaches. To achieve this, we revisit the grouping of the surveyed studies, motivated earlier. Thus, we group the surveyed studies into spatial, within-and-between-households, within-host, other transmission, and other intervention models. In Section four, we outline findings and limitations of the reported studies. We initially start with transmission determinants and terminate with interventions. In Section five, we conclude our work and discuss recommendations.

2.2 Methods

Many reviews were performed following the PRISMA statement for systematic reviews [109]. We follow the same procedure in the current study. In this section, we state the searching strategy for the literature and the eligibility criteria. Thereafter, we identify articles to be reported.

To conduct a systematic search for the current study, we focused on the PubMed database. PubMed provides a search engine for biomedical and life science literature. The database includes the National Library of Medicine (NLM) and the MEDLINE resources. It incorporates a bibliographic database composed of published literature including journals, conference proceedings and reports. It has been argued that PubMed is an optimal search engine for biomedical electronic publications [47]. To identify articles for the current study, we searched the PubMed database on 25 February 2019 using the following search constraints:

1. We used the search keys “ebola” and “model”;

2. We restricted the search to articles published between 1 January 2016 and 31 December 2018.

The following selection criteria were used to select eligible articles:

1. Studies that include mathematical models of EVD in humans;

2. Phylogenetic studies were excluded;

3. Articles not in English were excluded;

4. Review studies were excluded. It should be remarked that the excluded mathematical modelling of EVD reviews were already discussed, in addition to all similar reviews, earlier in the introduction to motivate the current research questions;

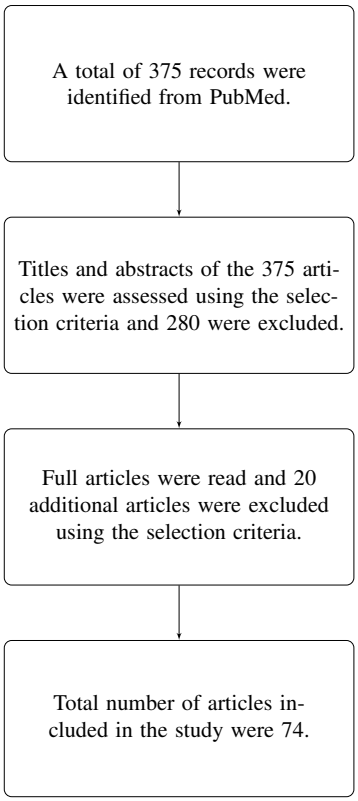
5. Studies that did not provide any quantifications or simulation using real or synthetic EVD data were excluded.

To identify the eligible articles, the titles and abstracts of articles obtained from the initial systematic search were screened, and those that did not fit the selection criteria were eliminated. The full articles were then read, and subsequently further refined using the selection criteria. The selection process and the results are shown in Figure 2.1.

2.3 Modelling issues and approaches

Mathematical models can be classified into phenomenological and mechanistic models. They can also be divided into deterministic and stochastic models. Models can be analysed using mathematical theory or computer simulations. Mathematical theory is beneficial in depicting general patterns from simple models, and computer simulations are useful in drawing specific and precise results from complex models. Still, they generally sacrifice drawing broad conclusions [9]. In this section, we group our reviewed models into five sets: Spatial, within-and-between-households, within-host, other transmission, and other intervention models. We discuss the issues addressed in these models and how they were approached.

Figure 2.1: Flow diagram of the selection process



2.3.1 Spatial transmission models

Several studies accounted for spatial transmission [97, 163, 133, 8, 89, 45, 111, 154, 131, 36, 124, 60, 85]. These studies addressed various issues and used different approaches to express spatial transmission.

Spatial models explored various issues including the risk of regional and international spread [97, 163, 133, 8], estimating the distance of EVD transmission [89], determining individual heterogeneities regarding the spread of EVD [89], and assessing spatially targeted control measures [45]. Spatial modelling was also used to identify the best international intervention measures against EVD [111], understand the spread of EVD in hypothetical cities [124], study the impact of a hypothetical EVD spread in India [133] and estimate the risk of EVD occurrence [60]. One [85] investigated the impact of several spatial spread assumptions made in modelling.

There are different approaches to express spatial transmission. These include using travellers data and either employing phenomenological [163] or mechanistic [97] models or using a geospatial epidemiological framework [133]. Some models also modified the transmission rate with a gravity type parameter [45, 8]. This parameter expresses the dependence of the transmission on the sizes of two interacting populations and the distance between them. When a gravity type parameter is considered, the force of infection decreases with increasing geographical distances and increases with the increase in population density. One [89] employed cell phone GPS data . Some studies [154, 131, 36] used either phenomenological models or a combination of phenomenological and mechanistic models. While one [124] used a compartment framework in an agent-based software called PISKaS, another [133] used a spatiotemporal epidemiological modeller software called STEM. Moss et al. [111] expressed spatial spread by considering different rates of transmission in rural and urban populations. Kramer et al. [85] used a network approach in which the nodes were assumed to be geopolitical administrative units in West Africa, and the edges were assumed to represent how strong were the potential infection routes were among the nodes.

2.3.2 Within and between households transmission models

Several models accounted for transmissions within and between households [3, 82, 5]. These models discussed various concerns and used different approaches to consider within

and between household transmission.

Several parameters have been found to be addressed by the within and between household transmission models. One [3] explored the consequence of a household structure, in particular a household size in epidemiological parameters such as the basic reproduction number, the intrinsic growth rate and the epidemic final size. Another [82] aimed to understand the role of community mixing in explaining the sub-exponential aggregation of EVD dynamics at the district-level in the 2014 WA EVD.

Models approached the within and between households transmission in different ways. Some [3, 82] considered transmission within households to be constant while one [5] considered different levels of transmission within households.

2.3.3 Within host transmission models

Some studies considered within-host transmission in their components [117, 67, 102].

Viral shedding data were used for different purposes. House et al. [67] employed viral shedding data to estimate model parameters, including the mean of the infectious period for high and low viraemia. Additionally, they aimed to explore the mechanism in which vaccines reduce infection. Nguyen et al. [117] employed the data to understand the impact of the within-host pathogen dynamics into the between-host dynamics and evaluate the impact of EVD vaccination. Martyushev et al. [102] explored how EVD therapies such as ZMapp, TKM-Ebola and Favipiravir mitigate Ebola virus spread. Further, they aimed to understand the relationship between EVD severity and Ebola virus replication.

There are different approaches to express within-host transmission. House et al. [67] used a compartment model composed of three stages, starting with an initial viraemia followed by a second stage consisted of a high and a low viraemia and a final stage that was either death or recovery. Nguyen et al. [117] used a logistic model that was embedded with an age-specific contact network to express transmission between individuals. Martyushev et al. [102] used a compartment model with two target cells: susceptible target cells (monocytes/macrophages and dendritic cells (CD)) and potential target cells (hepatocytes, splenocytes and endotheliocytes).

2.3.4 Other transmission models

Several studies predicted the occurrence of EVD [10, 11, 185, 62], and associated the incident of EVD outbreaks with environmental, population, socio-economic, and climatic factors [134, 86, 148]. One studied the role of bats on the EVD occurrence [95]. Some characterised the spread of EVD [129, 48, 158, 118, 88], estimated EVD natural history parameters [144, 55, 125, 151], and explored social and behavioural aspects that characterised the spread of EVD [183, 136]. Some studies [27, 56, 147, 7, 123, 58, 153, 99] forecasted EVD spread trajectories. Others explored the potential impact of EVD sexual spread from male survivors [1], studied the event of super-spreading [90], the factors that might have driven this circumstance [90], and investigated whether the Ebola virus can evolve to become less virulent in the human population [141].

Several models studied the relation of EVD occurrence with some environmental, behavioural, socio-economic, climatic and demographic factors. Others predicted reoccurrence of EVD. One [11] explored whether the effect of environmental transmission of EVD, including poor hygienic practices and the consumption of contaminated bush meat, can explain the re-occurrence of EVD in Africa. Another [10] explored the understanding and forecast of future EVD outbreaks. Schmidt et al. [134] predicted the timing and location of EVD spillover events. Krauer et al. [86] investigated the role of socio-demographic factors in the spread of EVD. Zinszer et al. [185] explored some demographic and environmental predictors of EVD spread. Valeri et al. [148] have systematically investigated the demographic and socio-economic predictors of EVD at the sub-national level in Guinea, Liberia and Sierra Leone. Guo et al. [62] forecasted future reoccurrence of EVD. These models employed different methodologies. One [10] considered a compartment model in which transmission was assumed to happen from humans, fruit bats, non-human primates, and other animals. Another [11] used a compartment model, included environmental transmission as one compartment in the model and assumed infectious humans to have shed the virus in the environment. Guo et al. [62] used a simple SIR model in the absence of intervention measures. Other studies [185, 134, 86, 148] used various statistical methods including regression and Bayesian hierarchical models.

Fruit bats of the Pteropodidae family were believed to be the reservoir for the Ebola virus [93, 113]. Li et al. [95] explored the impact of bats on the EVD spillover event. They used a compartment modelling structure and Markov Chain Monte Carlo simulation.

Several studies aimed to characterise the spread of EVD and analysed EVD data in West Africa. These studies used various approaches. One [129] used an activity-driven and time-varying network in which the set of nodes represented individuals, and the edges represented contacts between these individuals. Another [158] used an age-structured model in which each of the disease stages (e.g., incubation, infectiousness, hospitalisation) was considered as an age of the disease since infection. Ngwa and Teboh-Ewungkem [118] used a deterministic model that integrated EVD data, included quarantine and non-quarantine states and assumed EVD spread in the community to be different than health-care settings. Lachiany and Louzoun [88] considered EVD infection rates to have different distributions including constant, and normal distributions. Fang et al. [48] mapped EVD cases to their geographical locations and used statistical methods to analyse the spatiotemporal trajectories.

Several models were used to estimate various EVD natural history parameters. Taylor et al. [144] determined the basic reproduction number in the three most affected West African countries by the 2014 WA EVD. Frasso and Lambert [55] estimated the effective reproductive number. Pettey et al. [125] measured the mean incubation period of EVD and the serial interval. Vanhems et al. [151] approximated EVD emergence probability and secondary incidence cases when a patient with undetected EVD was hospitalised. Various approaches were used to find these estimates. Taylor et al. [144] used a hybrid stochastic-deterministic approach based on $SEIR$ type model and the Gillespie stochastic simulation. Frasso and Lambert [55] used a discrete-time Markov chain structure of EVD and Bayesian inferential framework. Pettey et al. [125] used publicly available online sources, conducted an online search about recorded EVD reports and built a transmission chain. Vanhems et al. [151] used a stochastic compartment model and the Gillespie simulation. They divided the population into patients, nurses, and physicians.

Some studies proposed alternative approaches to formulate an accurate description of epidemic dynamics [100], explored the problem of parameter identifiability [140] or assessed some common modelling assumptions [18]. One [140] derived a linear Volterra-type integral equation from a compartment model of the $SEIR$ type. Another [18] fitted cumulative EVD incidences to a logistic growth and used a simple compartment model to explain the underlying reasons for the EVD trajectories produced in the logistic growth.

Getz and Dougherty [100] proposed an alternative approach to the standard $SEIR$ modelling method using a discrete stochastic Erlang type modelling.

Social and behavioural aspects can characterise the trajectories of EVD outbreaks and explain the underlying reasons for the disease trajectories [183, 136]. One study [183] assessed the impact of individual behavioural changes on EVD trajectories. This study utilised four different EVD forces of infection to implement behavioural change and decided which of them had the best model fitting and disease prediction. Another [136] used a system dynamics approach to understand the impact of social and behavioural factors in the spread of EVD. This study incorporated twitter data about outbreak news as a measure of the psychological and behavioural changes.

To predict the spread of EVD, various methodologies were used with real or synthetic data. Several studies [27, 56, 147, 7, 123, 58, 153] used synthetic EVD data that were produced for the RAPIDD (Program of Research and Policy for Infectious Disease Dynamics of the United States) Ebola forecasting challenge. They aimed to forecast EVD trajectories using the different datasets provided in the challenge and employed different types of approaches (phenomenological, mechanistic, and mixed). Others [139, 99] adapted real data for the three major affected countries by the 2014 WA EVD and used global and phenomenological modelling approaches to forecast EVD incidence and to characterise EVD dynamics.

To study the potential impact of EVD sexual spread from male survivors, Abbate et al. [1] used a compartment model of the $SEIR$ type in which a further compartment C representing the convalescent population was added.

To investigate super-spreading and the factors that might have driven this circumstance, Lau et al. [90] used network-based and Bayesian frameworks. The approach focused on creating transmission trees among EVD cases. A Bayesian model then integrated the data and inferred the distribution of new cases.

To understand whether the Ebola virus can evolve to become less virulent in the human population, Sofonea et al. [141] used a compartment model. They assumed the case fatality rate to be proportional to the transmission rate. An evolution in the population was considered to occur by a rare mutation that creates a different case fatality rate.

To assess the impact of relapse and reinfection in the spread of EVD, Agusto [4] proposed a deterministic compartment model. Recovered individuals in the model were assumed to have a disease relapse or to become reinfected by being exposed to infectious individuals.

2.3.5 Other intervention models

Some models [119, 76, 57, 44, 110] assessed the impact of intervention measures including contact tracing, isolation, safe burials and vaccinations. Others [20, 39, 64] explored how to improve the performance of randomised intervention trials. Two studies [184, 75] determined the optimal procedure of eradicating EVD. Another [94] studied the impact of public health education on the spread of EVD. Various other studies evaluated the impact of EVD therapies and vaccines [107, 87, 12, 65, 15, 71].

Intervention trials aim to benefit participants and whole communities. Some models either intended to evaluate the performance of randomised intervention trials or to design intervention trials that have high attainments [20, 39, 64]. One [20] evaluated the feasibility of a prime-boost vaccination trial, while others [39, 64] increased the performance of randomised trials. These studies used various approaches. One [20] used a compartment model in which they assumed susceptible individuals to either be recruited to vaccinated or control groups. Another [39] utilised a metapopulation framework to project areas of the first order of incidence occurrence and those with the highest weekly cases. Harling et al. [64] proposed a class of connectivity-informed designs and utilised connectivity information between clusters in intervention scenarios.

The impact of intervention measures was characterised in many ways. Nieddu et al. [119] introduced a stochastic model that accounted for EVD spillover from its zoonotic reservoir. Interventions were considered by limiting the contact rate with infectious individual, safe burials or reducing the reservoir transmission. Jones-Konneh et al. [76] used an agent-based model. They considered both the initial status of individuals regarding their knowledge about EVD and the status when individuals are well-informed about EVD. Funk et al. [57] structured the population into the general community and the people within healthcare centres. The importance of community engagement was represented in the model as the healthcare-seeking behaviour parameter. Muhammad et al. [44] used a

compartment model of the $SEIR$ type with further hospitalisation, quarantine, and vaccination components.

Models are sometimes used to find the optimal strategy of eradicating EVD. One [184] was used to calculate the fastest road for drug and vaccine distribution, and to find the storage solution that results in the minimum total cost. Another [75] was used to find critical measures to eradicate EVD optimally. These models incorporated different methodologies. Zhu et al. [184] used a compartment structure and optimisation methods. Jiang et al. [75] proposed a compartment model that accounted for early and advanced stages of infectiousness, hospital isolation, EVD therapy, and vaccination.

To assess the impact of public health education on the dynamics of EVD in Sudan, Levy et al. [94] used a deterministic compartment model that divided the susceptible population into individuals who were knowledgeable about EVD and individuals who were not. They studied the effect of becoming knowledgeable about EVD on the spread of the disease.

To assess the effectiveness of contact tracing in the early phase of an outbreak, Shahtori et al. [110] used an activity driven network method. The contacts of an infectious person were observed for 21 days. Further, this observation was implemented after some delay, and the effects of this delay were evaluated.

EVD therapies and experimental vaccines were extensively used during the 2018-2020 DR Congo outbreak and the late period of the 2014 WA EVD. Several studies evaluated the impact of ring vaccination [107], explored the circumstance under which ring vaccination could control the spread of EVD [87], evaluated the impact of the rVSV-ZEBOV EVD vaccine [12], assessed ring vaccination trial design [65] and evaluated the voluntary vaccination strategy [15]. One [71] evaluated the convalescent blood transfusion therapy and explored vital factors that strengthen this treatment. Motivated by these concerns, the studies above applied various methodologies. One [107] applied a novel methodology that integrated transmission within households and extended families. Another [87] used a statistical method that explored the circumstance under which ring vaccination could control the spread of EVD. Bodine et al. [12] utilised a compartment model that accounted for various risks of infection. Hitchings et al. [65] used a compartment modelling structure and assumed individuals to either be infected by rings of contacts and contacts of contacts or by the general population. Further, they assumed vaccination to be implemented

immediately or after some delay.

Brettin et al. [15] considered a compartment of vaccination in a compartment model. They assumed a population to be well informed about the risk of the disease and the direct and indirect cost of vaccinations. Huo et al. [71] presented a treatment-donation-stockpiles compartment model and assumed that infected individuals to be efficiently hospitalised and safely buried when deceased.

2.4 Model conclusions and constraints

There are several questions asked by public health physicians when facing the possibility of an epidemic. These include:

- How severe will an outbreak be?
- How many individuals will be affected by a disease?
- What is the maximum number of individuals that should be treated to stop the spread of an outbreak?
- How long will the epidemic continue?
- How effective is the quarantine of victims in decreasing the seriousness of a plague?

Mathematical models are tools used to answer these questions, among others [9]. They are used to achieve this goal by describing the relationship between variables in a dataset where they seek only to describe the data or, they further explain how these variables are related to each other biologically. However, models are often constrained by simplifying assumptions (e.g., homogeneous mixing) or problems in the datasets (e.g., in-accurateness or incompleteness) [46]. In this section, we discuss model findings and limitations in addition to gaps for further work. We first start with transmission factors and issues followed by intervention factors.

2.4.1 Enviro-climatic, socio-geographic and socio-economical factors

In some studies, it was suspected that climatic changes and the expansion of population in addition to some population and socio-economic factors played a crucial role in the spread of EVD [148, 185, 134, 62]. Consequently, these issues were explored and found

to be important variables in associations of EVD occurrence. It has also been found that household and community sizes play an essential role in the spread of EVD [3, 82].

In order to forecast the spread of EVD, some studies [148, 185, 134, 62] used environmental and ecological predictors. Some of these studies made simplified modelling assumptions or did not explore important consequences of their findings. Others, on the other hand, could be applied to new contexts. Many statistical models [148, 185, 134] were used to associate rainfall, urbanicity and the number of households not owning a radio with a high risk of EVD occurrence. However, the causative relations between these risks and the human-to-human spread of EVD with a particular focus on how human mobility and healthcare accessibility are affected by these risks are not studied in any of our reviewed articles. One statistical association model [134] was used to show that the risk of EVD peaks in the transition period between wet and dry seasons and suggested that Central Africa, East Africa and Madagascar to have a high risk of EVD occurrence. However, the model did not incorporate local factors such as the level of hygiene and diet practices (e.g., eating of contaminated bush meat) that are often associated with EVD spillover [10, 11]. Guo et al. [62] forecasted the EVD epidemic to reoccur in 2035. Then it will continue to reoccur after eight to nine years. However, it is not generally simple to predict the reoccurrence of EVD without accounting for many factors that contribute to the probability of EVD spillover. These include environmental changes, urbanicity, and the consumption of bush meat [134].

Household and community sizes played an essential role in the spread of EVD. Adams [3] found that the increase in household sizes to have increased the risk of EVD spread. Further, communities with small household sizes required a modest level of case identification and quarantine. In contrast, those with large sizes required effective quarantine combined with case detection and isolation of the whole household. Kiskowski and Chowell [82] found that the community size and the basic reproduction number for the household and that of community to have characterised the spread of EVD. These studies [3, 82], however, either assumed that the transmission within and between households to be constant or did not account for heterogeneity of transmission within households. In reality, people who look after patients have a higher chance of EVD transmission as compared to other household members [120]. Further, transmission within relatives and friends is higher than transmission among the general community [120].

2.4.2 Transmission within healthcare units

Nosocomial transmission has historically played a crucial factor in the spread of EVD [21]. This transmission usually results from poor cleaning or ineffective decontamination at healthcare centres. Several models were used to specify factors that reduced the spread of EVD in healthcare settings and to identify people at high transmission risks [5, 76, 151].

Vanhems et al. [151] estimated EVD emergence probability at hospitals when EVD patients were misdiagnosed and found nurses to have a higher risk of EVD infection compared to other groups (physicians and other non-EVD patients). Their study, however, only assumed direct infection through contact with EVD patients and did not account for indirect transmission that could occur from bad cleaning or inefficient decontamination of the bodily fluids of EVD patients. Further, it was assumed that the isolation efficacy to be 100% as soon a patient was diagnosed with EVD which might also be an overly optimistic assumption given the high contagiousness of EVD.

Several factors were found to have caused a reduction in the spread of EVD within the healthcare system. Ajelli et al. [5] found that the relatively high preparedness of the healthcare system, the early availability of Ebola treatment centers and the application of case isolation and safe burials to have limited the spread in the early stage of the outbreak in Guinea during the 2014 WA EVD. Jones-Konneh et al. [76] found that the increase in the probability of seeking intensive training about EVD and practising appropriate care procedures to have caused a greater decline in EVD infection compared to the increase in the percent of healthcare workers (HCWs) who initially had some knowledge about EVD or those who attended little training about the disease. Jones-Konneh et al., however, did not account for any actual delay in establishing EVD training academies for HCWs.

2.4.3 Transmission from bats, animals and virus shed in the environment

Some models [119, 95] were used to determine the effects of the bat's spillover in the spread of EVD. Others [11, 10] were used to identify the impact of environmental transmission resulting from poor cleaning, inadequate decontamination, or unhygienic diet practices such as the provision of raw bush meat.

Some studies characterised the spread of EVD as a function of EVD spillover from the bats [119] and specified the effects of increasing the size of the spillover [95]. Nieddu et al. [119] simulated the vulnerability to EVD as a function of the bats infection rate and

determined a range of values for these rates that trigger isolated and endemic outbreaks. Li et al. [95] found that infected bats might have likely been the source of the EVD spillover. Further, they found increasing the number of daily captured infectious fruit bats to have only reduced the peak timing of an outbreak and not the peak value. Li et al., however, assumed bat's spillover rate to be zero during wet seasons while numerous studies [148, 185, 134] associated wet seasons with enhanced risk of EVD spillover.

Some studies [11, 10] investigated the transmission from a contaminated environment in a simple modelling framework and in the context of a complex life ecology composed of bats, humans and animals. Berge et al. [11] found that in the case of a virus-free environment (that is, no recruitment or provision of the Ebola virus in the environment), the number of infected individuals either became extinct or constant in the long run depending on the value of the basic reproduction number. In the case of a non virus-free environment, a constant number of infected individuals in the long run was found. This number was invariant to any changes in the initial number of infections when there was no virus shed by infectious individuals in the environment. In another model, Berge et al. [10] determined the basic reproduction number R_0 and the stability analysis of a disease-free equilibrium in a complex model that illustrated the interplay of EVD transmission within and among fruit bats, non-human primates and other animals, and the human population. The models [119, 11, 10] assumed the population to be homogeneously mixed regarding spatial spread. However, this assumption is not realistic with the most severe outbreaks that occurred during the last decade.

2.4.4 Spatial transmission

Several studies characterised EVD growth at the sub-national level in Guinea, Liberia and Sierra Leone [131, 154, 36, 86]. Some [48, 124] indicated factors that were associated with a spatial spread. Other studies [97, 8] estimated the risk of EVD from travellers. One [85] investigated the impact of a gravity type parameter in the spread of EVD as compared to other spatial modelling techniques. Another [60] associated the road density index (RDI) with a spatial transmission. D'Silva and Eisenberg [45] estimated the impact of spatially-targeted intervention measures.

Several investigations characterised the different growth profiles among the sub-national

levels in the three most affected West African countries by the 2014 WA EVD and determined some factors that were associated with a spatial spread. Some [131, 154, 36] found high variations in EVD growth in the various regions in Guinea, Liberia, and Sierra Leone. Krauer et al. [86] found that the spatial distribution of the disease in prefectures, districts and counties with the highest transmission rates in Guinea, Liberia and Sierra Leone to have clustered regionally whether there is a national border or not. Fang et al. [48] found that EVD invasion at chiefdom level in Sierra Leone to be remarkably correlated with the density of the population, the closeness of treatment centres and the transportation networks. Perez-Acle et al. [124] found that a higher degree of connectivity (through transportation and mobility) and higher proximity to EVD infected areas to have caused higher EVD risks. There are some limitations, however, for these investigations. The studies [131, 154, 36] did not reveal the causes of the high variations in EVD growth. Krauer et al. [86] used early stage data which were generally unreliable and contained case uncertainty due to resource limitations in West Africa and the resemblance of EVD symptoms with other diseases such as Malaria [32]. Further, they assumed the population at the district-level to be homogeneously mixed. Perez-Acle et al. [124] assumed that infected individuals could travel while in reality some might be too sick to travel, hospitalised or quarantined.

Some models were used to assess the impact of a gravity type parameter and the RDI in the spatial spread of EVD [85, 60]. Kramer et al. [85] found that models with a transmission parameter of a gravity type to have created the best characterisation to spatial spread as compared to those models that used diffusion spread or estimated the mobility using cellphone records. Gómez-Barroso et al. [60] found a strong association between the RDI and the risk of EVD occurrence. However, the latter study used data that might contain some unconsidered neighbourhood paths that connect villages. On the other hand, Kramer et al. [85] assumed a gravity-type parameter that does not account for the risk of air travel. Further, it does not consider natural barriers such as rivers or borders between countries.

Some studies estimated the risk of EVD from travellers [97, 8]. Lopez et al. [97] found that in the 15th week of 2014, three individuals among 10,000 travellers from Liberia had EVD. Wiratsudakul et al. [163] found that in early November 2014, the probability of EVD importation into each of the top 20 final destinations for commercial flight passengers travelling from Guinea, Liberia and Sierra Leone reached its peak. Backer et al. [8] found

that between four and ten percent of newly infected people travelled to other districts within the same countries (Guinea, Liberia or Sierra Leone). Further, between zero and 23% of the newly infected persons travelled to other countries. The models [97, 163] did not account for socioeconomic differences of the inhabitants as some could afford international travel while others could not, and did not consider whether frequent travellers were from the most infected areas. Furthermore, Backer et al. [8] did not assume any intervention scenarios such as border closure, check points or hygienity practices such as washing of hands to reduce the chance of disease transmission.

D'Silva and Eisenberg [45] found that when applying local interventions for a district with a high infection rate (0.1% of the total cases) in Guinea, Liberia or Sierra Leone, a reduction of 20% of the total EVD cases in these countries occurred. This study incorporated district and national scale dynamics. However, it did not account for transmission in small scales such as communities (neighborhoods) and villages which have been modeled by Kiskowski and Chowell [82].

To conclude, it was illustrated that just feeding high-speed computers with large amounts of data may not necessarily explain the fundamental processes and properties underlying a specific dynamic phenomenon [16]. Alternatively, it was suggested that the notion of the traditional geographic distance used in spatial models might be replaced with an effective distance [16]. In the notion of effective distance, it was assumed that two locations in the air-transportation network with many passengers should be effectively close compared to locations coupled only by a small number of travelling passengers, irrespective of these locations' geographical distance.

2.4.5 Behavioural changes

Some studies assessed the impact of the earlier implementation of behavioural changes and determined how the change in behaviour could be modelled [94, 183]. Levy et al. [94] revealed that the timing of the behavioural changes in addition to the initial proportion of informed and ill-informed susceptible individuals to have played an important rule in determining the magnitude of an outbreak. Yan et al. [183] found that the force of infection that includes an exponentially declining trajectory as a result of behavioural changes to have created the best model fitting and disease prediction. The force of infection found in the latter study can be adapted and used with data that include behavioural

changes to extract other information from the data such as understanding if the difference in age can explain the super-spreading event. On the other hand, the former model [94] can be applied to another context. For example, instead of considering educated and uneducated population groups, two population groups (vaccinated and unvaccinated) can be considered. Consequently, the impact of vaccination can be studied.

2.4.6 Other transmission issues

Many studies have explored the trajectory of EVD [27, 56, 147, 7, 123, 58, 99]. Some focused on estimating EVD natural history parameters [67, 139, 125, 137, 144]. Others measured the impact of super-spreaders and characterised population groups that might have contributed to the super-spreading event [90, 89], described the impact of sexual transmission from survivors [1], addressed the effect of disease relapse and reinfection of recovered individuals [4], or pointed out whether EVD could evolve to become less virulent [141]. One [18] provided important insights about common EVD modelling assumptions. Some studies either suggested an alternative structure to the $SEIR$ model [100] or determined a different approach to the nonlinear optimisation methods used in modelling [140].

Several studies [27, 56, 147, 7, 123, 58, 99] were used to predict the spread of EVD. However, some [56, 147, 58] either made a short time forecast of incidences or did not predict epidemic peaks. Champredon et al. [27] found that fitting a compartment model to synthetic data resulted in double bumps in the disease incidence trajectories. This result was explained to emerge from the effect of spatial spread. However, the authors did not include spatial transmission in their modelling. Mangiarotti et al. [99] created a model that only used EVD time series to simulate EVD trajectories and predicted the epidemic for a short period. This study assumed the population of Guinea, Liberia, and Sierra Leone to be homogeneously mixed. However, the spread of EVD in these countries was not similar due to the different healthcare system preparedness and the different contact structure [57, 82, 35].

Many studies estimated vital EVD natural history parameters [67, 139, 125, 137, 144]. House et al. [67] found the mean of the infectious period to be 5.3 days for a low viraemia and 6.8 days for a high viraemia. Smirnova and Chowell [139] predicted EVD final size for the 2014 WA EVD to be $1.7 \times 10^4, 1.1 \times 10^4$ and 3.5×10^3 in Sierra Leone, Guinea

and Liberia, respectively. Pettey et al. [125] estimated the mean incubation period and the serial interval to be 12.5 days and 19.4 days, respectively. Siettos et al. [137] estimated the effective reproductive number R_t to be 0.7 from 21 December 2014 to 18 February 2015. However, this figure had increased to 1.98 in the following two months. Taylor et al. [144] found the basic reproduction number R_0 for Guinea, Liberia, and Sierra Leone to be $1.24, 2.06$, and 1.71, respectively. The studies [67, 139, 125, 137, 144] had some limitations. Smirnova and Chowell [139] assumed the population of each country (Sierra Leone, Guinea and Liberia) to be homogeneously mixed. Pettey et al. [125] used an online news media report data that might have included misinformation or disclosed personal details of individuals. Further, these online resources might have been altered without prior notice. The strength of the methodology presented by Siettos et al. [137] depends on the accuracy of the data. It is believed that there were issues such as under-reporting in the 2014 WA EVD data [35]. The structure of the Taylor et al. model [144] was relatively simple. It did not include some realistic differences in EVD transmission among the population. Some of these variations were recorded to be among the different districts [154, 131, 36], age groups [5], and community structure [82].

Lau et al. [90, 89] estimated the impact of super-spreaders and characterised the population groups that might have contributed to super-spreading. They found that super-spreaders of about 3% of the total EVD cases to be responsible for more than 60% of all generated cases in a dataset from Sierra Leone. Further, they concluded that instantaneous super-spreading to have occurred, mostly, from age groups of less than 15 years old and larger than 45 years old. The studies [90, 89] incorporated only EVD death data. Therefore, the study can only conclude age-specific infectiousness heterogeneity for fatal cases. A different dataset composed of fatal and non-fatal cases can be considered, and age-specific infectiousness heterogeneity in the new context could be explored and contrasted against those of the fatal cases data.

Abbate et al. [1] found that there was generally an insignificant increase in the number of EVD cases resulting from survivor's sexual transmission, but this transmission extended the duration of the disease. The effect of sexual transmission from EVD survivors in metapopulation systems is a potential research project for extending this study.

Agusto [4] found that in the presence of disease reinfection of a recovered person by

an infectious individual, a backward bifurcation was found in which a disease-free equilibrium and an endemic equilibrium coexisted. Disease relapse of a recovered individual was found to lead to more infections compared to disease reinfection. While extending previous studies by including the relapse and reinfection of recovered individuals and studying their impact, Agusto [4] assumed transmission rates in the general population, healthcare settings, urban and rural areas to be equal.

Sofonea et al. [141] found that it was unlikely for the Ebola virus to evolve and become less virulent unless two conditions were satisfied. First, the proportion of unsafe burials should be reduced to less than 4%. Second, the case fatality rate and the EVD transmission rate must have very little or no genetic connection. While assuming transmission rates to be proportional to the case fatality rate (CFR), the model did not consider any heterogeneity in the CFR. However, it was believed EVD deceased to have the highest infection rate compared to living infectious individuals [94].

Burghardt et al. [18] found that EVD models with population-density dependent transmission rates might accurately predict the initial spread in an area. Further, initial growth was found to decrease as the population density increased. While suggesting metapopulation modelling could predict the initial spread of EVD through the flow of travellers, the model did not account for any control measures that might reduce or block the chance of the disease spread in the initial stage of an outbreak. For example, the behaviour of the population might show early positive change of avoiding infection if the population had learnt about the disease from a previous outbreak [94].

Two studies [100, 140] proposed an alternative framework to the $SEIR$ model and determined a different approach to the nonlinear optimisation methods used in modelling. Getz and Dougherty [100] found that an alternative discrete stochastic Erlang type model for the standard $SEIR$ method to have offered a more accurate description of epidemic dynamics. Smirnova et al. [140] found that a methodology based on a linear Volterra-type integral equation and regularization algorithms to have produced a moderate prediction of the impact of the epidemic in Sierra Leone. While the latter modelling framework was based on a compartment model of the $SEIR$ type, it could be extended to include more realistic transmission stages (e.g., infection from the environment and different levels of transmission among contacts). The Getz and Dougherty [100] modelling, on the other hand, considered the population under study to be homogeneously mixed and regarded

transmission only from living infectious persons.

2.4.7 Vaccinations and therapies

The Merck rVSV-ZEBOV and the Johnson & Johnson Ad26.ZEBOV/MVA-BN EVD vaccines, in addition to other EVD therapies, were the major treatments used during the 2018-2020 DR Congo EVD outbreak [105]. Several studies have evaluated the impact of vaccines and therapies [15, 117, 107, 102] and presented important conclusions. Others [65, 39] investigated the feasibility of vaccination randomised trials. One [184] provided an optimal way of storing and delivering EVD vaccines.

The impact of ring, mass, and voluntary vaccination strategies were explored, and valuable insights were provided. Brettin et al. [15] concluded that a voluntary vaccination might be able to eradicate EVD, particularly when added to other control measures. Nguyen et al. [117] found that mass vaccination of 85% coverage can eradicate the disease if it was launched between five months before and one week after the outbreak. Merler et al. [107] concluded that a ring vaccination to be effective in containing an epidemic up to the value of $R_0 = 1.6$. This figure was increased when other control measures were added. Kucharski et al. [87] found that when an epidemic is less severe, a ring vaccination could eradicate the outbreak. Camacho et al. [20] suggested that when a vaccination trial was started at an earlier time, the probability of eliminating the disease in vaccinated groups increased. The studies [15, 87, 20], however, contained some limitations. Brettin et al. [15] assumed the population to be rational enough to decide to be vaccinated voluntarily and assumed the population to be well informed about the risk of the disease and the direct and indirect cost of vaccinations. Kucharski et al. [87] did not account for different possible immunity periods that the Merck rVSV-ZEBOV vaccine might have [52]. Camacho et al. [20] did not account for any logistical constraints that may affect the feasibility of the vaccination trial in the studied areas.

Diakite et al. [39] found that if vaccination trials were started ten weeks after the onset of the disease, utilising metapopulation modelling to choose the districts with the highest modelling projection was effective. The proposed metapopulation modelling framework, however, did not account for natural barriers such as rivers that may affect the movement of individuals and create natural protection from the spread of the disease, particularly in the context of Central and West Africa where EVD had the highest level of spread.

EVD therapies and blood transfusions from survivors have increased the chance of recovery for EVD patients. Martyushev et al. [102] found the basic reproduction number to be six for EVD fatal cases and 2.8 for survivors. Further, combining siRNA-based and nucleoside analog-based therapies with an 80% inhibition rate was found to be more likely efficient for otherwise fatal cases even if it was started four days after the onset of symptoms. For non-fatal cases, mono-therapies were found to be sufficient. Huo et al. [71] found the plasma transfusion treatment to have a substantial advantage in increasing the blood bank stockpile and in reducing the CFR. Further, when more blood donors were recruited, and the right track of their contact was kept for re-donation, a more significant reduction in the CFR occurred. The latter study, however, assumed a homogeneously mixed population in a perfect context of hospitalisation and safe burial measures. On the other hand, Martyushev et al. [102] only considered within-host transmission. Their study could be extended to include between-host EVD spread and consequently used to explore EVD transmission and intervention related questions at the individual and population scales. Martyushev et al. [102] assumed a single homogeneous compartment representing multiple organs that are infected at the same time. Chertow et al. [28] criticised this modelling approach. They showed that a one-compartment assumption modelling for the Ebola virus infection and replication counter significant evidence that the Ebola virus infects cells and tissues throughout the body in a nonhomogeneous fashion. Further, they suggested that the multiple body compartment modelling approach will aid the development of more accurate predictive models for EVD.

Zhu et al. [184] found that the speeding up of drug production, and the systematical distribution of drugs and vaccines to be a powerful method for controlling the disease. They further calculated the fastest route for the drug and vaccine distribution and found the storage solution that results in the minimum total cost. This study, however, did not account for heterogeneity regarding the cost depending on the type of the vaccine stored. For example, the two widely used vaccines, the Merck rVSV-ZEBOV, and the Johnson & Johnson Ad26.ZEBOV/MVA-BN have different storage temperatures and consequently different logistical costs [77, 22].

2.4.8 Other intervention issues

Collective control efforts were combined to stop the spread of EVD. These include quarantine, symptom monitoring, contact tracing, and vaccination. Several modelling studies explored the consequence of these measures and obtained essential insights [136, 118, 44, 129, 111, 158, 110, 122].

Several models were used to study the impact of quarantine. Sharareh [136] found that the temporal increase in the rate of quarantine to have resulted from a rise in situation awareness. Ngwa and Teboh-Ewungkem [118] derived a threshold parameter R_0 as a function of the fraction of suspected cases to be quarantined. They found infection to have occurred in treatment centres when all cases were quarantined. Muhammad et al. [44] found the disease to be controlled if the transmission rate of isolated individuals was less than one-fourth of those non-isolated. Further, they found that time-varying optimal quarantine was more effective as compared to a high but fixed level of quarantine. The studies [136, 118, 44] contained some limitations. Sharareh [136] assumed that the three most affected countries by the 2014 WA EVD to be one entity and to have the same rate of transmission. However, the spread of EVD in these countries was not similar due to the different healthcare system preparedness and the different contact structure [57, 82, 35]. Ngwa and Teboh-Ewungkem [118] did not construct a complete treatment based on the most crucial model parameters in the disease spread, and the stochastic effects in the disease growth. Muhammad et al. [44] assumed the transmission to occur only from living infectious individuals (within the community or at hospitals). Thus, they did not consider transmission from deceased individuals or an unclean environment.

Several studies found that early application of control measures and safe burials to improve intervention efforts [129, 111, 158]. Rizzo et al. [129] concluded that the earlier use of intervention strategies to provide a vital decrease in the infected cases and the period of the outbreak. Moss et al. [111] found the early case detection of infected individuals to provide a high decrease in the probability of having a large outbreak. Further, the reduction in transmission resulting from the deceased was found to substantially increase the probability of controlling the outbreak. Webb and Browne [158] found the disease reduction in Guinea and Sierra Leone during the 2014 WA EVD was caused by increased and earlier hospitalisation or isolation of cases. While Rizzo et al. [129] considered individual heterogeneity, they did not account for spatial locations of contacts. Webb and Browne,

on the other hand, considered the entire population to be homogeneously mixed. However, EVD is highly heterogeneous depending on the contact structure and the density of a population [3, 82].

Contact tracing, symptom monitoring, and vaccination represented an essential part of combatting the spread of EVD. Shahtori et al. [110] found that contact tracing to be more effective if the identification of the traced persons was not delayed for more than ten days. Peak et al. [122] found symptom monitoring to be more effective measure in containing EVD compared to quarantine. The increased use of vaccinations [72, 81] motivates extending the latter model to account for vaccinations. One issue that could be investigated is the impact of vaccination measures in controlling EVD compared to non-pharmaceutical intervention measures.

2.5 Discussion

Previous reviews provided a brief comparative survey for natural history estimates [32, 150], reviewed only some EVD models [43, 186, 38], systematically reviewed models that were published at some period [164, 37] or discussed difficulties and conclusions of modelling efforts [35]. However, none of these studies had systematically reviewed any work published after January 2016. Further, none of them focused on reviewing each surveyed study with regards to identifying advantages and limitations in the modelling assumptions. In this study, we created a system of reviewing EVD models that resulted in 74 studies (Figure 2.1).

We classified articles broadly in terms of the modelling approaches as well as the model conclusions and constraints. The study has identified many limitations in the reviewed models and sometimes made brief suggestions for future work. We give two detailed examples of these recommendations.

Approximately 84% of EVD patients in Guinea were adults of age greater than 15 years old, but this group was only 54% of the total population [5]. Consequently, age could be an important factor in the spread of EVD. Few studies [5, 90, 89] used age to characterise the spread of EVD. Ajelli et al. [5] used a simple compartment model of the $SEIR$ type with two age groups: individuals with age younger or equal to 14 years; and individuals older than 14 years. Lau et al. [90, 89] studied whether age can explain super-spreading and proposed that individuals with age less than 15 and greater than 45 years to

be key predictors of super-spreading. However, the dataset used by Lau et al. [90, 89] only included fatal EVD cases and concluded the results to all cases (fatal and non-fatal). On the other hand, the findings concluded by Lau et al. [90, 89] suggest extending the Ajelli et al. [5] model to consider three age groups (individuals with age younger or equal to 14 years, individuals with age of 15 to 45 years, and individuals older than 45 years). The new model can then be used with data that include fatal and non-fatal cases to understand if age can explain super-spreading. In this regard, we propose using the Sierra Leone data presented in Fang et al. [48]. The data were stratified according to age.

The Merck rVSV-ZEBOV and the Johnson and Johnson Ad26.ZEBOV/MVA-BN EVD vaccines were extensively used during the 2018-2020 EVD DR Congo outbreak. The Merck vaccine is given in one dose and its immunity period is unknown. However, it induces high levels of immune responses that can be maintained through 12 months [81, 72]. The Johnson and Johnson vaccine, on the other hand, is believed to have a long-lived immunity [114]. However, the Johnson and Johnson vaccine is given in two doses. The question is, given the high mobility of a population that could affect the effectiveness of the two doses vaccine and an outbreak that lasts longer than one year that might results in an imperfect vaccination strategy for the Merck vaccine as some individuals lose the immunity acquired by the vaccine, what is the best vaccination strategy to be used. One way this problem could be approached is as follows: A compartment model composed of susceptible, exposed, infectious, hospitalised, deceased and recovered compartments can be considered. In this case, EVD transmission could occur by contact with infectious, hospitalised or deceased individuals, or via sexual contact with survivors. If we consider vaccination as one compartment, the sub-model will be the model without vaccination and the full model will be the model with vaccination. If two vaccination compartments were considered for the two types of vaccines, we have more sub-models. In the sub-models and full-model, the basic reproduction number can be derived and stability analysis of the equilibria can be established. Regarding the efficacy problem of the two vaccines, optimal control methods can be used to identify the optimal vaccination strategy in mitigating the spread of EVD.

While surveying models in this chapter and determining their strengths and limitations, we note to clarify that we accept that often research do not give enough data to quantify

detailed disease underlying mechanisms and therefore, they gloss over some details. However, that does not mean these details are not important and when more data are available, models can be improved to have better quantifications by considering these details.

To conclude, this study is the first EVD modelling review that has systematically identified limitations in the assumptions of each reviewed model and made collective presentations for these constraints. We hope that this work will help future researchers in developing more realistic models that could help mitigating the spread of EVD.

Chapter 3

The impact of geographically-targeted vaccinations during the 2018-2020 Kivu Ebola outbreak

3.1 Introduction

On 1 August 2018, the World Health Organisation (WHO) was notified about the emergence of a new outbreak of the Ebola virus disease (EVD) in North Kivu province in the eastern part of the Democratic Republic of Congo (DR Congo) [181]. The WHO recommended implementing proven strategies for controlling EVD outbreaks, including contact tracing, ring vaccination, and antiviral treatments. Despite these efforts, the outbreak continued for about two years and became the second-largest Ebola outbreak in history [166]. In the current study, we explore the impact of geographically-targeted vaccinations to areas in North Kivu and Ituri provinces when contact tracing, ring vaccinations and antiviral treatments were unsuccessful in containing the outbreak.

The 2018-2020 Kivu outbreak occurred in more than 18 health zones in North Kivu, and about eight health zones in Ituri provinces [69]. However, the spread of EVD was not similar in all regions. As of 25 August 2019, about 81% of infections occurred in only six health zones (Beni, Butembo, Kalunguta, Katwa, Mabalako and Mandima) in North Kivu and Ituri provinces [68]. Consequently, vaccinations targeted to high infection areas could be feasible when other intervention strategies could not successfully contain the outbreak spread. Indeed while some individuals who qualified to be vaccinated with the ring strategy might reject the vaccination, others who are at high risk because they live in areas with high infections but who do not qualify for the ring strategy might still agree to be vaccinated. The Strategic Advisory Group of Experts on Immunization (SAGE) approved geographically-targeted vaccinations to be used to contain the spread of EVD when ring vaccinations could not be adequately implemented [174]. This strategy assisted in successfully containing the EVD outbreak in Chowe in DR Congo [175].

A number of studies modelled the impact of EVD vaccinations in the past [87, 44, 12,

34, 135, 19] . Kucharski et al. [87] studied the impact of ring vaccinations and concluded that this strategy would control outbreaks when the spread is not very severe. Kucharski et al. [87] did not consider any other intervention measures that are implemented during outbreaks beside the ring strategy.

Muhammad et al. [44] studied the impact of vaccination, hospitalisation and quarantine and derived an optimal vaccination strategy. However, they did not consider EVD transmission from the deceased. Transmission from the deceased is an important transmission route. A single traditional funeral of a famous pharmacist was linked to a dramatic spike in the number of reported EVD cases during the 2014-2016 Ebola outbreak in West Africa [24].

Brettin et al. [15] modelled voluntary vaccination and concluded that a selfishly optimal vaccination drops under the herd immunity level. In contrast, voluntary vaccination can better eradicate the spread of EVD, particularly when added to other control measures. They assumed that the population was adequately rational to choose the vaccinations and that they were fully informed about EVD risks and the direct and indirect costs of vaccinations [2]. However, people do not always choose to be vaccinated or fully understand the risk of the disease. Brettin et al. [15] also did not account for the role of contact tracing or antiviral treatments that are used during outbreaks besides the vaccinations.

Bodine et al. [12] assessed the impact of the rVSV-ZEBOV EVD vaccine in Sierra Leone. They concluded that to eradicate an outbreak, 40% of the general population and 90% of healthcare should be vaccinated. The study did not account for the high variation in EVD trajectories among the different regions [2].

Chowell et al. [34] evaluated the impact of vaccination in the context of different levels of community accessibility. They concluded that ring vaccination would not successfully end EVD outbreaks due to household being inaccessible and significant delays in vaccinations are available. Similar to Muhammad et al. [44], Chowell et al. [34] did not consider the transmission from the deceased. Further, they also did not account for antiviral treatments used during outbreaks.

Seidu et al. [135] studied the long-term behaviour of a model with two susceptible population groups: a high-risk population composed of care-takers of infected persons and individuals who handle EVD deceased; and a low-risk population consisting of other individuals in the population. The authors determined factors that are of most importance

in the disease dynamics. Lin et al. [96] considered a model with two susceptible groups: Low-risk individuals who are vaccinated with the rVSV-ZEBOV vaccine or living in an EVD low-risk areas; and high-risk individuals who are not vaccinated with the rVSV-ZEBOV vaccine or living at an EVD high-risk areas. Seidu et al. [135], and Lin et al. [96] did not study EVD dynamics in imperfect ring vaccination, contact tracing and antiviral treatments contexts.

Most recently, Burton et al. [19] modelled contact tracing by explicitly considering two compartments, one for traced susceptible persons and one for the traced exposed. They put a limitation on the number of tracers. Burton et al. [19] did not assume any vaccination efforts applied besides contact tracing.

In the current study, we address the limitations of [87, 44, 15, 12, 34, 135, 96, 19]. In particular, unlike Kucharski et al., Seidu et al. and Lin et al. [87, 135, 96], we account for contact tracing and antiviral treatments, simultaneously. In contrast to Muhammad et al., Chowell et al. and Brettin et al. [44, 34, 15], we consider transmission from the deceased. Further, we account for the high variation in EVD trajectories among the different regions, unlike Bodine et al. [12].

This Chapter is organised as follows: In the second section, we discuss model assumptions and formulate the model. In Section Three, we discuss the theoretical analysis of the model. In particular, we consider the non-negativity and boundedness of the model solutions. Then, we derive the basic reproduction number. We also study the existence of the model equilibria and establish local stability around these equilibria. In Section Four, we consider model fitting. We introduce data to be used in the fitting, discuss the model fitting, explore the sensitivity of model parameters to the reproduction number and study the impact of ring and geographically-targeted vaccinations during the outbreak. In Section Five, we conclude the study and discuss recommendations.

3.2 Model formulation

Let N be the number of individuals in a population. We assumed this population to be located in areas with high and low levels of infections. Let S_H and S_L represent the number of susceptible individuals located in areas with high and low infections, respectively. Let V_1 and V_2 be the number of vaccinations among healthcare and frontline workers residing in areas with high and low infections, respectively. Let V_3 and V_4 be the number of

vaccinated contacts and contacts of contacts of infected individuals in the community who were located in areas with a high and a low level of infections, respectively. Let V_5 and V_6 be other vaccinated persons residing in areas with high and low infections. Let E, I, H, D and R be the number of exposed, infected, hospitalised, infectious deceased and recovered individuals in the population, respectively. Thus, we assume

$$N = S_H + S_L + V_1 + V_2 + V_3 + V_4 + V_5 + V_6 + E + I + H + D + R. \tag{3.1}$$

The 2018-2020 Kivu outbreak continued for nearly two years [167]. During such an extended period, natural births and deaths could play a role in the dynamics of the disease. We assume individuals were born at a rate Π and died naturally (reasons other than EVD) at a rate μ. Human-to-human spread of EVD occurs through bodily fluids or blood of infected individuals [2]. We assume that the effective contact rate among susceptible individuals living in high infection areas with live infectious individuals before any intervention to be β_0 and with the infectious deceased to be $\delta\beta_0$ where $\delta \in (0, 1)$. We assume the number of contacts for the infectious deceased to be less than those of living infectious persons since only living persons can voluntarily contact others. Let τ_1 be a modification parameter that accounts for transmission in low infection areas so that $\tau_1\beta_0$ and $\tau_1\delta\beta_0$ are the effective contact rates for the living infectious persons and the infectious deceased with the susceptible individuals residing in low infection areas, respectively. We assume the rates of vaccination in areas with high and low infections to be m_1 and m_2, respectively.

Ring vaccinations and contact tracing are considered along each other. When contacts and contacts of contacts are identified, they are being vaccinated using the ring strategy. At the same time, contacts are followed up and taken for treatments if they show any symptoms. In the current study, we assume that as contact tracing was considered during the outbreak, the effective contact rate declined. Note that $V_1 + V_2$ is the number of identified and vaccinated healthcare and frontline workers in the population. Thus, there exists $s_1 \geq 0$ such that $s_1(V_1+V_2)$ is the number of contacts for infected individuals among healthcare and frontline workers. Also, note that $V_3 + V_4$ is the number of of identified and vaccinated contacts and contacts of contacts for the infected persons in the community. Thus, there exists a real number $s_2 \geq 0$ such that $s_2(V_3 + V_4)$ is the number of contacts for infected individuals in the community. Let $s_3 \geq 0$ and $s_4 \geq 0$ be parameters used

to account for the effectiveness of contact tracing per each contact so that the effective contact rate becomes

$$\beta_1 + (\beta_0 - \beta_1)e^{-s_3 s_1(V_1+V_2)-s_4 s_2(V_3+V_4)}$$

during the contact tracing and that β_1 ($\beta_1 < \beta_0$) is the effective contact rate post contact tracing. Let $q_1 = s_3 s_1$ and $q_2 = s_4 s_2$. It follows that there exists no contact tracing when $q_1 = q_2 = 0$ and that the higher the values of q_1 and q_2 are, the higher the level of contact tracing. Let m_1 and m_2 be the rates of vaccinating healthcare and frontline workers living in areas with high and low infections, respectively.

Let the average number of contacts and contacts of contacts of an infectious living person be n_l and of an infectious deceased be n_d, with $n_d < n_l$. Let a be the fraction of healthcare and frontline workers in the population. Let $c = 1 - a$. The probability of individuals who are non-healthcare workers (non-HCWs) and non-frontline workers (non-FLWs) to be susceptible in the population (depending on where these individuals live) is $c\frac{S}{N}$ (S denotes S_L or S_H). It follows that the average number of contacts and contacts of contacts for an infectious living person and an infectious deceased with susceptible individuals who are non-HCWs and non-FLWs is $c\frac{S}{N}n_l$ and $c\frac{S}{N}n_d$, respectively. Let $\frac{1}{\gamma}$ and $\frac{1}{b}$ be the infectious periods in days for an infectious living person and infectious deceased, respectively. Thus, the daily rates for the average contacts and contacts of contacts of an infectious living person and an infectious deceased with the susceptible individuals who are non-HCWs and non-FLWs are $c\gamma\frac{S}{N}n_l$ and $cb\frac{S}{N}n_d$, respectively. Let p be the probability of the ring vaccination campaign coverage. Thus, daily, $c\gamma p\frac{S}{N}n_l$ and $cbp\frac{S}{N}n_d$, the average number of contacts and contacts of contacts of an infectious living person and an infectious deceased, respectively, were being vaccinated with the ring strategy. Let h be the fraction of hospitalised persons. There were hI and $(1-h)I$ infected persons in the population who were hospitalised and non-hospitalised, respectively. EVD exposure during the outbreak has only happened outside Ebola treatment centres (ETCs) [169]. Hospitalised individuals at ETCs were perfectly isolated during treatments and safely buried when they died [169]. Hence only non-hospitalised infectious individuals had EVD contacts. Thus, the recruitment rate for vaccinating the contacts and contacts of contacts of the living infectious individuals and the infectious deceased were $c\gamma(1-h)p\frac{S}{N}n_l I$ and $cbp\frac{S}{N}n_d D$, respectively.

We assume the rate of vaccination targeted to all other individuals living in areas with high and low infections to be g_1 and g_2, respectively. A fraction ϵ of vaccinated individuals were unprotected despite the vaccination [174]. Exposed individuals were assumed to become infectious at a rate of α.

EVD hospitalisation was traditionally undertaken by treating symptoms, rehydrating patients orally and intravenously and curing other infections that patients might have [94]. Several antiviral treatments (mAb114, Remdesivir, Zmapp and Regeneron) were investigated during the 2018-2020 Kivu outbreak [104]. Crucially, people who received the Regeneron (REGN-EB3) and mAb114 antiviral treatments soon after their infection showed up to a 90% survival rate [104]. Consequently, Zmapp and Remdesivir were interrupted by the end of August 2019, and only Regeneron (REGN-EB3) and mAb114 were being used instead. Since the interruptions of Zmapp and Remdesivir were expected to change the epidemic curve and since we are only interested in understanding the impact of vaccinations, in the current study, we considered the outbreak before the interruptions of the two vaccines. On the other hand, it was reported that the 2018-2020 Kivu outbreak spread to South Kivu on the 16th of August 2019 [175]. Since we are interested in understanding EVD dynamics in North Kivu and Ituri provinces only, we chose the data timeline before the 16th of August. Thus, to account for EVD spread in North Kivu and Ituri provinces before the interruption of Zmapp and Remdesivir, we considered the outbreak data from the beginning of the outbreak to the 11th of August 2019. We assumed ρ to be the rate of hospitalisation and treatment with mAb114, Remdesivir, Zmapp or Regeneron.

The rate of geographically-targeted vaccinations g_1 and g_2 can have different values. When $g_1 = g_2 = 0$ only ring vaccinations were applied in the population, similar to the actual data considered in the current study [168]. The complete process for the model is depicted in Figure 3.1 and a complete description for the model parameters is provided in Table 3.1 and Table 3.2. The model equations are given below:

$$
\begin{aligned}
\frac{dS_H}{dt} &= \sigma\Pi - (\lambda_1 + \lambda_2 + g_1 + m_1 + \mu)\, S_H \\
\frac{dS_L}{dt} &= (1-\sigma)\,\Pi - (\lambda_1\tau_1 + \tau_2\lambda_2 + g_2 + m_2 + \mu)\, S_L \\
\frac{dV_1}{dt} &= m_1 S_H - (\epsilon\lambda_1 + \mu)\, V_1 \\
\frac{dV_2}{dt} &= m_2 S_L - (\epsilon\lambda\tau_1 + \mu)\, V_2 \\
\frac{dV_3}{dt} &= \lambda_2 S_H - (\epsilon\lambda_1 + \mu)\, V_3 \\
\frac{dV_4}{dt} &= \tau_2\lambda_2 S_L - (\epsilon\lambda_1\tau_1 + \mu)\, V_4 \\
\frac{dV_5}{dt} &= g_1 S_H - (\epsilon\lambda_1 + \mu)\, V_5 \\
\frac{dV_6}{dt} &= g_2 S_L - (\epsilon\lambda_1\tau_1 + \mu)\, V_6 \\
\frac{dE}{dt} &= \lambda_1 \left(S_H + \tau_1 S_L + \epsilon V_1 + \epsilon\tau_1 V_2 + \epsilon V_3 + \epsilon\tau_1 V_4 + \epsilon V_5 + \epsilon\tau_1 V_6\right) - (\alpha + \mu)\, E \\
\frac{dI}{dt} &= \alpha E - (h\rho + (1-h)\,\gamma + \mu)\, I \\
\frac{dH}{dt} &= h\rho I - (\eta + \mu)\, H \\
\frac{dD}{dt} &= f_1\,(1-h)\,\gamma I - bD \\
\frac{dR}{dt} &= (1-h)\,(1-f_1)\,\gamma I + \eta\,(1-f_2)\, H - \mu R
\end{aligned}
\tag{3.2}
$$

where

$$
\begin{aligned}
\lambda_1 &= \frac{1}{N}\left(\beta_1 + (\beta_0 - \beta_1) e^{-q_1 \frac{(V_1+V_2)}{N} - q_2 \frac{(V_3+V_4)}{N}}\right)(I + \delta D)\,, \\
\lambda_2 &= c\frac{p}{N}\left(\gamma(1-h) n_l I + b n_d D\right).
\end{aligned}
$$

System (3.2) is naturally appended with the initial conditions:

$S_H(0) = S_{H,0}$, $S_L(0) = S_{L,0}$, $V_1(0) = V_{1,0}$, $V_2(0) = V_{2,0}$, $V_3(0) = V_{3,0}$, $V_4(0) = V_{4,0}$, $V_5(0) = V_{5,0}$, $V_6(0) = V_{6,0}$, $E(0) = E_0$, $I(0) = I_0$, $H(0) = H_0$, $D(0) = D_0$, and $R(0) = R_0$.

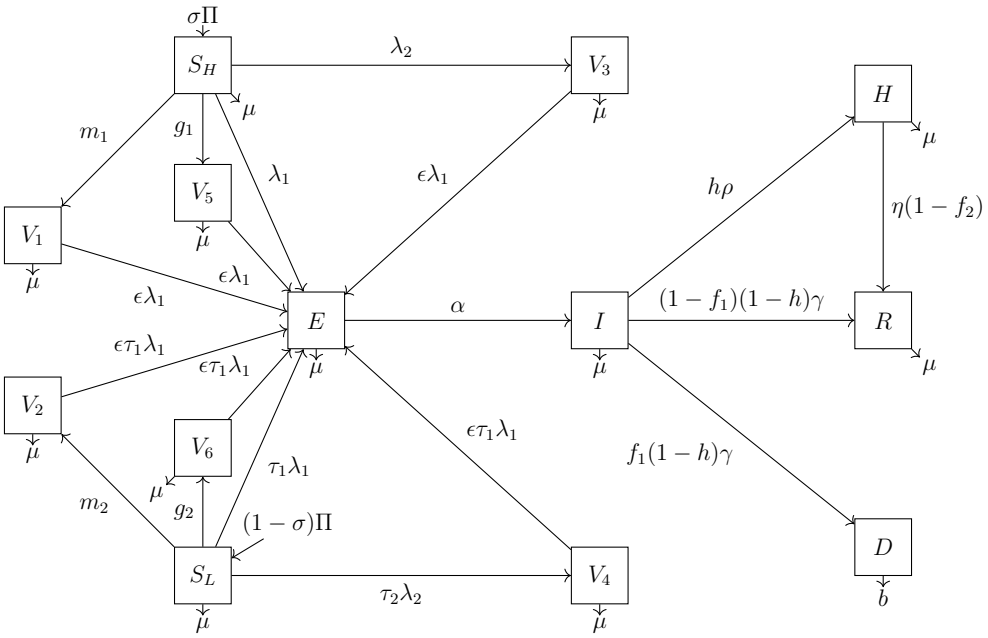


Figure 3.1: Transfer diagram for the model

3.3 Theoretical analysis

In this section, we first ascertain that all the model's state variables are non-negative for all time t and that the model's solution is bounded.

The basic reproduction number $\mathcal{R}_0$ is an important figure in characterising the spread of EVD. We used a well-documented method for finding $\mathcal{R}_0$ [149].

For the EVD model (3.2) to be biologically significant, it is essential to note that all state variables are non-negative at all times.

Proposition 3.3.1. *Let* $S_H(0), S_L(0), V_1(0), V_2(0), V_3(0), V_4(0), V_5(0), V_6(0), E(0), I(0), H(0), D(0)$ *and* $R(0)$ *be non-negatives. Then the solution of* (3.2) *is non-negative for all time* t.

We can now declare the statement below, which guarantees the boundedness of the solution for Model (3.2).

Proposition 3.3.2. *The non-negative solution of system* (3.2)*, characterised in Proposition 3.3.1 is bounded for all time* $t > 0$.

The proof for Propositions 3.3.1 and 3.3.2 are found in Appendix B.

From Propositions, 3.3.1 and 3.3.2 and the trivial existence and uniqueness of a local

solution, system (3.2) is a dynamical system in the biologically feasible compact set

$$\left\{(S_H(t), S_L(t), V_1(t), V_2(t), V_3(t), V_4(t), V_5(t), V_6(t), E(t), I(t), H(t), D(t), R(t)) \subset \mathbb{R}^{13}_{+} : N(t) \leq \psi\right\}$$

where

$$\psi = \max\left\{\frac{\Pi}{\mu}, N(0)\right\}.$$

3.3.1 Model Equilibria

The disease-free equilibrium (DFE) occurs when $I = D = 0$ and is given by

$$P_0 = (S_H^*, S_L^*, V_1^*, V_2^*, 0, 0, V_5^*, V_6^*, 0, 0, 0, 0, 0)$$

where $S_H^* = \frac{\sigma\Pi}{g_1+m_1+\mu}$, $S_L^* = \frac{(1-\sigma)\Pi}{g_2+m_2+\mu}$, $V_1^* = \frac{m_1 S_H^*}{\mu}$, $V_2^* = \frac{m_2 S_L^*}{\mu}$, $V_5^* = \frac{g_1 S_H^*}{\mu}$, $V_6^* = \frac{g_2 S_L^*}{\mu}$.

To calculate the controlled reproduction number ($\mathcal{R}_c$) of the model, we apply the standard method of the next generation matrix [149]. We distinguish between infected states (E, I, H, D) and uninfected states $(S_H, S_L, V_1, V_2, V_3, V_4, V_5, V_6, R)$. Let $\mathcal{F}$ and $\mathcal{W}$ be the vectors defining new and transported cases, respectively, into infected states.

As in [149], $\mathcal{R}_c$ is obtained as the dominant eigenvalue of the matrix FW^{-1} where F and W are the Jacobian matrices of $\mathcal{F}$ and $\mathcal{W}$ at the DFE, respectively.

We find

$$\mathcal{R}_c = A_2\left(\frac{\sigma}{m_1+g_1+\mu}\left(1+\frac{\epsilon(m_1+g_1)}{\mu}\right)+\frac{\tau_1(1-\sigma)}{m_2+g_2+\mu}\left(1+\frac{\epsilon(m_2+g_2)}{\mu}\right)\right) \tag{3.3}$$

where

$$A_2 = K_1\frac{\mu\alpha}{(\alpha+\mu)(\gamma(1-h)+\mu+h\rho)}\left(1+\frac{\delta f_1\gamma(1-h)}{b}\right),$$

and

$$K_1 = \left(\beta_1+(\beta_0-\beta_1)e^{-q_1\left(\frac{m_2\Pi(1-\sigma)}{\mu(m_2+g_2+\mu)}+\frac{m_1\Pi\sigma}{\mu(m_1+g_1+\mu)}\right)}\right).$$

When there is no intervention, we have $q_1 = h = g_1 = g_2 = m_1 = m_2 = 0$. Thus $\mathcal{R}_c$ becomes

$$\mathcal{R}_0 = \beta_0\frac{\alpha}{(\alpha+\mu)(\gamma+\mu)}\left(1+\frac{\delta f_1\gamma}{b}\right)(\sigma+\tau_1(1-\sigma)).$$

$\mathcal{R}_0$ can be rewritten as $\mathcal{R}_{0h} + \mathcal{R}_{0l}$ where

$$\mathcal{R}_{0h} = \beta_0 \sigma \left(\frac{\alpha}{(\alpha+\mu)(\gamma+\mu)} + \frac{\delta \alpha f_1 \gamma}{b(\alpha+\mu)(\gamma+\mu)} \right) \tag{3.4}$$

and

$$\mathcal{R}_{0l} = \beta_0 \tau_1 (1-\sigma) \left(\frac{\alpha}{(\alpha+\mu)(\gamma+\mu)} + \frac{\delta \alpha f_1 \gamma}{b(\alpha+\mu)(\gamma+\mu)} \right) \tag{3.5}$$

represent the contribution to infections for individuals living in areas with high and low levels of infections, respectively.

Next, we show the existence of an endemic equilibrium

$$(S_H^*, S_L^*, V_1^*, V_2^*, V_3^*, V_4^*, V_5^*, V_6^*, E^*, I^*, H^*, D^*, R^*)$$

where

$$\begin{aligned}
S_H^* &= \frac{\sigma \Pi}{\lambda_1 + \lambda_2 + g_1 + m_1 + \mu} \\
S_L^* &= \frac{(1-\sigma)\Pi}{\lambda_1 \tau_1 + \lambda_2 \tau_2 + g_2 + m_2 + \mu}, \\
V_1^* &= \frac{m_1 S_H^*}{\epsilon \lambda_1 + \mu}, \\
V_2^* &= \frac{m_2 S_L^*}{\epsilon \lambda_1 \tau_1 + \mu}, \\
V_3^* &= \frac{\lambda_2 S_H^*}{\epsilon \lambda_1 + \mu}, \\
V_4^* &= \frac{\lambda_2 \tau_2 S_L^*}{\epsilon \lambda_1 \tau_1 + \mu}, \\
V_5^* &= \frac{g_1 S_H^*}{\epsilon \lambda_1 + \mu}, \\
V_6^* &= \frac{g_2 S_L^*}{\epsilon \lambda_1 \tau_1 + \mu}, \\
E^* &= \frac{\lambda_1}{(\alpha+\mu)} \left(S_H^* + \tau_1 S_L^* + \epsilon V_1^* + \tau_1 \epsilon V_2^* + \epsilon V_3^* + \tau_1 \epsilon V_4^* + \epsilon V_5^* + \tau_1 \epsilon V_6^* \right), \\
I^* &= \frac{\alpha}{h\rho + (1-h)\gamma + \mu} E^*,
\end{aligned}$$

with

$$\begin{aligned}
H^* &= \frac{h\rho}{\eta+\mu}I^*, \\
D^* &= \frac{f_1(1-h)\gamma}{b}I^*, \\
R^* &= \frac{1}{\mu}\left((1-f_1)\gamma I^* + \eta(1-f_2)H^*\right), \\
N^* &= \frac{\Pi}{\mu} - (b-\mu)D^*, \\
\lambda_1 &= \left(\beta_1 + (\beta_0-\beta_1)e^{-q_1\frac{(V_1^*+V_2^*)}{N^*}-q_2\frac{(V_3^*+V_4^*)}{N^*}}\right)\left(\frac{I^*+\delta D^*}{N^*}\right), \\
\lambda_2 &= c\frac{p}{N^*}\left(\gamma(1-h)n_l I^* + bn_d D^*\right).
\end{aligned}$$

As in [108, 152], the equilibria of system (3.2) correspond the fixed points of the following system

$$\begin{pmatrix}\lambda_1\\ \lambda_2\end{pmatrix} = \begin{pmatrix}\phi_1(\lambda_1,\lambda_2)\\ \phi_2(\lambda_1,\lambda_2)\end{pmatrix}, \tag{3.6}$$

where

$$\begin{aligned}
\phi_1(\lambda_1,\lambda_2) &= \left(\beta_1 + (\beta_0-\beta_1)e^{-q_1\frac{(V_1^*+V_2^*)}{N^*}-q_2\frac{(V_3^*+V_4^*)}{N^*}}\right)\left(\frac{I^*+\delta D^*}{N^*}\right), \\
\phi_2(\lambda_1,\lambda_2) &= c\frac{p}{N^*}\left(\gamma(1-h)n_l I^* + bn_d D^*\right).
\end{aligned}$$

Note that $\phi_1(\lambda_1,\lambda_2)$ is continuous in $\lambda_1 \in [0,\infty)$. Further $\phi_1(0,\lambda_2) = 0$ and

$$\lim_{\lambda_1\to\infty}\phi_1(\lambda_1,\lambda_2) = B_1$$

where

$$B_1 = \frac{\alpha\beta_0\left(b+\delta f_1\gamma(1-h)\right)\mu}{\alpha f_1\gamma(1-h)\mu + \alpha b\left((1-f_1)\gamma(1-h)+\mu+h\rho\right) + b\mu\left(\gamma(1-h)+\mu+h\rho\right)}.$$

We have that B_1 is positive. Thus $\phi_1(\lambda_1,\lambda_2)$ is bounded for $\lambda_1 \in [0,\infty)$.

We also have that

$$\frac{d\phi_1}{d\lambda_1}(0,0) = \mathcal{R}_c.$$

Let $\mathcal{R}_c > 1$. We argue that there exists r in a neighbourhood of zero, say $(0,\delta_1)$ such

that $\phi_1(r,\lambda_2) > r$, otherwise, for all neighbourhoods near zero, $\phi_1(r,\lambda_2) \leq r$ which would imply that

$$\frac{d\phi_1}{d\lambda_1}(0,\lambda_2) = \lim_{\lambda_1 \to 0^+} \frac{\phi_1(\lambda_1,\lambda_2) - \phi_1(0,\lambda_2)}{\lambda_1} = \lim_{\lambda_1 \to 0^+} \frac{\phi_1(\lambda_1,\lambda_2)}{\lambda_1} \leq 0$$

which is a contradiction. It follows that there exists an $r \in (0,\infty)$ such that $\phi_1(r,\lambda_2) > r$. Since $\phi_1(\lambda_1,\lambda_2)$ is bounded as $\lambda_1 \to \infty$, there exists an $M > 0$ such that $\phi_1(M,\lambda_2) < M$. Let $Z(\lambda_1) = \lambda_1 - \phi_1(\lambda_1,\lambda_2)$. We have $Z(r,\lambda_2) < 0$ and $Z(M,\lambda_2) > 0$. Using the Intermediate Value Theorem, there exists a $\lambda_1^* \in (r,M)$ such that $\phi_1(\lambda_1^*,\lambda_2) = \lambda_1^*$.

We have $I^* = \frac{\alpha}{h\rho+(1-h)\gamma+\mu}E^* = A_3E^*$ where $A_3 = \frac{\alpha}{h\rho+(1-h)\gamma+\mu}$. Also $D^* = \frac{f_1(1-h)\gamma}{b}I^* = \frac{f_1(1-h)\gamma}{b}A_3E^* = A_4E^*$ where $A_4 = \frac{f_1(1-h)\gamma}{b}A_3$. We have

$$\phi_2(\lambda_1,\lambda_2) \;\; = \;\; c\frac{p}{N^*}\left(\gamma(1-h)n_lA_3 + bn_dA_4\right)E^*.$$

Note that $\phi_2(\lambda_1^*,\lambda_2)$ is continuous for $\lambda_2 \in [0,\infty)$. We have

$$\lim_{\lambda_2 \to 0}\phi_2(\lambda_1^*,\lambda_2) = cp\left(\gamma(1-h)n_lA_3 + bn_dA_4\right)\frac{A_6}{\frac{\Pi}{\mu} - A_5A_6} > 0,$$

where $A_5 = (b-\mu)\frac{f_1(1-h)\gamma}{b}A_3$, and A_6 is given by

$$\frac{\lambda_1}{(\alpha+\mu)}\left(\left(1+\frac{\epsilon(m_1+g_1)}{\epsilon\lambda_1+\mu}\right)\frac{\sigma\Pi}{\lambda_1+g_1+m_1+\mu} + \tau_1\left(1+\frac{\epsilon(m_2+g_2)}{\epsilon\lambda_1\tau_1+\mu}\right)\frac{(1-\sigma)\Pi}{\lambda_1\tau_1+g_2+m_2+\mu}\right).$$

Further

$$\lim_{\lambda_2 \to \infty}\phi_2(\lambda_1^*,\lambda_2) = cpA_3\gamma(1-h)\left(n_l + f_1n_d\right)\frac{\frac{\lambda_1^*\epsilon\Pi}{(\alpha+\mu)}\left(\frac{\sigma}{\epsilon\lambda_1^*+\mu} + \frac{(1-\sigma)\tau_1}{(\epsilon\lambda_1^*\tau_1+\mu)}\right)}{\frac{\Pi}{\mu} - A_5\left(\frac{\lambda_1^*\epsilon\Pi}{(\alpha+\mu)}\left(\frac{\sigma}{\epsilon\lambda_1^*+\mu} + \frac{(1-\sigma)\tau_1}{(\epsilon\lambda_1^*\tau_1+\mu)}\right)\right)}.$$

Thus, $\phi_2(\lambda_1^*,\lambda_2)$ is bounded in $\lambda_2 \in (r_1,\infty)$.

Let $\lim_{\lambda_2 \to 0}\phi_2(\lambda_1^*,\lambda_2) = k$. We have $k > 0$. Then there exists an $r_1 \in (0,\infty)$ such that $\phi_2(\lambda_1^*,r_1) > r_1$. Otherwise for all $r_1 \in (0,\infty)$, $\phi_2(\lambda_1^*,r_1) \leq r_1$, which contradictorily would imply that

$$\lim_{r_1 \to 0}\phi_2(\lambda_1^*,r_1) \leq \lim_{r_1 \to 0} r_1 = 0.$$

We conclude that there exists an $r_1 \in (0,\infty)$ such that $\phi_2(\lambda_1,r_1) > r_1$.

From the boundedness of $\phi_2(\lambda_1^*, \lambda_2)$ in $\lambda_2 \in (r_1, \infty)$, we deduce that there exists an $M_1 \in (r_1, \infty)$ where $\phi_2(\lambda_1^*, M_1) < M_1$. Let $Z_1(\lambda_2) = \lambda_2 - \phi_2(\lambda_1^*, \lambda_2)$. Then $Z_1(r_1) < 0$ and $Z_1(M_1) > 0$. From the intermediate value theorem, there exists a $\lambda_2^* \in (r_1, M_1)$ such that $Z(\lambda_2^*) = 0$. That is, $\phi_2(\lambda_1^*, \lambda_2^*) = \lambda_2^*$.

We now first concern ourselves with the stability of the model solution near the DFE. We first obtained the characteristic equation of the Jacobian matrix of Model (3.2), evaluated at the DFE (P_0):

$$\begin{aligned} 0 &= (-\lambda-\mu)^7(-(\eta+\mu)-\lambda)(-(g_1+m_1+\mu)-\lambda))(-(g_2+m_2+\mu)-\lambda) \\ &\quad [(-b-\lambda)(-(\alpha+\mu)-\lambda)\left(-(\gamma(1-h)+\mu+h\rho)-\lambda\right)+\lambda A_{11}+b(\alpha+\mu)(\gamma(1-h)+\mu+h\rho)\mathcal{R}_c] \end{aligned}$$

where

$$A_{11} = A_{12}\left(\frac{\sigma}{m_1+g_1+\mu}\left(1+\frac{\epsilon(m_1+g_1)}{\mu}\right)+\frac{\tau_1(1-\sigma)}{m_2+g_2+\mu}\left(1+\frac{\epsilon(m_2+g_2)}{\mu}\right)\right)$$

and

$$A_{12} = \alpha\mu\left(\beta_1+(\beta_0-\beta_1)e^{-q_1\left(\frac{m_2(1-\sigma)}{m_2+g_2+\mu}+\frac{m_1\sigma}{m_1+g_1+\mu}\right)}\right).$$

Let $c_1 = (\alpha+\mu)$ and $c_2 = \gamma(1-h)+\mu+h\rho$. Then the characteristic equation becomes

$$\begin{aligned} 0 &= (-\lambda-\mu)^7(-(\eta+\mu)-\lambda)(-(g_1+m_1+\mu)-\lambda))(-(g_2+m_2+\mu)-\lambda) \\ &= (-(b+\lambda)((c_1+\lambda)\left(c_2+\lambda\right)+\lambda A_{11}+bc_1c_2\mathcal{R}_c) \\ &= (-\lambda-\mu)^7(-(\eta+\mu)-\lambda)(-(g_1+m_1+\mu)-\lambda))(-(g_2+m_2+\mu)-\lambda) \\ &\left(-\lambda^3-a_1\lambda^2-a_2\lambda+bc_1c_2\left(\mathcal{R}_c-1\right)\right). \end{aligned} \tag{3.7}$$

where $a_1 = (c_1+c_2+b)$ and $a_2 = (c_1c_2+b(c_1+c_2)-A_{11})$.

Note that $\mathcal{R}_c < 1$ implies that

$$c_1c_2 > A_{11}+A_{13} > 0$$

where $A_{13} = A_{11}\frac{\delta f_1\gamma(1-h)}{b}$. Thus, $a_2 > 0$ and Equation (3.7) becomes

$$\begin{aligned} 0 &= (-\lambda-\mu)^7(-(\eta+\mu)-\lambda)(-(g_1+m_1+\mu)-\lambda))(-(g_2+m_2+\mu)-\lambda) \\ &= \left(\lambda^3+a_1\lambda^2+a_2\lambda+bc_1c_2\left(1-\mathcal{R}_c\right)\right). \end{aligned} \tag{3.8}$$

Using the Routh-Hurwitz criterion for stability, all eigenvalues have negative real parts when $\mathcal{R}_c < 1$. Hence the DFE is locally asymptotically stable when $\mathcal{R}_c < 1$. On the other hand, when $\mathcal{R}_c > 1$, using Descartes's rule of sign, Equation (3.8) has at least one positive root. Thus, the DFE is unstable when $\mathcal{R}_c > 1$.

The condition for the local stability of the endemic equilibrium is found as in [108]. The Jacobian matrix around the positive fixed point $(\lambda_1^*, \lambda_2^*)$ is given by

$$\begin{pmatrix} \frac{d\phi_1(\lambda_1^*,\lambda_2^*)}{d\lambda_1} & \frac{d\phi_1(\lambda_1^*,\lambda_2^*)}{d\lambda_2} \\ \frac{d\phi_2(\lambda_1^*,\lambda_2^*)}{d\lambda_1} & \frac{d\phi_2(\lambda_1^*,\lambda_2^*)}{d\lambda_2} \end{pmatrix}$$

The spectral radius ρ^* of this Jacobian matrix is used to determine the condition for the local stability at the endemic equilibrium. When $\rho^* < 1$, the endemic equilibrium is locally asymptotically stable and unstable when $\rho^* > 1$.

3.4 Numerical simulations

In this section, we introduce data to quantify the model, discuss the model fitting and sensitivity analysis and explore the impact of ring and geographically-targeted vaccinations.

3.4.1 Data

North Kivu and Ituri provinces are among the most densely inhabited provinces with a population of about 11 million persons [142]. As the 2018-2020 Ebola outbreak continued to spread in North Kivu and Ituri provinces for over one year, it became essential to integrate all available data to assess the impact of additional intervention measures to control the disease spread. To quantify system (3.2), we integrate the cumulative EVD cases and ring vaccination data. The cumulative EVD cases were adapted from the Humanitarian Data Exchange website [68] while the ring vaccinations data were manually collected from the WHO situation reports [168] and are made available in Table 3.3.

3.4.2 Model fitting

To solve the initial value problem (3.2), we applied the odeint function of Scipy [145]. This function is used to solve a system of ordinary differential equations using the ISODA algorithm from the FORTRAN library odepack. System (3.2) was fitted to the EVD data using the optimize.curve_fit function of Scipy [146]. This function uses non-linear least squares for the fitting. It also allows us to compute the 67% confidence interval of the parameter estimates. We fitted the cumulative cases function

$$\int_0^t (\alpha E(s))\ ds$$

of system (3.2) to the cumulative cases data. The cumulative ring vaccinations function

$$\int_0^t (m_1 S_H(s) + m_2 S_L(s) + \lambda_2 S_H(s) + \lambda_2 \tau_2 S_L(s))dt$$

of system (3.2) was fitted to the cumulative ring vaccinations data. The model fitting is shown in Figure 3.2 and the estimated parameters are reported in Table 3.1 and Table 3.2. The 67% confidence interval of the parameter estimates was used to calculate 95% confidence interval for the parameter estimates using the algorithm introduced by Kahil [78].

The basic reproduction number is a crucial figure in characterising the spread of EVD [2]. A number of studies have estimated $\mathcal{R}_0$ in the range of 1.36 and 4.71 [31, 50, 91, 92, 116, 53, 21]. From the parameters obtained from the model fitting, we estimated $\mathcal{R}_0$ to be 1.79 ($\mathcal{R}_{0h} = 1.46$ and $\mathcal{R}_{0l} = 0.33$).

3.4.3 Sensitivity analysis

To minimize EVD-related morbidity and mortality, it is essential to comprehend the relative significance of the various factors contributing to EVD transmission and prevalence. Sensitivity analysis is used to identify parameters that significantly impact EVD transmission and prevalence. In this subsection, we followed Chitnis et al. [30] to identify the impact of the different parameters on $\mathcal{R}_c$. They used the normalised forward sensitivity index method. The normalised forward sensitivity index of $\mathcal{R}_c$ to any parameter is the ratio of the relative change in $\mathcal{R}_c$ to the relative change in that parameter [30]. It can be

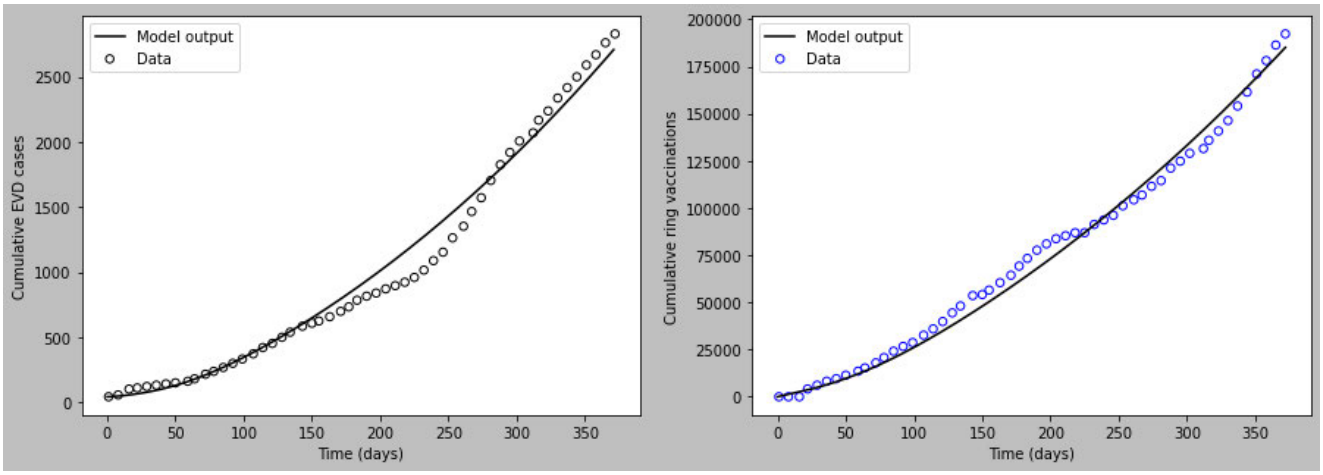


Figure 3.2: Model fitting with the cumulative EVD cases and cumulative ring vaccinations data.

defined using partial derivatives as follows:

$$\Upsilon_p^{\mathcal{R}_c} = \frac{\partial \mathcal{R}_c}{\partial p} \times \frac{p}{\mathcal{R}_c}$$

where p is any of the parameters that comprise $\mathcal{R}_c$. We obtain the sensitivity indices of $\mathcal{R}_c$ with respect to each parameter of $\mathcal{R}_c$ and present the results in Table. 3.2. The most sensitive parameter is the transmission rate of living infectious individuals who are located in areas with high infections (β_0). Other important parameters include the fraction of susceptible patients living in areas with high infections (σ) and the rate at which non-hospitalised persons recover or die (γ). For example, since $\Upsilon_\sigma^{\mathcal{R}_c} = +0.76$, decreasing (or increasing) σ by 10% decreases (or increases) $\mathcal{R}_c$ by 7.6%. On the other hand, as $\Upsilon_\gamma^{\mathcal{R}_c} = -0.643$, decreasing (or increasing) γ by 10% increases (or decreases) $\mathcal{R}_c$ by 6.43%.

3.4.4 The impact of ring vaccinations during the outbreak

Ring vaccinations were extensively applied during the 2018-2020 Kivu outbreak. There were over 185000 vaccinations on the 373rd day of the outbreak (the end date of the considered time window for the data). We estimated the cumulative ring vaccinations for susceptible persons who live in areas with a low level of infections on the 373rd day of the outbreak to be about 150000 (Figure. 3.3). On the other hand, only about 36300 persons were estimated to be vaccinated in areas with a high level of infections (Figure. 3.3).

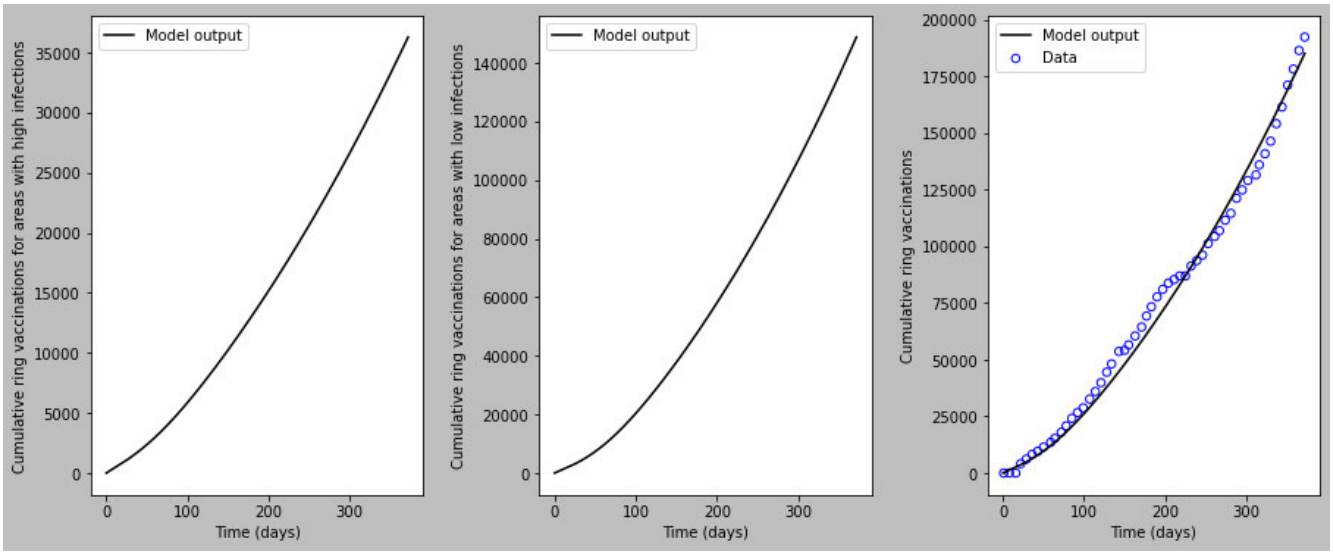


Figure 3.3: Ring vaccinations during the outbreak.

These findings show that the ring vaccination coverage was mainly focused on areas with low levels of infections. However, the contributions of infected persons living in areas with a low level of infections to $\mathcal{R}_0$ was only about 18%. The low level of ring vaccinations in areas with high infections might explain the continuation of the outbreak in these areas.

They were several reasons for the low vaccinations level in areas with high infections. Some people in high infection areas were inaccessible because they resided in unsafe areas that rebel groups controlled; some resisted the vaccinations or attacked the vaccination campaigns [34, 176]. For example, following community unrest in Butembo, the vaccination facilities were unreachable [171]. In Beni, it was estimated that about one-third of health care workers were not offered the vaccine [165].

3.4.5 The impact of geographically-targeted vaccinations

During the 2018-2020 Kivu outbreak, it was estimated that about 0.0158% of the total population were vaccinated on the 373rd day. If GTVs in areas with high infections were implemented so that total vaccinations in the population were increased by 60% by the 373rd day of the outbreak, the cumulative cases would have decreased by 15% (Figure. 3.4). Further, the need for ring vaccinations in the population was decreased by more than 15%. On the other hand, to achieve the 15% decrease in EVD cases, we found that it required increasing EVD vaccinations to more than 1000% by the 373rd day using GTVs

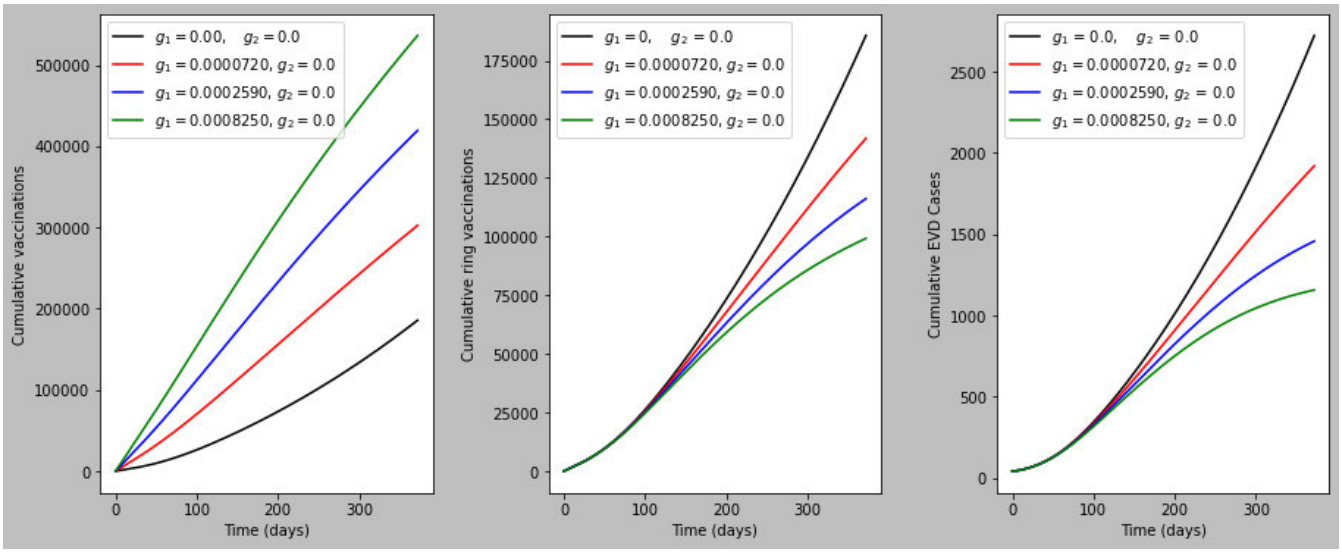


Figure 3.4: The impact of GTVs in areas with high infections in the spread of EVD

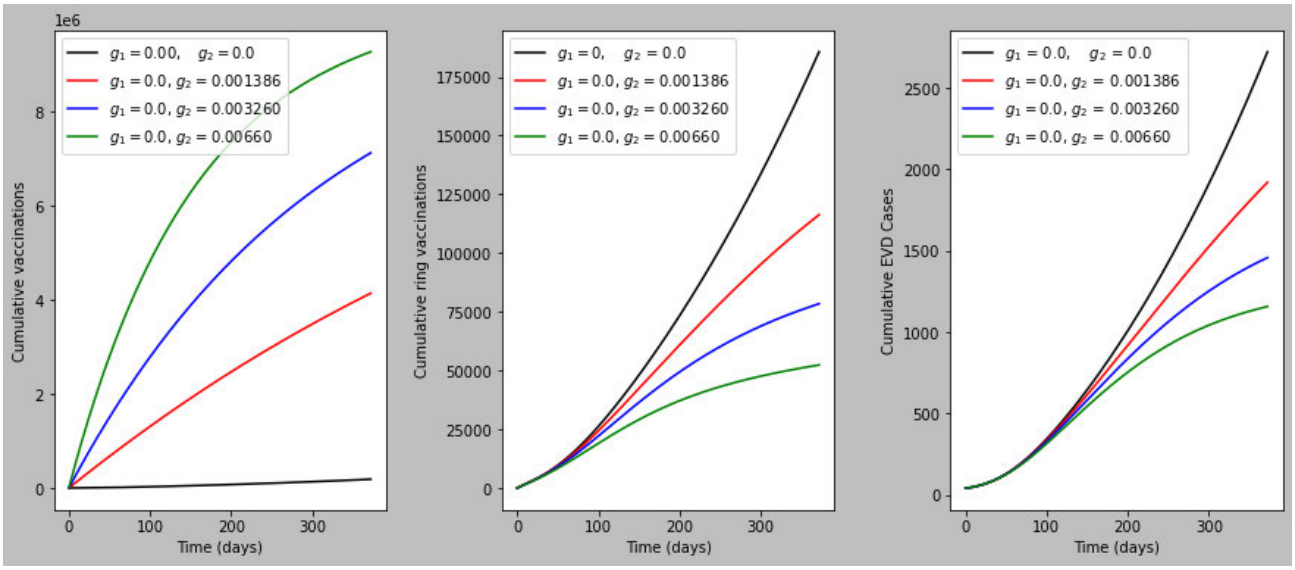


Figure 3.5: The impact of GTVs in areas with low infections

in areas with low infections (Figure. 3.5).

3.5 Discussion

Insecurity and community reluctance make combatting disease spread difficult. It is also challenging to apply public health interventions in locations where the government has little control. In particular, contact tracing, ring vaccinations, and antiviral treatments

might be unsuccessful. One prominent illustration of such issues is the 2018-2020 Kivu outbreak. Ring vaccinations were one of the essential measures applied during the 2018-2020 Kivu outbreak. Despite the ring vaccination efforts, the outbreak spread and became the second-largest outbreak in history.

The most helpful vaccination strategies to contain the spread of EVD should maximise the impact of vaccination while minimising global expenditures, actions, and human distress resulting from an outbreak. Mass vaccination is not readily achievable because the endemic region comprises much of West and Central Africa [172], placing over half a billion people at risk. It was found that vaccination coverage of 80% would be required to establish the herd immunity against EVD for a vaccine with a 90% efficacy and $\mathcal{R}_0$ of 4 [103]. Financial/logistical burdens and poor vaccine acceptance in the affected regions make mass vaccination challenging. Vaccinations with the ring strategy, similarly, confront different obstacles. Many EVD contacts and contacts of contacts might be inaccessible, or they refuse to be vaccinated [34].

The best vaccination strategy is tailor based on epidemiological characteristics and modelling of each situation. While early contact tracing and ring vaccination may be sufficient for small outbreaks in isolated populations, additional strategies may be required to contain large-scale outbreaks [103, 34, 138]. The current study found the geographically-targeted vaccination in areas with high infections to be an excellent intervention in the 2018-2020 Kivu outbreak when the disease spread could not be contained using contact tracing, ring vaccinations, and antiviral treatments. This strategy could also help foster vaccine trust as people start realising the benefits of vaccinations in containing the outbreak at an early stage of an outbreak.

We found that ring vaccination coverage was mainly focused in areas with low levels of infections as opposed to areas with high infections (Figure. 3.3). We explored the impact of geographically-targeted vaccinations (GTV) in areas with high levels of infections. We found that geographically targeted vaccinations (GTVs) in areas with high infections to be a much more feasible strategy compared to GTVs in regions with low infections. For example, if the GTVs in areas with high infections strategy was implemented so that vaccinations were increased by 60% by the 373rd day of the outbreak, the total EVD cases in the population would be decreased by 15% (Figure. 3.4). Further, the need for ring vaccinations in the population would be decreased by more than 15% (Figure. 3.4). On

the other hand, to achieve the 15% decrease in EVD cases, we found that it required increasing EVD vaccinations to more than 1000% by the 373rd day using GTVs in areas with low infections (Figure. 3.5).

During an outbreak, the most critical priority is maintaining and enhancing the effectiveness and efficiency of all elements of EVD responses, particularly determinating all possible contacts, closely following them up, isolating those who display EVD symptoms as soon as possible and strengthening other interventions pillars including ring vaccinations and antiviral treatments. These measures must be maintained and bolstered to interrupt transmission and control the outbreak. When EVD outbreaks are not contained with these measures, such as the 2018-2020 Kivu outbreak, then geographically-targeted vaccinations in areas with high levels of infections can successfully mitigate the spread of EVD.

Table 3.1: Model parameters and their interpretations.

Parameter	Interpretation
Π	Birth rate.
n_l	The number of contacts and contacts of contacts of a living infectious person.
n_d	The number of contacts and contacts of contacts of an infectious deceased.
p	The probability of coverage for the ring vaccination campaign.
$\frac{1}{\alpha}$	The incubation period.
$\frac{1}{\gamma}$	The average time from symptoms onset to either recovery or to EVD death for infectious individuals who were not hospitalised.
ϵ	The fraction of vaccinated individuals that are not immunised by the vaccination.
$\frac{1}{b}$	The average time from EVD death to burial.
β_0	The transmission rate before any intervention takes place for the living infectious individuals who are located in areas with high infections.
β_1	The transmission rate post contact tracing for living infectious individuals who are located in areas with high infections.
μ	Natural mortality rate.
$\frac{1}{\rho}$	The average time from symptoms onset to hospitalisation.
f_1	The probability of EVD deaths for non-hospitalised individuals.
f_2	The probability of EVD deaths for hospitalised cases.
$\frac{1}{\eta}$	The average time from hospitalisation to either recovery or to EVD death.
τ_1	A modification parameter. It accounts for the transmission from susceptible individuals living in areas with low levels of infections.
τ_2	A modification parameter that accounts for the ring vaccination in susceptible populations living in areas with low levels of infections.
m_1	Vaccination rate for healthcare and frontline workers located at areas with high level of infections.
m_2	Vaccination rate for healthcare and frontline workers located at areas with low level of infections.
σ	The fraction of susceptible individuals living in areas with high infections.
δ	A modification parameter that accounts for the transmission from the deceased.

Continued Table 3.1.

q_1	A parameter that accounts for the level of contact tracing among healthcare and frontline workers.
q_2	A parameter that accounts for the level of contact tracing in the community.
h	A fraction of the infected individuals that were hospitalised at Ebola treatment centres and treated with mAb114, Remdesivir, Zmapp or Regeneron antiviral treatments.
a	The fraction of healthcare or frontline workers in the population.
g_1	The rate of geographically-targeted vaccinations for areas with high infections.
g_2	The rate of geographically-targeted vaccinations for areas with low infections.

Table 3.2: Model parameter values and their Sensitivity Indices (S.I) and Confidence Intervals (C.I).

Parameter	Unit	Estimate	67% C.I	S.I	Estimates source
Π	$\frac{\text{people}}{\text{day}}$	534.33	—	—	Calculated
n_l	none	70	$[40.00, 100.0]$	—	Fitted
n_d	none	60	$[49.0, 71.0]$	—	Fitted
p	none	0.7	—	—	[174]
α	day^{-1}	0.1	—	$+0.000459788$	[150]
γ	day^{-1}	0.178	—	-0.642585	[150]
ϵ	none	0.025	—	$+0.0084987$	[173]
b	day^{-1}	0.580	—	-0.12427	[150]
β_0	day^{-1}	1.43	$[1.32, 1.54]$	$+0.99$	Fitted
β_1	day^{-1}	0.88	$[0.773, 0.990]$	$+0.00000867$	Fitted
μ	day^{-1}	$\frac{1}{60\times365}$	—	$+0.242062$	[83]
ρ	day^{-1}	0.182	—	-0.232887	[112]
f_1	none	0.74	—	$+0.12427$	[112, 170]
f_2	none	0.424	—	—	[112]
η	day^{-1}	0.073	$[0.00, 0.234]$	—	Fitted
τ_1	none	0.0410	$[0.0230, 0.0571]$	$+0.208498$	Fitted
τ_2	none	0.910	$[0.847, 0.973]$	—	Fitted
m_1	day^{-1}	0.0000180	$[0.00, 0.000609]$	-0.215163	Fitted
m_2	day^{-1}	0.00000726	$[0.00, 0.000113]$	-0.0276156	Fitted
σ	none	0.1536	—	$+0.753664$	[70]
δ	none	0.811	$[0.691, 0.932]$	$+0.12427$	Fitted
q_1	people^{-1}	0.000089	$[0.000079, 0.000098]$	-0.0000054	Fitted
q_2	people^{-1}	0.0001	$[0.00007, 0.00013]$	—	Fitted
h	none	0.229	—	-0.0420288	[112]
a	none	0.00311	—	—	[170]

Table 3.3: Cumulative cases and cumulative ring vaccinations data.

Date	Cumulative cases	Cumulative ring vaccinations
05-08-2018	43	0
12-08-2019	57	0
20-08-2018	102	0
26-08-2018	111	4130
02-09-2018	122	6134
09-09-2018	132	8229
16-09-2018	142	9572
23-09-2018	150	11417
02-10-2018	162	13550
07-10-2018	181	15285
15-10-2018	216	17976
21-10-2018	238	20789
28-10-2018	268	24142
04-11-2018	300	26687
11-11-2018	333	28727
19-11-2018	373	32625
26-11-2018	421	35958
03-12-2018	453	39845
10-12-2018	500	44447
16-12-2018	539	48119
25-12-2018	585	53610
01-01-2019	608	54153
06-01-2019	625	56509
14-01-2019	658	60460
21-01-2019	699	64403
28-01-2019	734	69231
03-02-2019	785	73309

Continued Table 3.3.

10-02-2019	816	77680
17-02-2019	840	80989
24-02-2019	872	83755
03-03-2019	897	853411
10-03-2019	923	86917
17-03-2019	960	86917
24-03-2019	1016	91283
31-03-2019	1089	93686
07-04-2019	1154	96133
14-04-2019	1264	101195
22-04-2019	1353	104342
28-04-2019	1466	106872
05-05-2019	1572	111494
12-05-2019	1705	114498
19-05-2019	1826	121147
26-05-2019	1920	124825
02-06-2019	2008	129001
10-06-2019	2071	131471
16-06-2019	2168	135887
23-06-2019	2239	140794
30-06-2019	2338	146319
07-07-2019	2418	154037
14-07-2019	2501	161400
21-07-2019	2592	171052
28-07-2019	2671	178121
04-08-2019	2763	186350
11-08-2019	2831	192257
18-08-2019	2887	197172
25-08-2019	2976	204730

Chapter 4

The impact of violent attacks on Ebola treatment centres during the 2018-2020 Kivu outbreak

4.1 Introduction

The Democratic Republic of the Congo (DR Congo) reported an Ebola virus disease (EVD) outbreak in North Kivu and Ituri provinces on 1 August 2018. The World Health Organization (WHO) announced the outbreak in DR Congo to be a Public Health Emergency of International Concern (PHEIC) [61].

Conflicts and community mistrust marked by kidnappings and murders of healthcare and frontline workers prevented intervention campaigns from being deployed in many areas in North Kivu, and Ituri provinces [159]. Furthermore, attacks on healthcare personnel and Ebola treatment centres (ETCs) have caused the closure of some ETCs, resulting in the inaccessibility of ETCs for EVD patients. Most seriously, attacks on ETCs put the attackers and the general community at risk of acquiring the disease from contaminated items or patients who fled the attacks to the community [73, 66].

Several major attacks on ETCs occurred in DR Congo and Liberia in the recent past. Two occurred during the 2018-2020 Kivu outbreak in Katwa, and Butembo [73]. In Butembo, some unknown assailants attacked an ETC, setting some facilities and cars on fire [73]. The centre included 57 patients, among which 15 were confirmed cases [73]. The incident happened a few days after another attack at an Ebola treatment centre (ETC) in Katwa. The Katwa centre included ten patients, among whom four were confirmed cases [73]. Some patients in Butembo's treatment centre fled to nearby forests, putting the community at risk of acquiring the disease [73]. Another attack occurred during the 2014-2016 West African (WA) EVD outbreak. A group of individuals from the community attacked an ETC near Monrovia [66]. They looted items, including mattresses containing blood and other bodily fluids of infected individuals [66].

Understanding the interplay between the effect of attacks on ETCs and the spread of

EVD can inform how the disease unfolds in conflict and community distrust zones. Several previous studies explored the impact of conflicts and community mistrusts on EVD spread. Kelly et al. [80] investigated the impacts of targeted and non-targeted violence on EVD spread. They found that the time-dependent reproduction number increased by 0.1 when a 2.92 increase occurred in violent events. Furthermore, the most substantial influence on EVD transmission arrived from Ebola-targeted violence, mainly caused by civilian-induced incidents. Kraemer et al. [84] explored the relationship between EVD transmission and the occurrence of conflicts and violence. They found that conflicts were associated with the magnitude of EVD outbreaks in health zones in North Kivu and Ituri. Wells et al. [159] investigated the relationship between conflicts and EVD spread. They found that preceding unrest and conflict events significantly affected the speed of case isolation and vaccination efficiency. Wannier et al. [157] compared transmission rates among different health zones during the 2018-2020 Kivu outbreak. They found that violence during the 2018-2020 Kivu outbreak significantly increased the spread of EVD.

Kelly et al. [80] and Kraemer et al. [84] are observational studies. While these studies provide insights into the associations between conflicts and EVD spread, they can not be used to simulate the number of EVD cases, deaths, hospitalisations, and vaccinations given different levels of community distrust. Wells et al. [159] also did not explicitly account for hospitalisations or whether some hospitalised individuals could escape the attacks on ETCs to the community. In addition, Wannier et al. [157] did not make use of the vaccination data to quantify their model. In the current study, we address these limitations while quantifying our model with actual data to assess the impact of the attacks on ETCs.

Our current EVD model also differs from other previous EVD modelling studies. Unlike Seidu et al. [135], Bodine et al. [12] and Lin et al. [96], we consider susceptible persons to have different risks of infections depending on their geographical locations. Further, unlike Brettin et al. [15], and Chowell et al. [34], we account for transmission from the deceased.

Finally, in the current study, we model the transmission dynamics of EVD while accounting for ring vaccinations, antiviral treatments and contact tracing measures that were used in recent EVD outbreaks.

This Chapter is laid out as follows: We explore model assumptions and formulation in

the second section. The theoretical analysis of the model is discussed in Section Three. We first discuss the model solution' non-negativity and boundedness. The basic reproduction number is then calculated. We obtain the model equilibria and discuss their stability analysis. In Section Four, we discuss the model fitting and numerical findings. In Section Five, we conclude our study and discuss recommendations.

4.2 Model formulation

During the 2018-2020 Kivu outbreak, 81% of EVD cases were located in six health zones: Beni, Butembo, Kalunguta, Katwa, Mabalako, and Mandima [68]. As a result at the beginning of the outbreak, we assume that 81% of infections are associated with these health zones. We call these health zones areas with high infections. Other health zones in North Kivu and Ituri are called areas with low infections. Let S_H and S_L be the number of susceptible individuals residing in areas with high and low infections, respectively. Let V be the number of vaccinated individuals in the population. Let E, I, H, D and R be the number of people exposed, infected, hospitalised, infectious deceased and recovered in the population, respectively. Let I_a be the number of hospitalised persons who fled the ETCs because of the attacks and joined the community. Let N be the population of the North Kivu and Ituri provinces so that

$$N = S_H + S_L + V + E + I + H + I_a + D + R. \tag{4.1}$$

The 2018-2020 EVD outbreak in North Kivu and Ituri continued for almost two years [167]. Natural births and deaths might play a role in the dynamics of a disease when the disease is extended for a long period. Thus, we assume Π and μ are the numbers of births and natural deaths (reasons other than EVD) in the population, respectively. The spread of EVD from one person to another occurs through contact with the bodily fluids of infected persons. Before any intervention was considered, we assume the effective contact rate among susceptible individuals residing in areas with high infections and living infectious persons is β_0. We assume β_2 is the effective contact rate among the susceptible individuals living in areas with high infections and the infectious deceased. Let δ be a positive number so that $\beta_2 = \delta\beta_0$. Let τ_1 be a modification parameter that accounts for transmission in low infection areas so that $\tau_1\beta_0$ and $\tau_1\beta_2$ are the effective contact rates for

the living infectious persons and the infectious deceased with the susceptible individuals residing in low infection areas, respectively. We assume the vaccination rates in areas with high and low infections to be m_1 and m_2, respectively.

Contact tracing involves identifying and isolating exposed individuals as soon as they are symptomatic. As contact tracing is considered, the effective contact rate declines due to the isolation of symptomatic persons. We remark the number of vaccinated persons V involves the contacts and contacts of contacts for infected persons. Thus, we can find a number $s_1 > 0$ such that the number of contacts among the vaccinated persons is $s_1 V$. Let $s_2 \geq 0$ be a parameter which accounts for the effectiveness of contact tracing per each contact person so that the effective contact rate β_0 becomes

$$\beta_1 + (\beta_0 - \beta_1)e^{-s_2 s_1 V}$$

during the contact tracing where β_1 ($\beta_1 < \beta_0$) is the effective contact rate post contact tracing. Let $q = s_2 s_1$. It follows that there exists no contact tracing when $q = 0$. On the other hand, the higher the value of q, the higher the effectiveness of contact tracing. It also follows that there exists a $\delta_1 \in (0, 1)$ such that $\beta_1 = \delta_1 \beta_0$.

EVD hospitalisation has generally been managed by treating symptoms, rehydrating patients orally and intravenously, and treating any additional infections that patients may have [94]. During the 2018-2020 Kivu outbreak, four antiviral medications (mAb114, Remdesivir, Zmapp, and Regeneron) were considered [104]. The rate of hospitalisation and treatment with mAb114, Remdesivir, Zmapp, or Regeneron are assumed to be ρ. Hospitalised individuals at ETCs are properly isolated throughout treatments and safely buried when they die at the ETCs [169]. Hospitalised persons may escape treatments due to the attacks on ETCs and put the community at risk of acquiring the disease [73, 73]. We assume the rate at which hospitalised individuals fled treatments due to the attacks on ETCs to be ζ_1 and the rate at which these individuals returned to ETCs to be ζ_2.

The complete process for the model is depicted in Figure 4.1, and a full description of

the model parameters is provided in Table 4.1. The model equations are described below:

$$\begin{aligned}
\frac{dS_H}{dt} &= \sigma\Pi - (\lambda_1 + m_1 + \mu)\, S_H \\
\frac{dS_L}{dt} &= (1-\sigma)\,\Pi - (\lambda_1\tau_1 + m_2 + \mu)\, S_L \\
\frac{dV}{dt} &= m_1 S_H + m_2 S_L - (\epsilon\lambda_1 + \mu)\, V \\
\frac{dE}{dt} &= \lambda_1 \left(S_H + \tau_1 S_L + \epsilon V\right) - (\alpha + \mu)\, E \\
\frac{dI}{dt} &= \alpha E - (h\rho + (1-h)\,\gamma + \mu)\, I \\
\frac{dH}{dt} &= h\rho I + l_2\zeta_2 I_a - ((1-l_1)\eta + l_1\zeta_1 + \mu)\, H \\
\frac{dI_a}{dt} &= l_1\zeta_1 H - ((1-l_2)\theta + l_2\zeta_2 + \mu)\, I_a \\
\frac{dD}{dt} &= f_1\,(1-h)\,\gamma I + (1-l_2)\theta f_3 I_a - bD \\
\frac{dR}{dt} &= (1-h)\,(1-f_1)\,\gamma I + \eta(1-l_1)\,(1-f_2)\,H + (1-l_2)\theta(1-f_3)I_a - \mu R
\end{aligned} \tag{4.2}$$

where

$$\begin{aligned}
\lambda_1 &= \frac{1}{N}\left(\beta_1 + (\beta_0 - \beta_1)e^{-qV}\right)(I + I_a + \delta D) \\
&= \frac{1}{N}\left(\delta_1\beta_0 + (\beta_0 - \delta_1\beta_0)e^{-qV}\right)(I + I_a + \delta D) \\
&= \frac{1}{N}\beta_0\left(\delta_1 + (1-\delta_1)e^{-qV}\right)(I + I_a + \delta D)\,.
\end{aligned}$$

System (4.2) is considered along with the initial conditions: $S_H(0) = S_{H0}$, $S_L(0) = S_{L0}$, $V(0) = V_0$, $E(0) = E_0$, $I(0) = I_0$, $H(0) = H_0$, $I_a(0) = I_{a0}$, $D(0) = D_0$ and $R(0) = R_0$.

To study the impact of the attacks on ETCs, we simulate the full model (4.2). However, we first created submodels in which we considered the cases when no attacks at ETCs exist and when no interventions are available. Then we quantify these submodels using the 2018-2020 Kivu outbreak data.

When there are no attacks on the ETCs, Model 4.2 becomes the sub-model, described below:

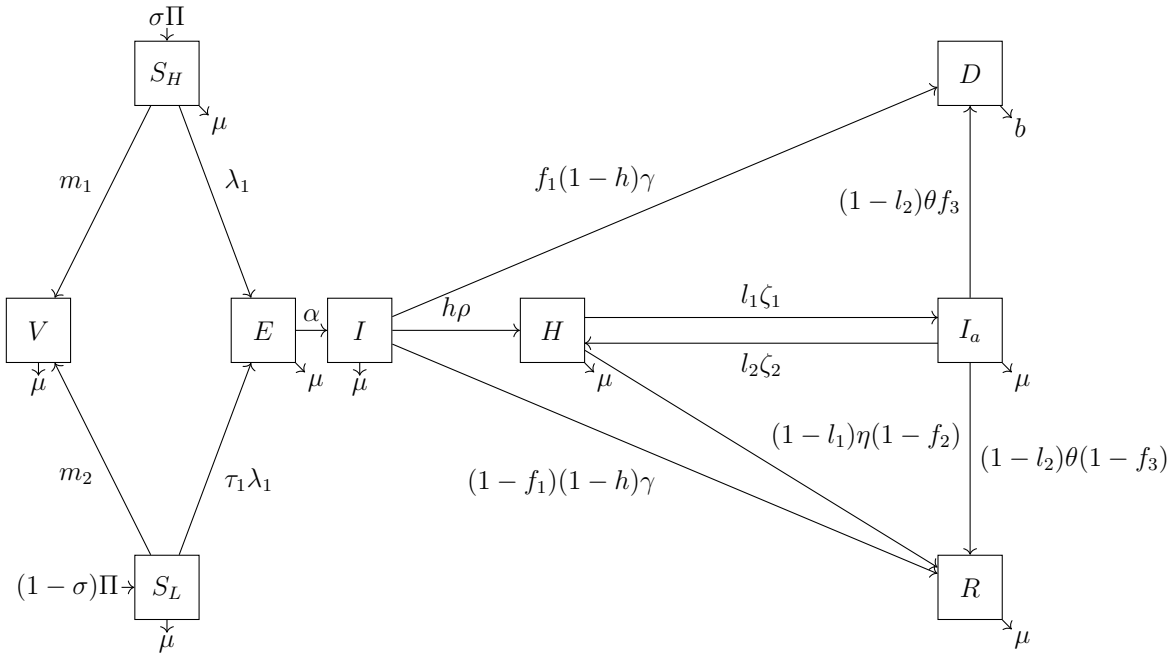


Figure 4.1: Transfer diagram for the model

$$
\begin{aligned}
\frac{dS_H}{dt} &= \sigma\Pi - (\lambda_1 + m_1 + \mu)\, S_H \\
\frac{dS_L}{dt} &= (1-\sigma)\,\Pi - (\lambda_1\tau_1 + m_2 + \mu)\, S_L \\
\frac{dV}{dt} &= m_1 S_H + m_2 S_L - (\epsilon\lambda_1 + \mu)\, V \\
\frac{dE}{dt} &= \lambda_1 \left(S_H + \tau_1 S_L + \epsilon V\right) - (\alpha + \mu)\, E \\
\frac{dI}{dt} &= \alpha E - (h\rho + (1-h)\,\gamma + \mu)\, I \\
\frac{dH}{dt} &= h\rho I - (\eta + \mu)\, H \\
\frac{dD}{dt} &= f_1\,(1-h)\,\gamma I - bD \\
\frac{dR}{dt} &= (1-h)\,(1-f_1)\,\gamma I + \eta\,(1-f_2)\,H - \mu R
\end{aligned}
\tag{4.3}
$$

where

$$
\lambda_1 \;=\; \frac{1}{N}\left(\beta_1 + (\beta_0 - \beta_1)e^{-qV}\right)(I + \delta D)\,.
$$

Further $S_H(0) = S_{H0}$, $S_L(0) = S_{L0}$, $V(0) = V_0$, $E(0) = E_0$, $I(0) = I_0$, $H(0) = H_0$, $D(0) = D_0$ and $R(0) = R_0$.

Further, when there are no attacks on the ETCs, vaccinations or antiviral treatments, Model 4.2 becomes the sub-model, described below:

$$\begin{aligned}
\frac{dS_H}{dt} &= \sigma\Pi - (\lambda_1 + \mu)\, S_H \\
\frac{dS_L}{dt} &= (1-\sigma)\,\Pi - (\lambda_1\tau_1 + \mu)\, S_L \\
\frac{dE}{dt} &= \lambda_1\,(S_H + \tau_1 S_L) - (\alpha + \mu)\, E \\
\frac{dI}{dt} &= \alpha E - (\gamma + \mu)\, I \\
\frac{dD}{dt} &= f_1\gamma I - bD \\
\frac{dR}{dt} &= (1-f_1)\,\gamma I - \mu R
\end{aligned} \tag{4.4}$$

where

$$\lambda_1 \;=\; \frac{\beta_0}{N}\,(I + \delta D)\,.$$

Further $S_H(0) = S_{H0}$, $S_L(0) = S_{L0}$, $E(0) = E_0$, $I(0) = I_0$, $D(0) = D_0$ and $R(0) = R_0$.

4.3 Theoretical analysis

This section establishes that the state variables for Model (4.2) are non-negative at all times and that the solution is bounded. The basic reproduction number ($\mathcal{R}_0$) is a critical figure in describing the spread of EVD. We obtain $\mathcal{R}_0$ using a well-documented approach, described in [149].

4.3.1 Non-negativity and boundedness

It is necessary to show that all state variables are non-negative for all times so that system (4.2) is biologically significant.

Proposition 4.3.1. *The solution for system* (4.2) *is non-negative whenever* $S_H(0), S_L(0), V(0), E(0), I(0), H(0), I_a(0), D(0)$ *and* $R(0)$ *are non-negatives.*

We can now declare the statement below, which guarantees the boundedness of the solution for system (4.2).

Proposition 4.3.2. *The solution of system* (4.2)*, determined in Proposition 4.3.1, is bounded for all time* $t > 0$.

The proofs for Propositions 4.3.1 and 4.3.2 are done similar to the proofs of Propositions 3.3.1 and 3.3.2.

From Proposition 4.3.1, Proposition 4.3.2 and the trivial existence and uniqueness of a local solution, it follows that system (4.2) is a dynamical system in the biologically feasible compact set

$$\Big\{(S_H(t), S_L(t), V(t), E(t), I(t), H(t), I_a(t), D(t), R(t)) \subset \mathbb{R}^9_+ : N(t) \leq \psi\Big\},$$

where

$$\psi = \max\Big\{\frac{\Pi}{\mu}, N(0)\Big\}.$$

4.3.2 Model Equilibria

The disease-free equilibrium (DFE) is found when $I = I_a = D = 0$ and it is given by

$$P_0 = (S_H^*, S_L^*, V^*, 0, 0, 0, 0, 0)\,,$$

where $S_H^* = \frac{\sigma\Pi}{m_1+\mu}$, $S_L^* = \frac{(1-\sigma)\Pi}{m_2+\mu}$, $V^* = \frac{m_1 S_H^* + m_2 S_L^*}{\mu}$.

We use the next-generation matrix method [149] to obtain the controlled reproduction number ($\mathcal{R}_c$). We differentiate between the infected states (E, I, H, I_a, D) and uninfected states (S_H, S_L, V, R). We assume $\mathcal{F}$ and $\mathcal{W}$ as vectors representing the new and transported cases into the infected states, respectively.

Let F and W be Jacobian matrices of $\mathcal{F}$ and $\mathcal{W}$, described in [149]. Thus, $\mathcal{R}_c$ is defined to be the dominant eigenvalue of FW^{-1}. We find $\mathcal{R}_c$ to be:

$$A_2\left(\beta_1 + (\beta_0 - \beta_1)e^{-q\left(\frac{m_2\Pi(1-\sigma)}{\mu(m_2+\mu)} + \frac{m_1\Pi\sigma}{\mu(m_1+\mu)}\right)}\right)\left(\frac{\sigma}{m_1+\mu}\left(1 + \frac{\epsilon(m_1)}{\mu}\right) + \frac{\tau_1(1-\sigma)}{m_2+\mu}\left(1 + \frac{\epsilon(m_2)}{\mu}\right)\right), \tag{4.5}$$

where

$$A_2 = \left(\frac{\mu\alpha}{(\alpha+\mu)(\gamma(1-h)+\mu+h\rho)}\left(1+\frac{\delta_1 f_1\gamma(1-h)}{b}\right)+A_{21}\right),$$

$$A_{21} = A_{22}\left(1+f_3(1-l_2)\theta\right),$$

and

$$A_{22} = \frac{l_1\zeta_1 h\rho}{\left(\mu+(1-l_2)\theta+l_2\zeta_2\right)\left(\eta(1-l_1)+\mu+l_1\zeta_1\right)-l_1l_2\zeta_1\zeta_2}.$$

When there are no interventions, we have $q_1 = h = m_1 = m_2 = 0$. Thus, $\mathcal{R}_c$ becomes

$$\mathcal{R}_0 = \beta_0\frac{\alpha}{(\alpha+\mu)(\gamma+\mu)}\left(1+\frac{\delta f_1\gamma}{b}\right)\left(\sigma+\tau_1(1-\sigma)\right).$$

When there are no attacks on ETCs ($\zeta_1 = 0$), we have $A_{22} = 0$. Hence $\mathcal{R}_c$ becomes $\mathcal{R}_{c,\text{na}}$

$$\mathcal{R}_{c,\text{na}} = A_3\left(\frac{\sigma}{m_1+\mu}\left(1+\frac{\epsilon(m_1)}{\mu}\right)+\frac{\tau_1(1-\sigma)}{m_2+\mu}\left(1+\frac{\epsilon(m_2)}{\mu}\right)\right)$$

where

$$A_3 = \left(\beta_1+(\beta_0-\beta_1)e^{-q\left(\frac{m_2\Pi(1-\sigma)}{\mu(m_2+\mu)}+\frac{m_1\Pi\sigma}{\mu(m_1+\mu)}\right)}\right)\left(\frac{\mu\alpha}{(\alpha+\mu)(\gamma(1-h)+\mu+h\rho)}\left(1+\frac{\delta_1 f_1\gamma(1-h)}{b}\right)\right).$$

Next, we show the existence of an endemic equilibrium

$$(S_H^*, S_L^*, V^*, E^*, I^*, H^*, I_a^*, D^*, R^*),$$

where

$$\begin{aligned}
S_H^* &= \frac{\sigma\Pi}{\lambda_1+m_1+\mu}\\
S_L^* &= \frac{(1-\sigma)\Pi}{\lambda_1\tau_1+m_2+\mu},\\
V^* &= \frac{m_1S_H^*+m_2S_L^*}{\epsilon\lambda_1+\mu},\\
E^* &= \frac{\lambda_1}{(\alpha+\mu)}\left(S_H^*+\tau_1S_L^*+\epsilon V^*\right),\\
I^* &= \frac{\alpha}{h\rho+(1-h)\gamma+\mu}E^*,
\end{aligned}$$

with

$$\begin{aligned}
H^* &= \frac{h\rho I^*}{((1-l_1)\eta + l_1\zeta_1 + \mu) - \frac{l_2\zeta_2 l_1\zeta_1}{(1-l_2)\theta + l_2\zeta_2 + \mu}}, \\
I_a^* &= \frac{l_1\zeta_1 H^*}{((1-l_2)\theta + l_2\zeta_2 + \mu)} \\
D^* &= \frac{f_1(1-h)\gamma}{b} I^* + \frac{(1-l_2)\theta f_3 I_a^*}{b}, \\
R^* &= \frac{1}{\mu}\left((1-h)(1-f_1)\gamma I^* + \eta(1-l_1)(1-f_2)H^* + (1-l_2)(1-f_3)\theta I_a^*\right), \\
N^* &= \frac{\Pi}{\mu} - \frac{(b-\mu)D^*}{\mu}, \\
\lambda_1 &= \left(\beta_1 + (\beta_0 - \beta_1)e^{-qV^*}\right)\left(\frac{I^* + I_a^* + \delta D^*}{N^*}\right).
\end{aligned}$$

As in [108, 152], the equilibria points of system (4.2) correspond the fixed points of the following system

$$\lambda_1 = \phi(\lambda_1) = \left(\beta_1 + (\beta_0 - \beta_1)e^{-qV^*}\right)\left(\frac{I^* + I_a^* + \delta D^*}{N^*}\right). \tag{4.6}$$

The variables I^*, I_a^* and D^* can be rewritten as

$$\begin{aligned}
I^* &= \frac{\alpha}{h\rho + (1-h)\gamma + \mu} E^*, \\
I_a^* &= \frac{l_1\zeta_1 h\rho\alpha}{((1-l_2)\theta + l_2\zeta_2 + \mu)\left(((1-l_1)\eta + l_1\zeta_1 + \mu) - \frac{l_2\zeta_2 l_1\zeta_1}{(1-l_2)\theta + l_2\zeta_2 + \mu}\right)(h\rho + (1-h)\gamma + \mu)} E^*, \\
D^* &= \frac{\alpha\left(f_1(1-h)\gamma\right)}{b\left(h\rho + (1-h)\gamma + \mu\right)} E^* \\
&\quad + \frac{\left((1-l_2)\theta f_3\right) l_1\zeta_1 h\rho\alpha}{b((1-l_2)\theta + l_2\zeta_2 + \mu)\left(((1-l_1)\eta + l_1\zeta_1 + \mu) - \frac{l_2\zeta_2 l_1\zeta_1}{(1-l_2)\theta + l_2\zeta_2 + \mu}\right)(h\rho + (1-h)\gamma + \mu)} E^*.
\end{aligned}$$

Note from (4.6) that $\phi(\lambda_1)$ is continuous in $\lambda_1 \in [0, \infty)$. Further $\phi(0) = 0$. On the other hand,

$$\lim_{\lambda_1 \to \infty} \left(\beta_1 + (\beta_0 - \beta_1)e^{-qV^*}\right) = \beta_0.$$

Thus, to find $\lim_{\lambda_1 \to \infty} \phi(\lambda_1)$, it is enough to find $\lim_{\lambda_1 \to \infty} E^*$. We have

$$\lim_{\lambda_1 \to \infty} E^* = \frac{\Pi}{\alpha + \mu}.$$

Hence $\phi(\lambda_1)$ is bounded for $\lambda_1 \in [0, \infty)$.

We also have that

$$\frac{d\phi}{d\lambda_1}(0) = \mathcal{R}_c.$$

Let $\mathcal{R}_c > 1$. We propose that we have r in a neighbourhood of zero, say $(0, \delta_1)$ such that $\phi(r) > r$. Otherwise, for all neighbourhoods near zero, $\phi(r) \leq r$ which implies that

$$\frac{d\phi}{d\lambda_1}(0) = \lim_{\lambda_1 \to 0^+} \frac{\phi(\lambda_1) - \phi(0)}{\lambda_1} = \lim_{\lambda_1 \to 0^+} \frac{\phi(\lambda_1)}{\lambda_1} \leq 0,$$

which is a contradiction. Hence, there exists an $r \in (0, \infty)$ such that $\phi(r) > r$. Since $\phi(\lambda_1)$ is bounded as $\lambda_1 \to \infty$, we have an $M > 0$ such that $\phi(M) < M$. Let $Z(\lambda_1) = \lambda_1 - \phi_1(\lambda_1)$. We have $Z(r) < 0$ and $Z(M) > 0$. Using the Intermediate Value Theorem, we have a $\lambda_1^* \in (r, M)$ such that $\phi(\lambda_1^*) = \lambda_1^*$. Hence, there exists a non-zero solution λ_1^* to Equation (4.6). Equivalently, system (4.2) has an endemic equilibrium. The condition for the local stability is computed as in [108]. The Jacobian matrix around the zero fixed point $\lambda_1 = 0$ for system (4.6) is given by

$$\frac{d\phi_1(0)}{d\lambda_1} = \mathcal{R}_c.$$

Thus, the DFE is locally asymptotically stable if $\mathcal{R}_c < 1$ and it is unstable if $\mathcal{R}_c > 1$. On the other hand, the endemic equilibrium is locally asymptotically stable if $\frac{d\phi_1(\lambda_1^*)}{d\lambda_1} < 1$ and it is unstable if $\frac{d\phi_1(\lambda_1^*)}{d\lambda_1} > 1$.

4.4 Model fitting and numerical simulations

To study the impact of the violent attacks on ETCs, we use cumulative cases and ring vaccination data to quantify our models. The cumulative case data are collected from the WHO situational reports, while the cumulative ring vaccinations are adapted from the Humanitarian Data Exchange website [68]. We consider a timeline for these data which starts from the beginning of the outbreak (5 August 2018) to the last date after which ETCs are attacked (23 February 2019). This timeline was divided into two periods: the first three weeks (5 August to 25 August 2018) and the next six months (26 August 2018 to 23 February 2019). During the first period, vaccinations and antiviral treatments were not considered. We fit systems (4.4) and (4.3) to the data reported during the first and the

second periods, respectively.

We discuss the impact of vaccinations, contact tracing and antiviral treatment during the outbreak. We are then concerned with the numerical insights on the impact of the attacks on ETCs during the 2018-2020 Kivu outbreak.

4.4.1 Model fitting

To solve the initial value problems (4.3) and (4.4), we apply the odeint function of Scipy [145]. This function is used to solve a system of ordinary differential equations using the ISODA algorithm from the FORTRAN library odepack. Sub-models (4.3) and (4.4) are fitted to the EVD data using optimize.curve_fit function of Scipy [146]. This function uses non-linear least squares for the fitting. It also allows to compute the 67% confidence interval of the parameter estimates.

To quantify Model (4.3), we use the values of known parameters as shown in Table 4.2. We fit the cumulative cases function

$$\int_0^t \alpha E(s)\ ds \tag{4.7}$$

of Model (4.4) to the cumulative cases data reported for the period of 5 August to 25 August 2018 and estimated $\mathcal{R}_0$ to be 3.28. Other parameters of Model (4.3) are estimated by fitting the cumulative cases function Equation (4.7) and vaccination function

$$\int_0^t (m_1 S_H(s) + m_2 S_L(s))ds$$

of Model (4.3) to the data reported for the period of 26 August 2018 to 23 February 2019. We present the model fitting in Figure 4.2 and Figure 4.3. The complete list of the estimated parameters and 67% confidence interval is presented in Table 4.1 and Table 4.2.

4.4.2 Sensitivity analysis

To understand morbidity and mortality related to the attacks on ETCs, it is critical first to understand the relative importance of the various factors influencing EVD transmission and prevalence when there are no attacks on ETCs. Sensitivity analysis is used to identify

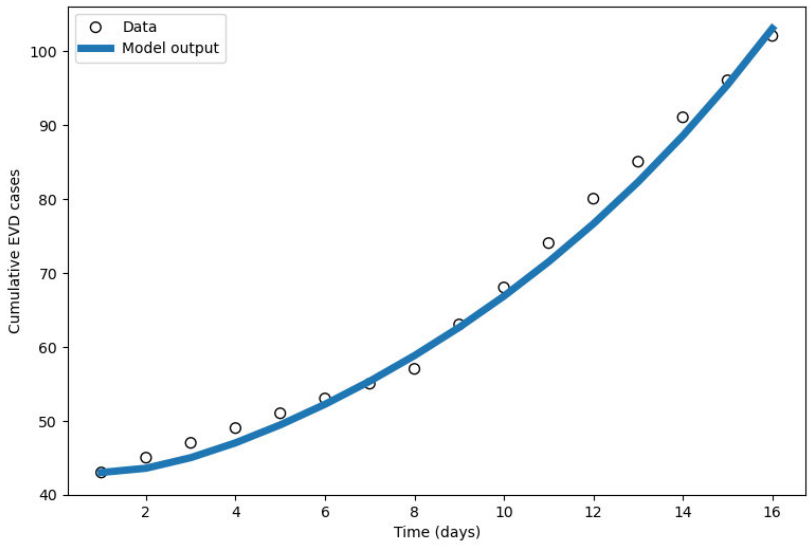


Figure 4.2: Model fitting when there are no vaccinations or antiviral treatments.

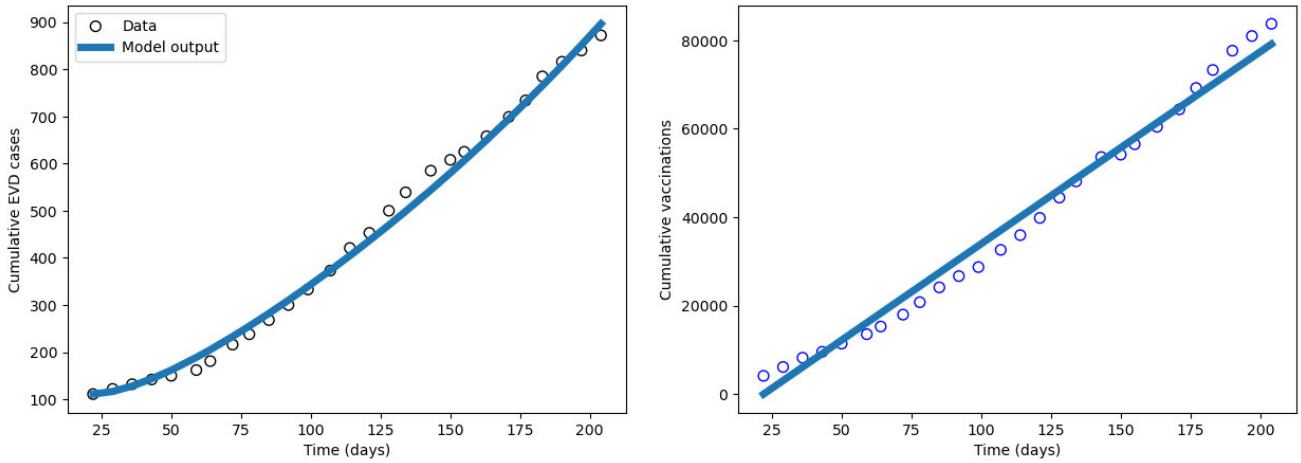


Figure 4.3: Model fitting when there are vaccinations and antiviral treatments but there are no attacks on ETCs.

variables that significantly impact EVD transmission and prevalence. In this subsection, we follow Chitnis et al. [30] to identify the impact of the different parameters on $\mathcal{R}_{c,\text{na}}$. They used the normalised forward sensitivity index method. The normalised forward sensitivity index of $\mathcal{R}_{c,\text{na}}$ to any parameter is the ratio of the relative change in $\mathcal{R}_{c,\text{na}}$ to the relative change in that parameter [30]. It can be defined using partial derivatives as follows:

$$\Upsilon_p^{\mathcal{R}_{c,\text{na}}} = \frac{\partial \mathcal{R}_{c,\text{na}}}{\partial p} \times \frac{p}{\mathcal{R}_{c,\text{na}}}$$

where p is any of the parameters that compose $\mathcal{R}_{c,\text{na}}$. We obtain the sensitivity indices of $\mathcal{R}_{c,\text{na}}$ to each parameter of $\mathcal{R}_{c,\text{na}}$ (Table. 4.2). We find that the most sensitive parameter is the effective contact rate among susceptible individuals residing in areas with high infections and the living infectious persons β_0. Other important parameters include the fraction of susceptible patients living in areas with high infections (σ) and the rate at which non-hospitalised persons recover or die (γ). For example, since $\Upsilon_{\sigma}^{\mathcal{R}_{c,\text{na}}} = +0.754$, decreasing (or increasing) σ by 10% decreases (or increases) $\mathcal{R}_{c,\text{na}}$ by 7.54%. On the other hand, as $\Upsilon_{\gamma}^{\mathcal{R}_{c,\text{na}}} = -0.643$, decreasing (or increasing) γ by 10% increases (or decreases) $\mathcal{R}_{c,\text{na}}$ by 6.43%.

4.4.3 The impact of the attacks on Ebola treatment centres

As previously anticipated in this study, the epidemic curve would change after August 2019, specifically after the 373rd day of the outbreak, due to the new policy on antiviral treatments. To assess the impact of ETCs attacks during the 2018-2020 Kivu outbreak, we consider the outbreak data from the beginning of the outbreak to the 373rd day of the outbreak.

We compare the actual data between February 2019 (the date on which the attacks on ETCs started) and August 2019 with the model outputs (Figure 4.4). We find that the attacks on ETCs increased the number of cases in the population by about 17% on the 373rd day of the outbreak. Indeed, the number of cases dramatically increased in Katwa and Butembo following the attacks on ETCs [74]. However, from Figure 4.4, it should be remarked that the number of cases in the population did not increase immediately after the attacks on ETCs, probably because it usually takes a few latent periods before the number of cases in the population dramatically rises due to the attacks on ETCs.

We have no data for the parameters $\zeta_1, \zeta_2, \theta, l_1$ and l_2. It follows however, from the definition of these parameters that their values lie in the interval $[0, 1]$. Also, we have no data for f_3. However, it is natural to assume EVD patients have the highest probability of EVD deaths if not hospitalised. That is, $f_2 \leq f_1$ and $f_3 \leq f_1$. Further, hospitalised individuals who interrupted treatments because of the attacks have a higher probability of EVD deaths than other hospitalised individuals. That is $f_2 \leq f_3$. It follows that $f_2 \leq f_3 \leq f_1$.

To explore the interplay between the different levels of attacks on ETCs and the level

of infections in the population, we assume that $f_3 = \frac{f_1+f_2}{2}$. Further, we fix the value of four other parameters ($\zeta_1, \zeta_2, \theta, l_1$ and l_2), while we vary one of them. As a result, when 10% of the hospitalised flee the attacks after they spend three days at ETCs, the cumulative cases on the 373rd day increase by more than 30% if these patients spend three days in the community, after which they all return to the ETCs (Figure. 4.5). When half of these individuals return to ETCs, the cumulative cases increase by about 50% (Figure. 4.6). Further, when these patients spend one more day in the community, after which they all return to treatments, the cumulative cases rise by an additional 10% (Figure. 4.7). We also find that when the patients are treated for one more day before they flee the attacks, the cumulative cases are reduced by 10% (Figure 4.8).

We remark that the interactions among the parameters $\zeta_1, \zeta_2, \eta, \theta, f_3, l_1$ and l_2 produce non-obvious dynamics for EVD (Figures: 4.5, 4.6, 4.8 and 4.7). In particular, it is still unclear which of these parameters is the most influential in the dynamics of EVD on the space of all possible values for these parameters. To identify parameters that have the highest impact on the prevalence of EVD, we conduct sensitivity analysis using the Latin Hypercube Sampling (LHS) scheme with Partial Rank Correlation Coefficients (PRCC) approach.

To proceed with the sensitivity analysis, let $\alpha_1 = l_1\zeta_1, \alpha_2 = l_2\zeta_2$, $\alpha_3 = (1-l_2)\theta f_3$, $\alpha_4 = (1-l_2)\theta(1-f_3)$ and $\alpha_5 = (1-l_1)\eta(1-f_2)$. Thus, α_1, α_2 and α_3 are the rates at which hospitalised individuals flee the attacks, patients who escaped the attacks return to the ETCs, and patients who escaped the attacks die in the community due to EVD. The parameters α_4 and α_5 represent the rate at which individuals who fled the attacks recover and the rate at which they die in the community after they fled the attacks, respectively.

We remark that the parameters $\zeta_1, \zeta_2, \eta, \theta, l_1$ and l_2, lie in the interval $[0, 1]$ while f_3 lies in the interval $[f_1, f_2]$. It follows that the parameters $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5$ lie in the interval $[0, 1]$.

We generate 400 samples for each parameter $\alpha_1, \alpha_2, \alpha_3, \alpha_4$ and α_5, using a uniform distribution over the interval $[0, 1]$. We use PRCC to identify how sensitive the cumulative cases with respect to changes in the different parameter values. Figure 4.9 shows that the most influential parameters in the dynamics of EVD are, in order, the rates at which hospitalised individuals flee the attacks, individuals who fled the attacks recover from EVD and patients who escaped the attacks return to the ETCs. These rates must be given

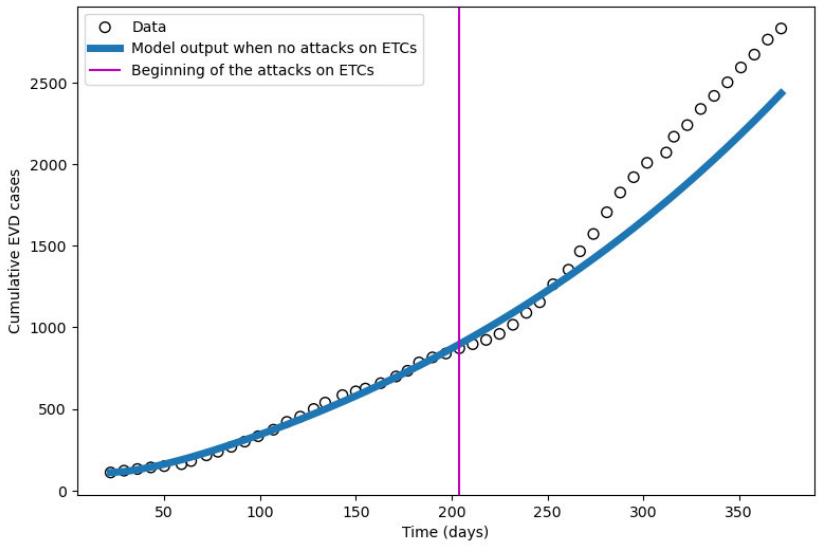


Figure 4.4: The impact of the attacks on ETCs during the 2018-2020 Kivu outbreak. By the model output here, we mean the output of Model (4.3). It should be remarked this represents the case in which no attacks on ETCs is considered.

priority during EVD interventions.

4.5 Discussion

Ebola virus disease is a highly contagious lethal infection. On 1 August 2018, the Ministry of Health of DR Congo declared the tenth EVD outbreak in DR Congo. The outbreak occurred in areas with ongoing armed conflicts in Kivu and Ituri provinces. In addition to armed conflicts, community distrust largely contributed to the spread of EVD during the 2018-2020 Kivu outbreak. Healthcare was particularly a victim of systematic attacks. In the current study, we concern ourselves with studying the impact of attacks on ETCs. Attacks on ETCs can be very destructive because hospitalised EVD patients might flee ETCs due to the attacks and join the community. Additionally, attackers can become exposed to EVD by contact with the patients or by touching or stealing beddings, mattresses or other items that patients use.

During the 2018-2020 Kivu outbreak, patients fled the attacks on ETCs in Katwa and Butembo. A spike of cases increased in these areas following the attacks on ETCs. In the current study, we developed a mathematical model to understand the impact of the attacks on ETCs during the 2018-2020 Kivu outbreak. We estimate that the attacks on

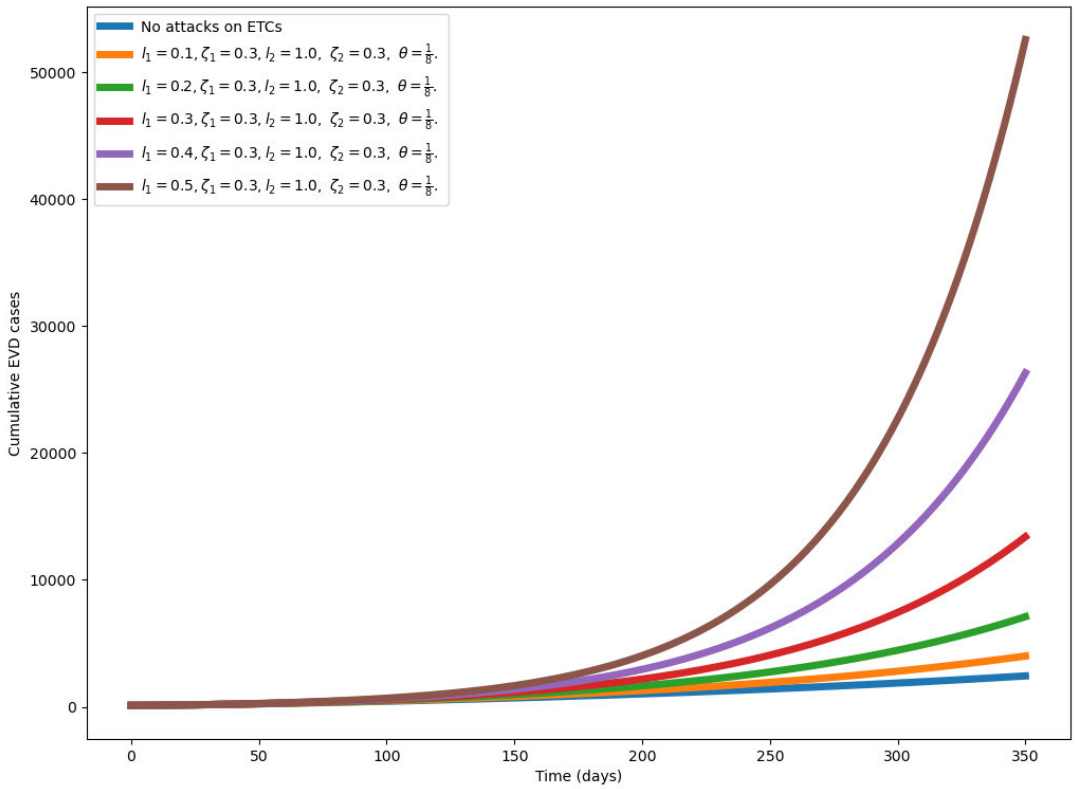


Figure 4.5: The impact of the attacks when the percentage of patients who fled the attacks is $10\%, 20\%, 30\%, 40\%$ and 50%.

ETCs caused the cases to rise by 17% in August 2019. We also find that if 10% of the hospitalised flee the attacks on ETCs, the cumulative cases on the 373rd-day increase by more than 30% (Figure. 4.5) if these individuals spend three days in the community, after which they all return to ETCs. If half of these individuals return to ETCs for treatments, the cumulative cases increase by about 50% (Figure. 4.6). If these individuals' return to the ETCs is delayed by one day, the cumulative cases are raised by an additional 10% (Figure. 4.7). On the other hand, when patients are treated for one more day before they flee the attacks, the cumulative cases are reduced by about 10%.

Global sensitivity analysis shows that the most influential parameters in the dynamics of EVD are, in order, the rates at which hospitalised individuals flee the attacks, individuals who fled the attacks recover from EVD and patients who escaped the attacks return to the ETCs. Thus, these rates must be prioritised during EVD interventions.

The rate at which hospitalized individuals flee the attacks can be minimized by tackling the reasons for hostilities against EVD response teams. Three significant reasons can be

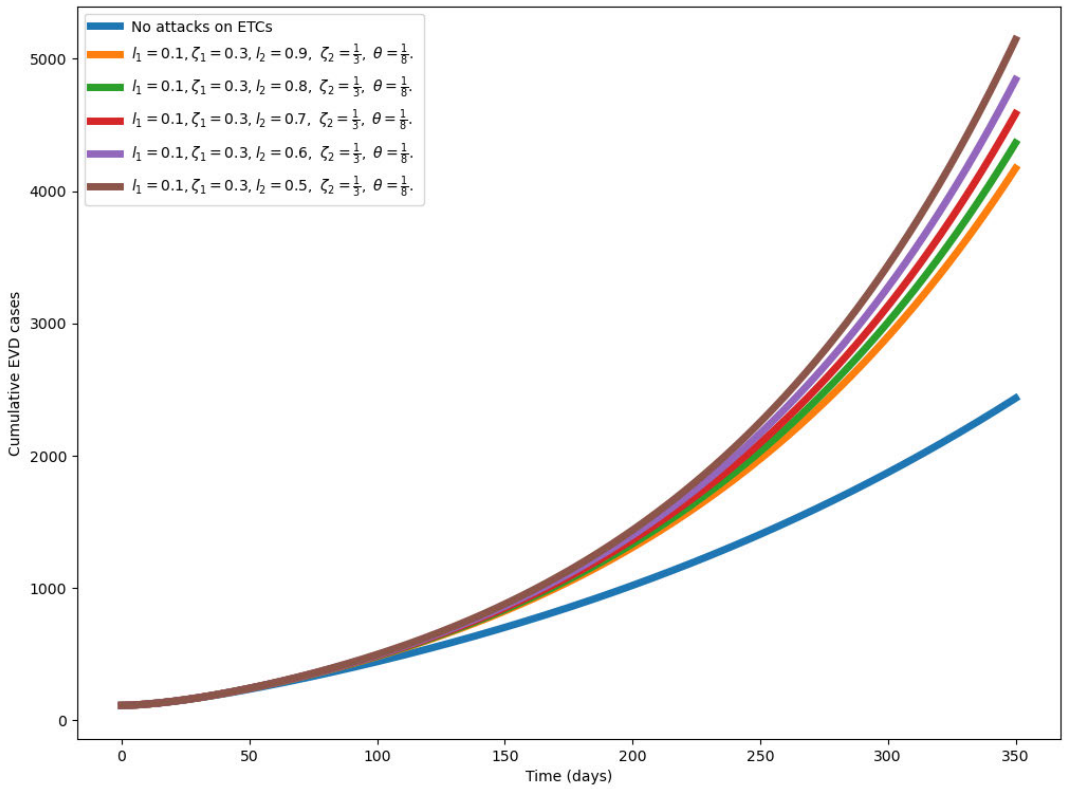


Figure 4.6: The impact of the attacks when the percentage of patients who did not return to treatments after they fled the attacks is $10\%, 20\%, 30\%, 40\%$ and 50%.

identified for the distrust and hostility towards EVD response efforts [128]. First, EVD symptoms are similar to more familiar diseases such as malaria and Lassa Fever. EVD is revealed distinctively only at later stages. Isolated rural people value high-quality home care for diseases such as malaria and feel deprived when they cannot provide the same for EVD. Secondly, EVD diagnosis is based on Phlebotomy. Many believe that ETCs are places for mining of blood. A village chief remarked that they have heard of giving ill persons blood transfusions but have not heard of sick people forced to give blood [128]. These suspicions are based on unethical practices of blood sample extraction and sample theft during EVD outbreaks [128]. Thirdly, people in many parts of Africa have priorities other than EVD. These include poverty, other endemic diseases and instability. Many people question the reasons that foreigners care so much about EVD [128]. Some believe that foreigners are probably scared of EVD or that there is money in patients' body parts or blood [128]. Also, some believe the virus could have some hidden utility (facts about cold war germ and unknown molecular patents) [128].

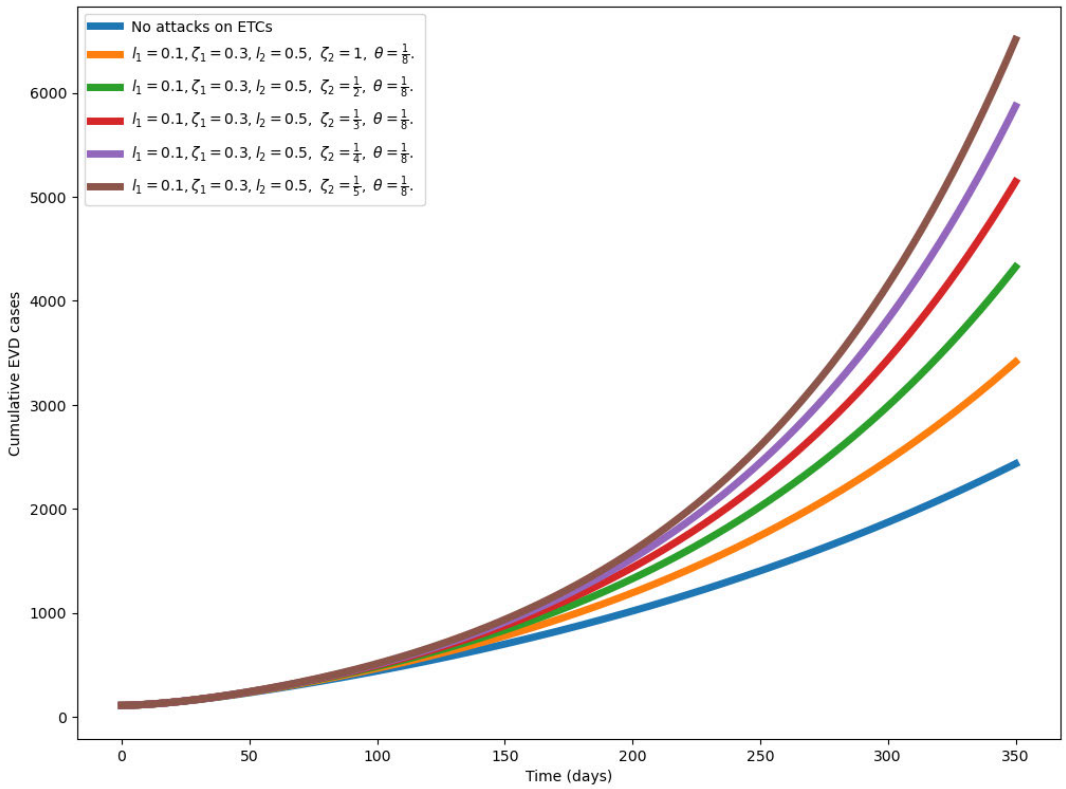


Figure 4.7: The impact of the attacks if the return of individuals to treatments was delayed by one, two, three, four and five days.

Evidence is thus needed to support the change of attitudes. For example, families must recognise that those most involved in care for patients at home are at the highest risk of becoming infected. A steady flow of discharged survivors from ETCs can also change perceptions that the ETCs are where people went only to die. Social learning about EVD through trusted village chiefs, friends and family members can also be effective.

To conclude, while hostility towards ETCs can dramatically hinder EVD control efforts, addressing the reasons for these hostilities is highly recommended.

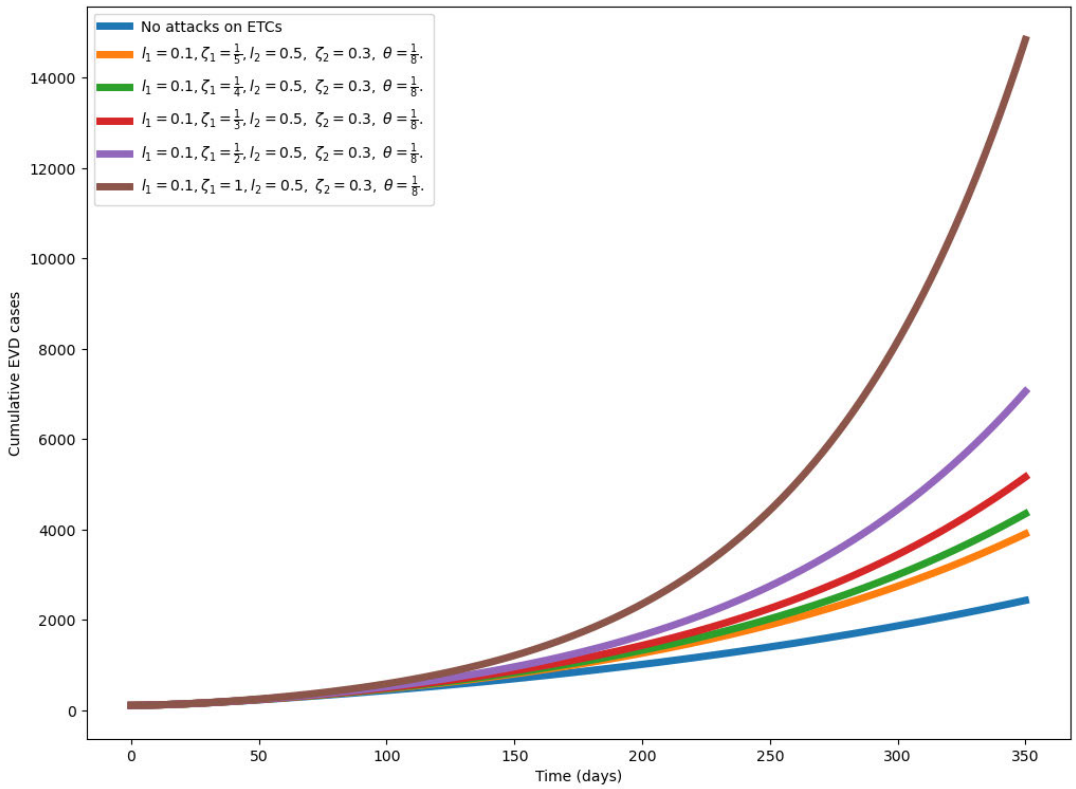


Figure 4.8: The impact of the attacks when patients are treated for one, two, three, four and five days at ETCs before they flee the attacks.

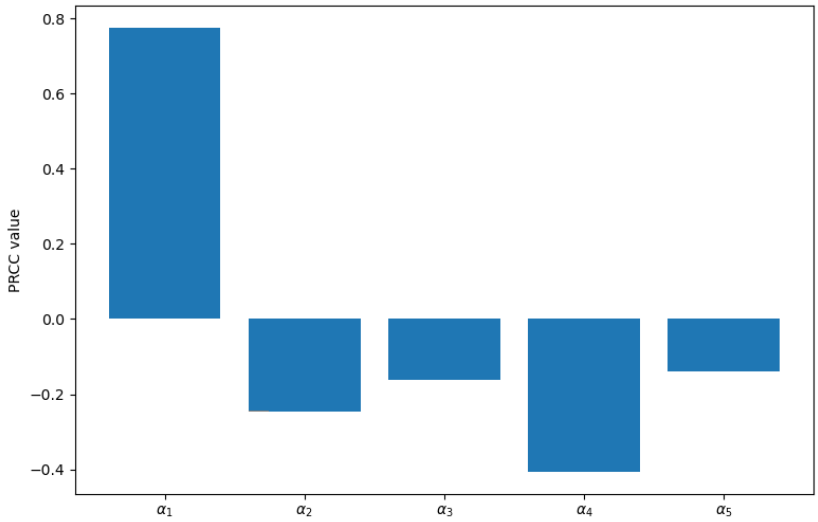


Figure 4.9: PRCC for the cumulative cases at $t = 373$.

Continued Table 4.1.

Table 4.1: Model parameters and their interpretations.

Parameter	Interpretation
Π	Birth rate.
$\frac{1}{\alpha}$	The incubation period.
$\frac{1}{\gamma}$	The average time from symptoms onset to either recovery or to EVD death for an infected person.
ϵ	The fraction of vaccinated individuals that are not immunised by the vaccination.
$\frac{1}{b}$	The average time from EVD death to burial.
$\frac{1}{\zeta_1}$	The average time from hospitalisation to escaping treatments due to the attacks on ETCs.
$\frac{1}{\zeta_2}$	The average time in which individuals who escaped treatments returns to ETCs.
l_1	The proportion of hospitalised individuals who escaped treatments due to the attacks on ETCs.
l_2	The proportion of people who returned to the ETCs after fleeing the attacks.
β_0	The effective contact rate among susceptible individuals residing in areas with high infections and the living infectious persons.
μ	Natural mortality rate.
$\frac{1}{\rho}$	The average time from symptoms onset to hospitalisation.
$\frac{1}{\theta}$	The average time from fleeing ETCs to recovery or to deaths.
f_1	The probability of EVD deaths for non-hospitalised individuals.
f_2	The probability of EVD deaths for hospitalised cases.
f_3	The probability of EVD deaths for hospitalised who escaped treatments.
$\frac{1}{\eta}$	The average time from hospitalisation to either recovery or to EVD death.
τ_1	A modification parameter that accounts for the transmission to individuals living in areas with low levels of infections.
m_1	Vaccination rate for healthcare and frontline workers located in areas with high level of infections.
m_2	Vaccination rate for healthcare and frontline workers located in areas with low level of infections.

Continued Table 4.1.

σ	The fraction of susceptible individuals living in areas with high infections.
δ	A modification parameter that accounts for the transmission from the deceased.
δ_1	A modification parameter that accounts for the impact of contact tracing.
q	A parameter which accounts for the effectiveness of contact tracing per each contact person.
h	A fraction of the infected individuals that are hospitalised at Ebola treatment centres and treated with mAb114, Remdesivir, Zmapp or Regeneron antiviral treatments.

Table 4.2: Model parameter values and their Sensitivity Indices (S.I) and Confidence Intervals (C.I).

Parameter	Unit	Estimates	67% C.I	S.I	Estimate' source
Π	day^{-1}	534.33	–	–	Calculated
α	day^{-1}	0.1	–	$+0.000101938$	[150]
γ	day^{-1}	0.178	–	-0.0758866	[150]
ϵ	none	0.025	–	$+0.0235735$	[173]
b	day^{-1}	0.580	–	-0.0955563	[150]
β_0	day^{-1}	1.860394	$[1.36, 2.34]$	$+0.223347$	Fitted
μ	day^{-1}	0.0000456621	–	$+0.136341$	[83]
ρ	day^{-1}	0.182	–	-0.0518473	[112]
f_1	none	0.74	–	$+0.0955563$	[112, 170]
f_2	none	0.424	–	–	[112]
η	day^{-1}	0.068	–	–	Fitted
τ_1	none	0.0244	–	$+0.0238758$	Calculated
m_1	day^{-1}	0.00003637094	$[0, 0.12]$	-0.0810586	Fitted
m_2	day^{-1}	0.000037468	$[0, 0.02]$	-0.0174366	Fitted
δ_1	none	0.3800	$[0, 0.95]$	$+0.173929$	Fitted

Continued Table 4.2.

σ	none	0.1536	–	$+0.171541$	[70]
δ	none	2.89195	$[2.1, 3.68]$	$+0.0955563$	Fitted
q	people^{-1}	0.00012598	$[0, 0.01]$	-0.0380043	Fitted
h	none	0.229	–	-0.0293077	[112]

Chapter 5

Conclusion

Mathematical modelling is used to understand the dynamics of a disease, handle disease outbreaks in real time, assess the impact of therapeutic and non-therapeutic control measures, and assist in formulating policy decisions [14]. While many models were suggested to advise public health physicians to understand the dynamics of EVD and control its spread, the disease continued to spread in Africa. Thus, we first explored the limitations of EVD modelling studies. Unlike previous models, we reviewed articles published from 2016 to 2018. We focused on surveying each article to identify its advantages and limitations. We classified articles broadly according to the modelling approaches and the model conclusions and constraints. We identified many limitations in the reviewed models and provided brief suggestions for future work. We then explored two important problems in EVD dynamics: the impact of vaccinations and the interplay between the attacks on ETCs and EVD spread.

The most effective vaccination plan is a customized response based on epidemiological traits and context-based modelling. Early contact tracing and ring vaccination may be sufficient for small epidemics in isolated groups, but further measures are needed to control widespread EVD outbreaks [103, 34, 138]. We explored the impact of GTVs in areas with high infections when EVD cannot be contained using contact tracing, ring vaccinations, and antiviral treatments. We quantified our model with the 2018–2020 Kivu outbreak data. We first estimated that 81% of the basic reproduction number is associated with areas of high infections. Further, we found that implementing GTVs in areas with high infections so that the total vaccinations are increased by 60% decreased EVD cases by 15%. On the other hand, we needed to increase the vaccinations to more than 1000% to achieve the 15% decrease in EVD cases if we implement GTVs in areas with low infections. We concluded that it is essential to maintain all intervention measures during outbreaks, including contact tracing, ring vaccinations and antiviral treatments. When the spread of EVD is not contained despite these measures, GTVs in areas with high infections can be implemented

to mitigate the spread of EVD.

During the 2018-2020 Kivu outbreak, EVD patients fled the attacks on ETCs in Katwa and Butembo. A spike in cases occurred following the ETCs attacks in these areas. We explored the interplay between ETCs attacks and EVD spread. We estimated that due to the attacks on ETCs, the cumulative cases during the 2018-2020 Kivu outbreak increased by 17% in August 2019. We also found that when 10% of the hospitalised individuals fled the attacks on ETCs after spending only three days under treatment, the cumulative cases increased by more than 30% even if these individuals all returned to the ETCs three days later. On the other hand, if only half of these individuals returned to ETCs for treatment, the cumulative cases increased by approximately 50%. Further, when these patients spent one more day in the community, after which they all return to ETCs, the cumulative cases are raised by an additional 10%. Global sensitivity analysis showed that the most influential parameter in the dynamics of EVD is the rate at which hospitalised individuals escaped the attacks, followed by the rate at which individuals who fled the attacks recovered from EVD and the rate at which patients who escaped the attacks returned to the ETCs.

Mathematical theory is beneficial in depicting general patterns from simple models. On the other hand, computer simulations are good at drawing specific results from complex models but sacrifice drawing general conclusions. A trade-off exists between a model's complexity level and the ability to parametrise the model with the available data reliably [130]. The complexity of a model is a function of the number of parameters needed to characterise the states of the system and the range of the dynamics that can be identified from the model (e.g. the number of equilibrium points, oscillations, bifurcation, chaos) [130]. Simple models have fewer parameters to be characterised from the data. We are working on a project that involves developing a simple $SEIR$ model which includes constant rates to describe contact tracing and vaccinations. The model is much simpler compared to the models considered in this thesis. Further, the estimated parameters have narrower confidence intervals. Thus there are more reliable estimates. We will also study a stochastic version of our simpler model in future work.

In this thesis, we reviewed previous EVD models and contributed to understanding critical issues of EVD dynamics. We hope our review will help researchers develop more realistic models to help mitigate the spread of EVD. We also hope that our models will guide public health practitioners to take steps to limit EVD outbreak spread.

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Appendix A

Detailed review of individual studies

Some reviews were structured according to estimated EVD parameters [32, 43, 150]. One [32] created a comparison between each natural history parameter for the past EVD outbreaks and the 2014 WA EVD. Another [37] listed critical uncertainties among different models. One [164] recorded the approaches, assumptions, and datasets of each reviewed model. Another [35] discussed different conclusions acquired from the 2014 WA EVD models. In this section, we survey each of our reviewed study in terms of the research problem, type of data, approaches, results, preferences, and constraints or gaps for further research. We describe this survey in Table A.1.

Table A.1: Detailed review.

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[97]	Addressing EVD spread through international travel.	The weekly EVD incidence data of Liberia available from the WHO website.	A compartment model was used for estimating the fraction of the latent population. It was assumed that only latent individuals could travel internationally and the probability of exporting EVD from Liberia to the USA was estimated.	The probability of exporting EVD from Liberia to the USA in the 15th week of 2014 was estimated to be 0.3 per 1,000 persons.	The model incorporated the volume of airline travellers from infected countries and calculated the risk of disease exportation.	The study assumed the people in Liberia to be homogeneously mixed and did not account for whether areas of frequent travellers were the most affected areas by the disease.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[163]	Addressing the risk of exporting EVD to the top 20 final destinations for commercial flight passengers travelling from Guinea, Liberia, and Sierra Leone.	The cumulative EVD cases data for Guinea, Liberia and Sierra Leone was used. This data was made available by the WHO.	The classical SIR model was used to estimate the effective reproductive numbers for Guinea, Liberia, and Sierra Leone. The average weekly number of travellers were adapted from the literature and stochastically simulated with a Poisson distribution to account for uncertainty. These in addition to the fraction of infected individuals in Guinea, Liberia, and Sierra Leone were used to estimate the weekly number of EVD imported cases using a Binomial distribution.	The daily effective reproductive number was estimated to be from 0.27 to 1.32, 0.62 to 1.38, and 0.81 to 1.32 for Guinea, Liberia, and Sierra Leone, respectively. In early November 2014, the probability of EVD importation into each of the top 20 final destination countries reached its peak. The restriction of air travel resulted in a reduction of the risk of EVD importation to about 67%.	The model helped in identifying the critical risk of EVD importation, and consequently assisted in the preparedness and the allocation of resources to control EVD.	The study assumed that the population of the three most affected West African countries to be homogeneously mixed regarding air travel ignoring socio-economic status. Further, the model did not account for any other EVD importation routes, such as roads, navy ships, or connecting flights.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[133]	Improving public health planning to combat a hypothetical EVD spread in India.	The model was quantified using parameter estimates that were adapted from the literature.	The proposed framework was a geospatial epidemiological modelling. It was simulated using a spatiotemporal epidemiological modelling software. The epidemic model considered was an $SEIR$ compartment model. This model incorporated EVD natural history estimates from the literature and simulated the worst case scenario.	The study described the spatiotemporal distribution of EVD and found that within two years almost half of the population of India would have been infected by the disease.	The combination of the epidemic model with a geospatial modelling framework gave insights about the spatial spread of the disease. This information is important for public health planners to target areas at high risks effectively.	The study had only considered the worst case scenario and did not account for any interventions that may happen during outbreaks.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[8]	Monitoring the spatial spread of EVD in administrative units in Sierra Leone, Liberia, and Guinea.	The WHO weekly EVD incidence, location coordinates, and population size for each administrative unit (county, prefecture, and district) for Guinea, Liberia, and Sierra Leone.	The new incidences in each administrative unit in the three countries were assumed to be generated by locals and travellers. The observed disease incidences were assumed to have a Poisson distribution, and the EVD parameters were estimated using a Bayesian Markov Chain Monte Carlo (MCMC) framework.	It was found that between four and ten percent of newly infected people travelled to other districts within the same country, and between zero and 23% of them travelled to other countries.	The model only requires disease incidence data, which is generally available at the beginning of an epidemic.	The estimated results depend mainly on the accuracy of the data. Issues such as under-reporting were common in the 2014 WA EVD data [35]. Additionally, the model did not account for any intervention scenarios such as border closure among countries, checking points among districts or hygienity practices.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[89]	Characterising the spatiotemporal spread and estimating key outbreak parameters of EVD.	GPS locations of where the bodies of 200 EVD deceased were collected for safe burials. Information regarding age, sex, and the burial time were also included in the dataset. The data was collected in Sierra Leone by the International Federation of Red Cross.	A statistical framework was first used in which new incidences were assumed to follow a non-homogeneous Poisson process. The probability of a new infection being a certain distance and direction from the source of infection depended only on the pattern of movement of the infected persons and the density of the susceptible individuals.	The degree of super-spreading was estimated to be 0.47, indicating significantly high super-spreading. Further, age groups younger than 15 and older than 45 were found to be more infectious compared to others. The median distance of EVD spread was found to be 0.85 kilometres which might indicate a higher transmission within a nearby community such as households and extended families.	The study enabled extracting vital information. It highlighted the importance of considering age-specific heterogeneities and community transmission. Further, it ascertained the role of super-spreaders in the transmission of EVD.	The study only incorporated EVD fatal cases. However, it concluded age specific infectiousness to all cases in the community (fatal and non-fatal).

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[45]	Examining spatially targeted control measures.	The 2014 WA EVD WHO data for Guinea, Liberia, and Sierra Leone were considered for the period of May to October 2014.	The proposed approach was a compartment model formulated for the district and national scales. Spatially targeted control measures were examined, while the mobility of individuals was expressed using a gravity type parameter. Further, the role of local intervention (e.g., quarantine of individuals at the district-level) and long-range intervention measures (e.g., border closure between countries) was evaluated.	Local interventions were found to be mostly effective in Liberia, while long-range control measures were dominantly relevant in Sierra Leone. Furthermore, results at the district-level showed that when applying local interventions at a district with a high infection rate (0.1% of the total cases) in Sierra Leone, Liberia or Guinea, a reduction of 20% on the total EVD cases occurred in the three countries.	The model accounted for the disease dynamics at the district and national levels. It was used to predict incidences and deaths in Guinea, Liberia, and Sierra Leone, and to assess spatially targeted control measures.	The model did not account for transmission in small scales such as communities (neighbourhoods) and villages. Kiskowski and Chowell [82] have considered this scale of transmission. It will be interesting to combine the latter approach with the current to assess the impact of interventions targeted to a village or a community.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[111]	Evaluating the risk of a possible spread of EVD in the Asia-Pacific region and assessing different control strategies.	EVD natural history and other model parameters were either assumed or adapted from the literature. Further, Papua New Guinea was used as a case study. Population density data were obtained from the Centre for International Earth Science Information Network of Colombia University.	The proposed model was a stochastic compartment model. The transmission was assumed to occur in rural and urban settings, with the latter considered to have higher infectiousness for patients. Further, the transmission from the deceased varied according to the dominant religion. This model was used to study several intervention strategies.	Early case detection was found to provide a higher decrease in the probability of having a large outbreak. Further, the reduction in the transmission from the deceased individuals was found to have substantially increased the probability of controlling the outbreak.	The model considered the transmission in rural settings to be different from urban. Crucially, high population density was repeatedly associated with high risk of transmission in the literature [148, 185, 134]. Additionally, the transmission from deceased individuals in the model was assumed to vary according to the dominant religion.	The model did not account for vaccination. However, it can be extended to include this situation. One issue that could be addressed in this case is determining the best distribution strategy for a vaccine.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[124]	Addressing a spatial heterogeneity of EVD among hypothetical cities.	The estimates that were used to parametrize the model were adapted from the 2014 WA EVD literature.	A compartment model composed of susceptible S, exposed E, infected I, removed R, and deceased D compartments was used. A population of a hypothetical country composed of four cities was assumed. These cities were connected using bidirectional roads and a free movement of individuals. The model was analysed using an agent-based software called PISKaS.	Both a higher degree of connectivity and higher proximity were connected with higher values of EVD growth rates.	The agent-based model combined the topology of connectivity among the cities and the population density.	The assumption of free mobility for infectious individuals is not realistic as some of these individuals might be too sick to travel, hospitalised, or quarantined.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[154]	Characterising the early phase trajectories of EVD.	The daily and weekly EVD incidence time series of the 1976 DR Congo outbreak, the 2000 Uganda outbreak and for several regions of West Africa during the 2014 WA EVD. The data were obtained from the WHO and from historical EVD literature.	A phenomenological model called a generalised growth model was proposed. It was assumed the disease incidences to be proportional to the cumulative number of cases depending on an EVD growth rate (r) and a declaration of growth parameter (p). The parameters r and p were estimated by fitting the model to EVD incidence data using the least square methods.	While the districts of Margibi of Liberia, and Bo and Bombali of Sierra Leone showed a nearly exponential growth with p close to one, Kenema of Sierra Leone and Bomi of Liberia had shown slow growth with p near 0.1. Generally, a sub-exponential growth was the most prevalent for the different EVD growth profiles at the district-level.	This modelling provided a useful tool to characterise the early growth profile for a disease, especially when there is not enough data to quantify mechanistic modelling.	The study did not explore the causes of the sub-exponential growth.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[131]	Evaluating the district-level spatial heterogeneity of the 2014 WA EVD.	The WHO cumulative cases and deaths for each district in Guinea, Liberia, and Sierra Leone.	Several quantities were estimated, including the spatiotemporal distribution of the EVD growth rates and the weekly expected number of new cases at each district, using Bayesian inference. Furthermore, a compartment model was composed, and several parameters, including the under-reporting rate, were estimated by fitting this model to the EVD cases and death data.	Several district-level parameters were estimated, including the district-specific effective reproductive. Further, a variation was found in the growth of the disease in various regions in Guinea, Liberia, and Sierra Leone.	The variability in the strength of the outbreak at the district-level highlighted the importance of spatially-targeted control measures.	The study did not investigate the underlying reasons for the high variability of EVD spread at the district-level.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[36]	Expanding the characterisation of the early sub-exponential growth of an outbreak using the generalised growth model and estimating the effective reproduction number (R_t).	The daily and weekly EVD incidence time series of the 1976 DR Congo outbreak, the 2000 Uganda outbreak and for several regions of West Africa during the 2014 WA EVD. The data were obtained from the WHO and from historical EVD literature.	The generalised growth model was first fitted to the first three to five disease generations of the data. Consequently, an EVD growth rate (r) and a declaration parameter (p) were estimated. These estimates and the generalised growth model were used in the simulation of EVD incidences. The generation interval along with the simulated incidences were used to estimate R_t.	A declining trajectory of R_t was found as the generation interval increased. Further, R_t was found to be sensitive to small changes in the declaration parameter p. The effective reproductive number was also found to have varied across the different geographical areas during the 2014 WA EVD. The highest recorded value of R_t was 2.5 in Montserrado in Liberia, whereas the lowest was 1.03 in Bomi.	This study has implications for vaccination trials. In the standard SIR model, it is established that $(1 - \frac{1}{R_0})\%$ of the population must be vaccinated to eradicate the disease. However, this fraction may be lower when the outbreak shows a sub-exponential initial growth that was indicated in the current study.	The study is a data-driven one and that the accuracy of the estimated parameters depends on the precision of the data. Issues such as under-reporting were common in the 2014 WA EVD data [35].

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[60]	Estimating the risk of EVD occurrence using the road density index (RDI).	The spatial locations of the districts in the three most affected countries by the 2014 WA EVD, and the road network data were obtained from the Socioeconomic Data and Applications Center (SEDAC).	The RDI was used to determine the mobility of people in districts. It was calculated by dividing the road lengths (measured in kilometres) by the district area (measured in square kilometres). A stochastic model was used to understand the relation between the risk of EVD occurrence and RDI.	A strong association was found between RDI and the risk of EVD occurrence. For example, a three percent increase in the risk of EVD infection was recorded when the RDI increased by 0.01.	This study used the RDI and confirmed that the number of people living and moving in an area to have played an important rule in the spread of EVD. As a result, the RDI can be used in future models to quantify spatial transmission models.	It is possible that the data that were used in the study might have missed some paths that connect villages.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[85]	Assessing several assumptions that are used to model spatial transmission.	Digital maps of administrative units in Guinea, Liberia, and Sierra Leone was obtained from the GADM database. Other population and mobility information were obtained from various other resources including WorldPop and Flowminder.	The model used was a network approach in which the nodes were assumed to be the geopolitical administrative units in the three countries, and the edges were assumed to represent how strong were the potential infection routes among the nodes. Different assumptions that weight the links among the nodes were assumed including diffusion and gravity-type force of infections.	The generalised gravity model was found to have created the best characterisation to the spatial spread compared to other models that used diffusion spread or estimated the mobility using cellphone records. On the other hand, a lower transmission probability was found among countries compared to within-country probability.	The results of this study outlined the importance of geographical considerations when modelling spatial spread. These results have also shown the weakness in using diffusion spread and cellphone data records to estimate the mobility as compared to the gravity-type assumption.	The gravity-type assumption that was chosen in this study does not predict the risk of air travel.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[17]	Characterising the spatial spread of EVD.	The WHO EVD incidences for the 1995 EVD in Kikwit city in Uganda and the 2014 WA EVD.	A discrete spatial model was proposed. The probability that a person at some spatial location and point of time becomes infected was calculated as a function of the spatiotemporal exposure intensity, the proportion of the distance between spatial locations, and the proportion of infected persons. In addition to further assumptions, these enabled deriving a newly adjusted spatial basic reproduction number (R_0).	The model was applied to the 2014 WA EVD, and although with a weak confidence, it was used to predict that as of January 2015, the epidemic would gradually slow down until finally being contained in April or May 2015.	A realistic estimation for the disease trajectories was provided using the newly derived $\mathcal{R}_0$ in the modelling as opposed to the classical $\mathcal{R}_0$ that assumes a homogeneously mixed population.	The exposure intensity parameter in the modelling is different among various places depending on the contact structure. Determining the value of this parameter requires expert knowledge.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[3]	Determining the relationship of the size of households and the balance of transmissions within and between households and the spread of EVD.	EVD natural history and the demographic parameters for Guinea, Liberia, and Sierra Leone were adapted from the literature.	The dynamics of the fraction of households at each epidemiological susceptible, exposed, infectious, and recovered ($SEIR$) state was described using a compartment model. The transitions among these states were modelled using a continuous-time Markov process. These models were modified to account for case identification measures followed by quarantine of households.	The study found that communities with small household sizes require a moderate level of case identification and quarantine. On the other hand, when the size of households was large, effective quarantine combined with case identifications and isolation of the whole household were required.	Transmission within a household and extended family represented the majority of transmission in the 2014 WA EVD [49]. Indeed structuring the transmission according to households in this study allowed for investigating the role of household structure in the spread of EVD. Further, it allowed for assessing household-targeted control measures.	The study assumed the transmission within and between households to be constants. However, those who look after patients have a higher chance of EVD transmission as compared to other household members. Further, transmission within relatives and friends is also higher than transmission with the general community.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[82]	Characterising the sub-national (district) level dynamics of the 2014 WA EVD.	EVD natural history parameters and the average household size were adapted from the literature.	The approach used was an individual-based $SEIR$ network model in which individuals were exposed to infectiousness as a result of transmissions within their households and neighbourhoods. Intervention measures in the network were applied locally within a community (neighbourhood) and globally in the entire network (entire population).	In the absence of control measures and the initial phase of the outbreak, an endemic state travelling waves of new infections existed moving through the population network. The community sizes and $\mathcal{R}_0$ for the household and community characterised these waves. Further, a small wave of infectious individuals was realised when there was a 45% epidemic control.	The model simulation indicated consistent patterns with the district-level dynamics in Guinea, Liberia, and Sierra Leone. It successfully reproduced exponential growth for the second and the third generation of infections followed by a sub-exponential growth for several subsequent disease generations.	The model did not account for the heterogeneity of transmission within households where active contact occurs with persons who closely care for patients. In contrast, less frequent contact occurs with individuals who do not.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[5]	Understanding the transmission dynamics in Guinea and assessing the impact of control interventions.	Several datasets were obtained from various resources including the Guinean Ministry of Health, the WHO and the Guinean national census. The datasets include the weekly EVD incidences, age group and household size distributions.	The approach used was a stochastic individual-based modelling in which transmission within households, extended families, within healthcare units, and during burials were explicitly modelled. Control measures, including contact tracing and safe burials, were considered.	The relatively high preparedness of the healthcare system, the early availability of Ebola treatment centres, and the application of case isolation and safe burials were found to have limited the spread from the initial stage. Further, contact tracing was found to be a critical factor in eliminating the disease.	The study included several datasets and considered EVD heterogeneity among the different age groups and the general population. The study has further combined various methodologies to estimate model parameters.	The model did not explicitly account or estimated the resistance of people that could reduce the effectiveness of contact tracing during epidemics (people behaviour was the important factor during the 2014 WA EVD and the 2018-2020 EVD of the DR Congo [136]).

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[102]	Analysing EVD viral data and exploring how anti-Ebola virus therapies, including ZMapp, TKM-Ebola, and Favipiravir restrain Ebola virus replication and reduce EVD infection.	The number of Ebola virus RNA copies per millilitre in a patient serum (viral load) of 18 EVD survivors and 27 fatalities from the Uganda outbreak of the year 2000. This data were adapted from the literature.	Three compartments composed of susceptible target cells, infected cells, and viral load were assumed. The susceptible compartment was partitioned into potential target cells and susceptible target cells, and the infected into non-productively infected cells and productively infected cells. The model was fitted to the fatal and non-fatal case data. The effect of anti-Ebola virus therapies, including anti-body based, siRNA-based, and nucleoside analog-based therapies, was assessed.	High viral loads in fatalities were preserved by recruiting a large number of potential target cells. For the fatal cases, $\mathcal{R}_0$ was found to be approximately six, while that of survivors was approximately 2.8. Further, it was found that combining siRNA-based and nucleoside analog-based therapies with an 80% inhibition rate was more likely efficient for otherwise fatal cases even if it was started four days after the onset of symptoms. For non-fatal cases, monotherapies were found to be sufficient.	The study employed viral data to estimate critical immunological and virological parameters. Further, it assessed the effects of experimental treatments. The findings improved knowledge about Ebola virus spread within-host and determined optimal use of therapies.	The model did not account for between-host EVD spread and has not been used to explore EVD transmission and intervention related questions at the population scale.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[67]	Analysing Ebola viral load dataset.	An EVD viral shedding data were adapted from the literature. The data were stratified into high and low viraemic disease pathways for a sample of hospitalised Ebola cases for the 1995 DR Congo outbreak.	The proposed method was a compartment model composed of three stages, starting with an initial viraemia followed by a second stage which consists of a high and a low viraemia and a final stage that is death or recovery. Model parameters were estimated using a Bayesian approach.	The mean of the infectious period was found to be 5.3 days for a low viraemia and 6.8 days for a high viraemia.	The model employed a modern a Bayesian Markov chain Monte Carlo method, reproduced the trends of the data, and estimated some natural history parameters of EVD.	The study assumed the basic reproduction number to be fixed while this might generally be slightly different depending on the contact structure and mixing patterns.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[117]	Understanding the effect of the within-host pathogen dynamics into the between-host dynamics.	Model parameter estimates were adapted from the literature.	The within-host viral load dynamics was modelled using a logistic model. It was embedded with an age-specific contact network to express transmission between individuals. A variation of the disease susceptibility between different age groups and the initial viral load exposure was considered.	The overall estimate of $\mathcal{R}_0$ was found to be 1.43. However, this estimate was different among different age groups, with the highest being 4.7 for the age group of 10 to 14 years old. Mass vaccination of 85% coverage was found to eradicate the disease if it was started between five months before and one week after the outbreak.	This study considered a multi-scale aspect of modelling, connecting within-host and between-host scales. It allowed for assessing the timing and the effectiveness of vaccination strategies and indicated the importance of considering EVD heterogeneity among different age groups.	The study did not consider heterogeneity regarding spatial locations. However, people within-households and those located close to EVD patients such neighbours were believed to have a higher transmission as compared to other community members [89].

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[11]	Determining whether the effect of environmental transmission of EVD, including poor hygienic practices and the consumption of contaminated bush meat, can explain the re-occurrence of EVD in Africa.	Model parameters were either assumed or adapted from the literature.	A compartment model was considered in which environmental transmission was considered as one compartment, and the recruitment of such transmission was assumed to be constant. Further, infectious living and deceased individuals were assumed to shed infectiousness in the environment. The existence of non-negative solutions and the stability analysis were established.	In the case of a virus-free environment, the number of infected individuals either became extinct or constant (endemic) in the long run depending on the value of $\mathcal{R}_0$. In the case of a non-virus-free environment, a constant number of infected individuals in the long run was found. This number was invariant to any change in the initial number of infectious individuals when there was no virus shed by the contagious individuals and the deceased in the environment.	The study focused on environment-to-humans-to-environment transmission routes, and the theoretical and numerical analyses were carefully conducted. The existence of an endemic equilibrium with environmental transmission could explain the re-occurrence of EVD in Africa.	The model was relatively simple. It did not account for realistic stages of EVD infectiousness, including the incubation period. Further, the population was assumed to be homogeneously mixed. Also, the model considered the transmission rate to be constant; however, in reality, this varied depending on the level of control intervention and people's perception of the disease.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[10]	Understanding the spread of EVD and predicting future EVD outbreaks.	EVD natural history parameter values utilised in the modelling were contained in the literature.	A deterministic compartment model was considered. It described the interplay of EVD transmission within and among three essential populations: fruit bats, non-human primates and other animals, and the human population. Furthermore, a new compartment composed of the free virus shed in the environment by infectious individuals was considered.	Non-negativity and boundedness of the solutions of the full model were established. Further, the basic reproduction number $\mathcal{R}_0$ was found for the disease-free equilibrium of the full model, and global stability analysis of this equilibrium was established.	The introduced paradigm was a novel model that accounted for the spread of EVD in a complex life ecology involving the reservoir, the non-human primates and bush animals, and the human population.	The study did not consider EVD spread among different geographical locations. This is particularly important consideration since EVD spillover usually occurs in remote areas and spreads to urban regions with the mobility of people.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[134]	Predicting the timing and location of EVD spillover events.	Several datasets were integrated including EVD spillover origin, timing, spatial predictors and other triggering candidates. These datasets were obtained from various resources including the WHO and the Columbia University Center for International Earth Science Information Network.	The region of interest in the study was the part of Africa, which receives over 500 millimetres of rainfall every year. A statistical modelling approach was used for associating EVD spillovers with spatiotemporally changing covariates such as rainfall, vegetations, and the size of the human population.	Annual EVD spillover risk peaks were found in Central Africa, while at some months of the year, new areas were found to be at high risks, including East Africa and Madagascar. Further, the risk of EVD spillover was found to be the lowest in the driest months of the year, while this risk peaks in the transition periods between wet and dry seasons. An increase in the human population was also found to increase the risk of EVD spillover.	This study associated new areas that had not been viewed previously to have a risk of EVD spillover, including East Africa and Madagascar.	The study did not consider diet and hygiene factors, and the eating of contaminated bush meat when predicting the spread of EVD.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[86]	Investigating the role of socio-demographic factors in the spread of EVD.	WHO data on the weekly EVD incidences at the subnational level in Sierra Leone, Guinea, and Liberia.	EVD growth rates were estimated for the early stage of the outbreak using a generalised linear mixed-effects statistical model (GLMM). Based on this estimation and the reported serial interval distribution, the basic reproduction number $\mathcal{R}_0$ was derived. An association between socio-demographic factors and $\mathcal{R}_0$ was measured using a uni-variable linear regression model.	The spatial distribution of the disease at the districts, préféctures or counties with the highest transmission rate in Liberia, Guinea, and Sierra Leone, respectively, appeared to cluster regionally, whether there is a national border or not. A positive association was also found between $\mathcal{R}_0$ and urbanization factors such as high population density and high wealth index.	The model was used for estimating the growth rates at the sub-national level in the three countries simultaneously, unlike some models (e.g., [57]) that consider each outbreak in a region separately.	Early-stage EVD data used in this modelling were generally unreliable, under-reported, or reported with delays [32]. Further, the model has assumed the population of the sub-national regions to be homogeneously mixed.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[185]	Investigating some demographic and environmental predictors of EVD spread.	EVD confirmed cases data were obtained from the WHO. Demographic and environmental data were obtained from demographic and health surveys and satellites.	A Bayesian hierarchical Poisson model was used to determine EVD risk and to assess the spatial variability described by the selected predictors.	EVD risk was associated with increases in rainfall, the area that urban land covers, the number of households not owning a radio, and the number of years of education.	This study suggested environmental and population-level characteristics associated with EVD.	The causative relations between the identified associations and the human-to-human spread of EVD with a particular focus on how the human's mobility and healthcare accessibility are affected by these risks were not studied.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[148]	Systematically investigating the demographic and socio-economic predictors of EVD at the sub-national level in Guinea, Liberia, and Sierra Leone.	Cumulative reported cases data at the sub-national level of the three countries were obtained from the WHO.	The early stage of EVD growth rates at the sub-national level in the three countries was estimated using polynomial, logistic, and exponential growth models. These rates and the epidemic size were then associated with various socio-economic and demographic features using regression models.	A positive association was found between areas of a higher level of education and higher severity of EVD. This was explained by also finding a positive association between a high severity of the epidemic and other factors that are strongly associated with education, such as urbanicity, wealth, and population density.	Three different models were used to determine the best fit for the EVD growth rates. Furthermore, the factors which were found to be associated with the severity of EVD can be used in the future by countries to understand the spread of EVD in real-time and to determine areas of high risks.	The data used contained case uncertainty due to resource limitations in West Africa and the resemblance of EVD symptoms with other diseases such as Malaria [32]. Further, it contained a delay between the time a case was found until it was documented nationally first and by the WHO afterwards.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[62]	Forecasting future reoccurrence of EVD.	EVD cases and death data for Guinea, Liberia, and Sierra Leone were used in the modelling. The data were obtained from the WHO.	A simple SIR model was proposed in the absence of intervention. The model was extended with detailed compartments, and different types of intervention measures and transmission routes were considered.	In the absence of intervention measures, the model was used to predict a high mortality rate for the outbreak and to forecast the epidemic to reoccur in 2035. Then it will continue after eight to nine years. As a result, mass vaccinations were proposed.	The SIR model in the study accounted for vitality rates that many models overlooked. This consideration is essential in modelling a disease that lasts for an extended period, such as the 2014 WA EVD and the 2018-2020 DR Congo outbreak [11].	The study predicted reoccurance of EVD. However, it is not simple to predict EVD reoccurrence without accounting for factors that contribute to the probability of EVD spillover. These include environmental changes, urbanicity, and the consumption of bush meat [134].

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[95]	The impact of media coverage on controlling the spread of EVD and the role of bats on EVD spillover on humans.	EVD reported cases and deaths for Guinea, Liberia, and Sierra Leone were obtained from the Centers for Disease Control and Prevention (CDC) website. Model parameters were either adapted from the literature or estimated.	A compartment model was used. The model was composed of susceptible (S), exposed (E), quarantined (Q), infectious (I), hospitalised (H) and deceased but not buried (F) compartments. A Markov Chain Monte Carlo simulation was used to fit the model to the cumulative case and death data and for searching the optimal values for the estimated parameters.	It was found that media coverage to have significantly reduced EVD peaking time and value and that infected bats might have likely been the source of the EVD spillover. Further, increasing the number of daily captured infectious fruit bats only reduced the peak timing and not the peak value.	The model had successfully combined exponentially declining transmission rates resulting from people consciousness about the spread of the disease and the likelihood of EVD spillover from infected bats. It utilised available EVD cumulative case and death data to estimate the community, healthcare, and the bat rate of infection.	The bats' spillover rate was assumed to be zero during wet seasons. However, numerous studies (e.g., [148, 185, 134]) associated wet seasons with enhanced risk of EVD spillover.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[48]	Characterising the spread of EVD and understanding the impact of control interventions in the 2014 WA EVD in Sierra Leone.	A database of EVD suspected and infected cases in Sierra Leone from May 2014 to September 2015 was obtained from the Sierra Leone Ministry of Health and Sanitation (SLMHS). The database also contained individual information including age, gender, residential address, and EVD onset date.	EVD cases were mapped to their geographical locations, and statistical methods were used to analyse the spatiotemporal trajectories. Poisson modelling was used to model case importation and local transmission by adjusting socio-demographic and intervention factors. Chain binomial distribution was used to model households' transmissibility (i.e., the potential infection of an index case at a household to another member in the household).	The disease invasion at chiefdoms was found to be remarkably correlated with the density of the population, the closeness of treatment centres, and the transportation network. At the chiefdom level, the secondary infection caused by an infected person per week was found to have been reduced by 65% at the end of December 2014, and the household transmissibility was also decreased by about 80% after December 2014.	The study integrated rich EVD data available for an extended period. It accounted for different intervention phases. Additionally, this study was used to model household transmissibility and to analyse the spatiotemporal dynamics of EVD. Furthermore, the study identified vital factors contributing to the spread of EVD and assessed the impact of control interventions.	The study has not investigated whether age have played an important factor in the spread of EVD. The EVD patient dataset used in the study can be adapted to explore this issue.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[158]	Analysing EVD dynamics in Guinea and Sierra Leone.	The WHO cumulative EVD reported cases for the 2014 WA EVD in Guinea and Sierra Leone.	Different stages of EVD such as incubation, infectiousness, hospitalisation were considered as a different age of disease since infection, and an age-structured model was applied. Removal rates due to isolation or hospitalisation, unreported disease mortality, and recovery were connected with epidemic outcomes. Further, the impact of these rates was quantified.	It was found that disease reduction in Guinea and Sierra Leone was caused by an increased early hospitalisation or isolation of cases. The latter was also connected with an increase of case identification or contact tracing.	The study considered a continuous variable for the age of disease since infection which most studies approximate using disease compartments. Therefore, the study accounted for all types of infection including sexual transmission resulting from EVD survivors and post-death infection.	The study considered the entire population to be homogeneously mixed. However, EVD is generally highly heterogeneous depending on the contact structure and the population density [3, 82]. On the other hand, different types of functions can be employed for the removal rates to accommodate new applications, for example, studying the impact of vaccinations.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[118]	Characterising the spread of EVD in an imperfect quarantine situation.	Model parameters were either adapted from the literature or assumed.	A deterministic compartment model was proposed. The model accounted for quarantine and non-quarantine states. It was used to study EVD in the community and healthcare settings. Individuals were assumed to be susceptible, suspected, probable, infected with either early dry or late wet stages, and removed due to recovery or EVD death.	A threshold parameter $\mathcal{R}_0$ was derived as a function of the fraction of suspected cases who will be quarantined. When this fraction was zero, the infection was high and occurred in the community. When all cases were quarantined, the infection only occurred in treatment centres. An endemic equilibrium existed when $\mathcal{R}_0 > 1$ whose size was determined by the magnitude of $\mathcal{R}_0$.	This study provided a comprehensive model in a complex-life environment in which quarantine was not efficient. It accounted for those individuals who escaped quarantine and returned at a later stage.	The study did not provide a complete treatment on determining the most crucial parameters in the spread of the disease and the stochastic effects in the disease growth.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[88]	Understanding the effects of infectiousness heterogeneity in the spread of EVD.	The observed EVD cases in Guinea, Liberia and Sierra Leone were used in the study. These data were collected by the health authorities in those countries.	The infection rates were assumed to have different distributions including constant, scale-free, Gaussian, uniform and normal distributions. The rates of infection were coupled with the standard SIR model. The SIR model was fitted to the EVD data in the three countries.	In Liberia and Sierra Leone, the scale-free and the Gaussian distributions were found to be more favoured in fitting the data compared to the uniform distribution. In Guinea, on the other hand, all distributions fitted the data better than the constant distribution.	The study assumed people to have different tendencies to be infected. For example, individuals who closely care for patients have a higher chance of been infected compared to other members in a community.	The study assumed the population in each country to have the same distribution for the rate of infection. However, EVD trajectories were different among the different regions in each country depending on the contact structure and mixing patterns [154, 82].

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[129]	Characterising the spread of EVD.	The WHO EVD data of Liberia for the period of April to December 2014.	The approach used was an activity-driven model with a time-varying network in which the set of nodes represented individuals, and the edges represented contacts between these individuals. Individuals were classified into different disease compartments. The model was fitted to the WHO data, and used to assess time-varying intervention measures.	The model made a one-year projection. Further, it was deduced that the earlier application of the intervention policies would produce a more significant reduction of the infected cases and the period of the outbreak.	The study accounted for social and behavioural activities in the network of contacts using the function of activity potentials.	The study did not account for or describe spatial locations of contacts explicitly.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[144]	Proposing a hybrid stochastic-deterministic approach for estimating the basic reproduction number.	The cumulative and incidence cases data of the 2014 WA EVD were obtained from the WHO website. Other model parameters were either assumed or also adapted from the literature.	A compartment model of the susceptible-exposed-infectious-recovered-deceased type was used. A stochastic version of the model was simulated using the Gillespie framework focusing only on realisations that produce more than 50 cases.	The basic reproduction number for Guinea, Liberia, and Sierra Leone were found to be $1.24, 2.06$, and 1.71, respectively. The 95% confidence interval to these values were respectively $(1.04, 1.42)$, $(1.93, 2.27)$ and $(1.40, 1.82)$. Further, it was found that the difference between fitting to cumulative or incidence cases to be negligible.	The study obtained the confidence interval of $\mathcal{R}_0$ and suggested including process noise to create a narrower confidence interval.	The structure of the model did not include realistic EVD differences in transmission among the population. Some of these were recorded to be variations among the different districts [154, 131, 36], age groups [5], and community structure [82].

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[55]	Analysing the 2014 WA EVD in Sierra Leone.	The EVD incidence data that was utilised in the modelling were adapted from the Ministry of Health and Sanitation of Sierra Leone. The data were reported for the period of May 2014 to January 2015.	A discrete-time Markov chain structure of EVD transmission was constructed. This structure was associated with a set of ordinary differential equations when the population was large. A Bayesian inferential framework was used to estimate model parameters. The model accounted for under-reporting in the data using the negative binomial distribution.	Model parameters, including the incubation period, EVD onset to recovery, onset to death, and the effective reproductive number were estimated. The latter was found to be robust to under-reporting.	The study presented an important stochastic tool for understanding EVD dynamics. It enabled estimating the effective reproductive number while accounting for under-reporting.	The model did not account for transmission in the healthcare context nor the variation of transmission among the different regions in Sierra Leone.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[125]	Estimating EVD spreading parameters.	EVD onset of transmission and outcomes data that were used were reported in various online news media sources in Nigeria and Liberia.	An online search was conducted about recorded EVD reports, and consequently, a transmission chain was built. Model parameters were estimated and compared with estimates from other studies.	The mean incubation period and serial interval were estimated to be 12.5 days and 19.4 days, respectively.	The study used news media reports. The advantage of using these data is that they might identify vital and detailed information related to the transmission which might otherwise become undetected. Further, these data are often published in near the actual time.	An online news media report where the study data were obtained might include misinformation or disclosed personal details of individuals. Further, these online resources might be altered without prior notice.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[137]	Analysing EVD in Sierra Leone for the period of 21 December 2014 to 17 April 2015.	The WHO 2014 WA EVD data for Sierra Leone.	The model used was a small world network and agent-based approach in which individuals and their daily social interactions were simulated. The transition between the different epidemic states was modelled using a discrete non-Markovian random process. Model parameters were estimated by fitting the model to the WHO reported data using optimisation methods.	The simulation revealed a decline in the epidemic trajectories from 21 December 2014 to 18 February 2015 compared to previous months. The effective reproductive number R_t was estimated to be 0.7 in this period. However, that increased to 1.98 in the next two months. Further, the model projected that the epidemic would increase through July 2015.	The framework combined agent-based modelling and complex network approaches simultaneously. Furthermore, various parameters were evaluated, and an accurate short term forecast was made.	The strength of these types of methodologies usually depends on the accuracy of the data supplied in the modelling. Issues such as under-reporting were common in the 2014 WA EVD data [35].

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[151]	Estimating EVD emergence probability and secondary incidence cases when a patient with undetected EVD is hospitalised.	The contact data between patients and healthcare workers were adapted from the literature. This dataset was composed of 200 patients and 46 healthcare workers, including 27 nurses and 11 physicians.	A stochastic compartment model was proposed. The studied population was divided into patients, nurses, and physicians. The impact of varying the transmission probability per contact, the daily number of contacts, and the duration of EVD non-specific symptoms were studied. The Gillespie algorithm was used to simulate the model.	The emergence probability, defined to be the number of simulations having a minimum of one secondary incidence case divided by the whole number of simulations, was estimated. As the transmission probability increased, the emergence probability moderately increased from 7% to a plateau at about 84%. Further, nurses were remarked to have a higher EVD emergence probability as compared to physicians or non-EVD patients.	The model was used to assess the risk of EVD occurrence at hospitals in areas that are un-associated with EVD risk. Crucially, it was assumed EVD patients to be in the dry phase, and either misdiagnosed or under-diagnosed.	The study did not assume any indirect transmission that could occur, for example, from poor cleaning or ineffective decontamination in hospitals. Further, it was assumed isolation efficacy to be 100% as soon the patient was diagnosed with EVD. However, achieving such an efficacy might be an overly optimistic assumption given the high contagiousness of EVD.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[140]	Proposing an alternative approach to the nonlinear optimisation method of solving the problem of fitting model parameters to data.	The WHO EVD data of Sierra Leone and Liberia for the 2014 WA EVD.	A compartment model of the $SEIR$ type was proposed. Consequently, a linear Volterra-type integral equation was derived from the model equations. The solution to the integral equation was projected into a finite subspace spanned by Legendre polynomials, and three regularizing algorithms were compared to assess the reliability of the forecasts.	It was found that the approach can produce a moderate prediction of the impact of the epidemic. For example, using the modified truncated singular value decomposition algorithm for two districts in Sierra Leone, the transmission rate was found to adequately been reduced in urban settings. Still, this decline in infections was found to be more erratic in rural regions.	The study considered a time-varying transmission rate and employed a mathematical method to avoid the problem of parameter identifiability that might result from limited data of an emerging disease.	The compartments assumed in the model were relatively simplified stages for EVD transmission. For example, it did not account for post-death infection of EVD nor sexual transmission from male survivors.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[18]	Evaluating some common EVD assumptions made in modelling, including the homogeneous mixing.	The WHO cumulative EVD incidences at the sub-national level in the major West African countries affected by the 2014 WA EVD. Data on the international migration and population information were adapted from the Flowminder and the Geohive datasets.	The cumulative EVD cases at the administrative level were modelled using logistic growth. A simple compartment model composed of susceptible, decreasingly infectious, and recovered compartments was used to explain the underlying reasons for the EVD trajectories produced by the logistic growth. A statistical method was also used to understand whether all EVD strains can have a uniform transmissibility.	It was found that EVD models with population-density dependent transmission rates might accurately predict the initial spread. Further, initial growth was found to decrease as the population density increased which might be caused by an improved healthcare system in areas with high population density. Further, it was concluded that it is appropriate to assume all EVD strains to have the same probability of occurrence.	This study has simultaneously assessed homogeneous mixing assumption and studied whether all strains have an equal chance of occurrence.	The study did not account for any control measures that might reduce or block the chance of the disease spread in the initial stage of an outbreak. For example, the behaviour of the population might show early positive change of avoiding infection if the population had learnt about the disease from a previous outbreak [94].

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[100]	Proposing an alternative approach to the standard $SEIR$ modelling method using a discrete stochastic Erlang type modelling.	The 2014 WA EVD incidence data for Liberia for a period of 74 weeks starting from the initial outbreak in March 2014 were used in the modelling. The data were obtained from a previous study.	A modified $SEIR$ model in which each of the E and I compartments were divided into sub-compartments was presented. A discrete stochastic version of this model was formulated with some additional assumptions about the exposed and infectious compartments.	The proposed models were fitted to the data, and the results were compared to the classical $SEIR$ modelling forecast. The proposed models were found to utilise a substantially longer computational time as compared to the classical $SEIR$. However, they offered a more accurate description of epidemic dynamics.	The study included realistic stages of residence time at the disease compartments. It also accounted for stochasticity, which plays a significant role in the initial phase of epidemics since all outbreaks begin with small cases.	The modelling only considered the early exponential phase of an epidemic and did not assume any intervention scenario. Further, it was assumed the population to be homogeneously mixed, and only considered transmission from living persons.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[183]	Understanding the effects of the individual behavioural changes on EVD trajectories.	The WHO EVD reported data from 17 June 2014 to 3 May 2015 for the most serious regions during the 2014 WA EVD including Guinea, Liberia and Sierra Leone were used.	A phenomenological model was fitted to the hospital notifications data to estimate behavioural changes. Further, the rate of behavioural changes was implemented to four different EVD force of infection in a susceptible-infectious-recovered-deceased compartments model. The impact of the force of infections on behavioural changes was studied.	The force of infection that includes an exponentially declining trajectories of EVD incidences as a result of behavioural changes was found to create the best model fitting and prediction. Further, a larger rate of behavioural change was found to have caused a more significant reduction in the number of hospital notifications, including infected cases and deaths.	This methodology combined behavioural changes and a population-based compartment model that enabled an understanding of how individuals behaviour could affect the spread of the disease.	The force of infection that created the best fitting and prediction can be adapted in future studies when data include behavioural changes.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[136]	The impact of social and behavioural factors in the spread of EVD.	The WHO number of EVD incidences and deaths in Guinea, Liberia, and Sierra Leone. Another dataset used was the Twitter news data about EVD.	A systems dynamics approach was used in the modelling. It created causal loops for social and behavioural aspects, including quarantine, perception of EVD death, and situation awareness. It included public attention by incorporating twitter data about the disease news as a measure of the psychological and behavioural changes.	The model simulation showed that the increase in the rate of quarantine over time to have resulted from the rise in the situation awareness and practising of safe burials. However, public attention did not have a significant impact on reducing the spread of EVD.	This modelling approach followed the behavioural aspect of EVD spread in detail in causal loops, and identified important factors that impact the spread of the disease.	The spread of EVD in the three countries was not similar due to different healthcare system preparedness [35]. Therefore, it would have been more practical if the model was used to study the dynamics of EVD in each of the three countries differently.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[27]	Exploring two methods of forecasting EVD trajectories.	A synthetic EVD data were used. This data was produced for the purpose of the Program of Research and Policy for Infectious Disease Dynamics of the United States (RAPIDD) EVD forecasting challenge.	Two modelling approaches were used. The first model was a stochastic compartments model with a general community and healthcare workers. The epidemic parameters in this model was estimated using a Bayesian approach. A generalised renewal equation (GRE) with a latent variable was used in the second model. The latter used a Markov Chain Monte Carlo method for the fitting.	Models were fitted to the data, and parameters were estimated. Fitting the compartment model to the data resulted in double bumps in the disease incidence trajectories. This was explained to emerge from a spatial spread in which one subepidemic has reached its maximum in a region while another is still growing in another area.	The compartment model used a population that was structured into a general community and healthcare workers. This allows for identifying EVD incidences in each group and understanding the impact of targeted interventions. The GRE model, on the other hand, uses few parameters to be identified from the data.	The study did not account for a spatial structure in the modelling, while the data indicated the existence of spatial spread.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[56]	Analysing EVD data in actual time.	The RAPIDD EVD synthetic data.	A semi-mechanistic model was proposed. The model was described using a compartment modelling framework, and transmission between individuals was assumed to follow a random walk. The model was fitted to the data using a Bayesian approach.	The model was able to reproduce the data trajectories. Individual variability in trajectories was found depending on the transmission rate and the stochasticity of the observed incidence.	The study made use of EVD natural history parameters from previous outbreaks. Additionally, it did not describe detailed underlying mechanisms by which the disease variables are linked. The latter is useful when models do not get enough data to quantify the detailed underlying mechanisms.	The model made only a short time forecast of incidence and did not make a long term prediction for the final size, the peak size, or the peak timing.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[147]	Forecasting the spread of EVD using a phenomenological model.	The RAPIDD EVD synthetic data.	A simple phenomenological model was proposed in which new incidences were assumed to be proportional to the basic reproduction number ($\mathcal{R}_0$) and inversely proportional to a control intervention measure (d). The disease incidences were assumed to follow a Poisson distribution. The maximum likelihood approach was applied for the model fitting, and consequently, $\mathcal{R}_0$ and d were determined.	It was found that model estimates made later in the epidemic, in three of the four RAPIDD data scenarios, approximated the true peak week more closely. Further, the model performance was found to be among the best 60% participant models in the RAPIDD EVD forecasting challenge.	The approach used was relatively simple and had few assumptions unlike some mechanistic approaches which include many parameters and assumptions. The latter might face identifiability issues in the case of limited data.	The study did not make effective use of the detailed data provided in some of the RAPIDD data scenarios. Further, the study did not correctly predict the epidemic peak in Scenario four of the RAPIDD data.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[7]	Analysing the EVD RAPIDD synthetic data and forecasting the disease trajectories.	The RAPIDD EVD synthetic data.	The model proposed was a discrete-time and discrete states, stochastic compartment model. The reproductive number was modelled as a multiplicative normal random walk, and new infection was assumed to follow a Poisson distribution.	The study predicted the timing and sizes of the peak incidences before one month. Furthermore, the model projected a reasonably precise final outbreak size 30 to 40 weeks earlier.	The model was relatively simple and required less computational power. Further, it had a strong overall performance and used fewer parameters.	The model was used to forecast EVD spread at the national level and did not account for heterogeneity in transmission among different districts. Further, the model did not account for variation among different transmission routes, including within-healthcare, within-households, and community transmissions.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[123]	Predicting the size and trajectories of EVD.	The RAPIDD EVD synthetic data.	A logistic model that assumes an early exponential growth was used to forecast EVD spread. These predictions were compared with another phenomenological model -the Generalised Richard's (GR) model - that assumed a varied growth from exponential to sub-exponential.	The logistic model was found to have underestimated the peak size, the timing of the peak, and the final size. However, the GR model performed well regarding disease forecast - predicting a range of epidemic dynamics profiles (sub-exponential to exponential).	The proposed phenomenological models were relatively simple and do not contain many model assumptions as compared to compartment models.	Phenomenological models used in the study do not make effective use of natural history parameters that are obtained from previous outbreaks as compared to mechanistic models.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[58]	Reviewing the performance of the 2014 WA EVD EbolaResponse model [106] forecasts and suggesting a further development on the model.	The RAPIDD EVD synthetic data.	The EbolaResponse model [106] was a mechanistic Markov chain model. Some modifications were made. For example, the transmission categories were slightly modified to transmission at Ebola treatment centres (ETCs), transmission in the community while practising safe burials effectively, and transmission in the community without practising a safe burial or any other control measure.	To control EVD, it was found in the modified model that more than 80% of EVD cases were needed to be hospitalised at ETCs or effectively isolated at homes and safely buried if they are deceased. On the contrary, the original model was used to determine this figure to be 70%.	The EbolaResponse tool was modified to facilitate the applicability to the RAPIDD challenge data. This modification provided a comparison of the model performance corresponding to other models that were used to model the 2014 WA EVD.	The EbolaResponse tool and its modified version were not able to make a long term prediction, nor were they able to spatially disaggregate EVD transmission.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[153]	Forecasting the spread of EVD using an agent-based approach.	The RAPIDD EVD synthetic data.	A data-driven agent-based approach was used. The framework accounted for synthetic population, social contact network, and an $SEIR$ compartment structure. Model calibration was proceeded using optimisation and Bayesian approaches.	The model showed an excellent performance in the data-rich scenario of the RAPIDD challenge. In this case, the model findings included epidemic timing, the final size of infected individuals and $\mathcal{R}_0$.	This modelling described a detailed agent-based mechanistic framework and used rigorous approaches for model calibration.	The study did not account for spatial transmission. On the other hand, the modelling structure has utilised many parameters and quantifying these parameters might lead to identifiability issues in the case of limited data.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[99]	Estimating the time evolution of EVD incidences.	The infections and the deceased individuals time series for Guinea, Liberia, and Sierra Leone. The WHO recorded this data during the 2014 WA EVD for the period of March 2014 to January 2015.	The modelling used was a chaotic theory framework that obtained models that can reproduce global solutions by only using EVD time series. Model simulations were compared with the observed data to evaluate the accuracy of the predictions.	The model was used to simulate the trajectories of the data and to predict the epidemic for a short period while assuming the behaviour of the population to have not changed in such a period.	The modelling framework allowed for analysing a problem with highly interactive environmental, biological, behavioural, and economical factors that are combined to create challenging dynamics.	The study assumed the population of Guinea, Liberia, and Sierra Leone to be homogeneously mixed. However, the spread of EVD in these countries was not similar due to the different healthcare system preparedness and the different contact structure [57, 82, 35].

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[139]	Forecasting EVD incidence and characterising its dynamics using a phenomenological model.	The WHO EVD incidence data about the 2014 WA EVD in Sierra Leone, Guinea, and Liberia were used.	The model used was phenomenological. Model parameters, including intrinsic growth rate and the final epidemic size, were estimated using the least square methods.	A sub-exponential growth was found to have mostly characterised estimates from the early stage EVD growth data in the three countries. The model predicted the final size to be $1.7 \times 10^4, 1.1 \times 10^4$ and 3.5×10^3 for Sierra Leone, Guinea and Liberia, respectively.	One advantage of this model is that it can be used during the early disease epidemic, particularly in the case of the scarcity of reliable information about the disease mechanisms of spread.	The studied population in each country was assumed to be homogeneously mixed.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[1]	The potential impact of EVD sexual spread from male survivors.	The 2014 WA EVD incidence data in Sierra Leone. The data were obtained from the WHO patient database and situational reports.	A compartment model of the $SEIR$ type was used in which a new compartment C that represent the convalescent population was added. The $SEIR$ model was fitted to the EVD data while assuming the number of the reported cases to have followed a negative binomial distribution. Consequently, model parameters were estimated using the maximum likelihood approach. The sensitivity of the model outputs to changes in the components of the transmission rate of the survivors was studied using Monte Carlo simulations.	It was found that in general, there was an insignificant increase in the number of EVD cases resulting from survivor's sexual transmission, but this number extended the period of the disease. For example, when there was a 0.1% transmission probability per sex act and three months of convalescence, only a few EVD additional cases occurred, but the period of the outbreak increased by 83 days.	The study suggested a novel method for investigating the impact of EVD male survivors. It described the rate of sexual transmission from survivors according to the average sexual activities and the per act probability of transmission. The study considered a range of values for these components from studies in human immunodeficiency virus and predicted the effect of sexual transmission from EVD survivors.	The study did not account for any potential transmission from female survivors, while this has been recorded in the literature (e.g., [42]). The effect of sexual transmission from EVD survivors in metapopulation systems was also not considered.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[90]	Determining the effect of super-spreaders and characterising factors that might have driven super-spreading.	The dataset includes GPS locations of where the bodies of 200 EVD deceased were collected for safe burials. Further, it contained age, sex, time of burial, and the onset of symptoms. The data were collected in Sierra Leone by the International Federation of Red Cross.	The approach used was a transmission network-based method which concentrated on creating transmission trees among EVD cases. These were established by using a Bayesian model that integrated the data and inferred the distribution of new cases.	Few super-spreaders of about 3% of the total EVD cases were found to be responsible for more than 60% of all generated cases. Further, most of the EVD spread happened within a relatively short distance of 2.5 kilometres. Instantaneous EVD spread risk was found to have mostly been exerted by the age groups of less than 15 years old and larger than 45 years old.	The findings of the model suggested the significance of targeted-intervention. In this case, the importance of focusing on super-spreaders when planning control measures.	The dataset used in the study only included fatal EVD cases. However, the study concluded the results for all cases (fatal and no-fatal).

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[141]	Understanding whether the Ebola virus can evolve to become less virulent in the human population.	Model parameter estimates used were adapted from the literature.	A compartment model of $SEIR$ type with a further transmission from deceased individuals and survivors was assumed. Viral load was considered to be positively correlated with the case fatality rate (CFR) and transmission rate to be proportional to the CFR. An evolution in the population was assumed to proceed by a rare mutation that creates a different CFR.	The study concluded that it is unlikely for the Ebola virus to evolve and become less virulent unless two conditions were satisfied. First, the proportion of unsafe burials must be reduced to a very low figure and be brought to less than 4%. Second, the CFR and the EVD transmission rate must have very little or no genetic connections.	The model introduced a novel study of understanding the virulence of EVD that accounts for transmissions from living infectious (patients and survivors) and from the deceased. The high virulence of the Ebola virus was explained by its life cycle that adapt the three aforementioned stages of infectiousness.	The model did not account for an age or a sex-related heterogeneity in the fatality rate.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[4]	Assessing the impact of relapse and reinfection in the spread of EVD.	Model parameter estimates that were used to quantify the model were adapted from the literature.	A deterministic compartment model was proposed. It incorporated the early and late stages of infection in addition to immune and susceptible recovered individuals. The latter was assumed to have a disease relapse or to become reinfected. Model well-posedness and stability of equilibria analyses were conducted.	The basic reproduction number $\mathcal{R}_0$ was derived and found to be increasing as the relapse parameter increased. In the presence of disease reinfection, a backward bifurcation was found in which a disease-free equilibrium and an endemic equilibrium coexisted. Disease relapse was found to lead to more infections as compared to disease reinfection. Further, models that do not include relapse and reinfection underestimated the disease trajectories.	The current study extended previous studies by including the relapse and reinfection of recovered individuals and studying their impact.	The model did not account for transmission heterogeneity regarding infection in the community and healthcare settings. It also did not consider transmission to be different according to spatial locations (e.g., urban and rural areas).

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[20]	Assessing the feasibility of a prime-boost vaccination trial in three areas in Sierra Leone.	The WHO weekly EVD incidences for three areas in Sierra Leone, viz. Kambia, Port Loko, and Western Area.	A stochastic model was used in which individuals were divided into susceptible (S), exposed (E), infectious but not yet reported (I), infectious and reported (J), and removed (R) compartments. Susceptible individuals were assumed to be recruited to either vaccinated or control groups. A Bayesian approach, viz. Markov Chain Monte Carlo was used for fitting the model to the data.	When the vaccination trial was started at an earlier time, the probability of eliminating the disease in the vaccinated groups increased. The probability of detecting the difference between the number of disease incidences in the vaccinated and control groups increased when the vaccination trial was started at a later time.	The model gave a mean of assessing the feasibility of a vaccination trial. Further, fitting the model to the data of the three regions enabled understanding the different impacts of the vaccine trial among these regions.	The vaccinated and control groups were partitioned into clusters. However, the model was fitted to EVD incidences at the district-level and not at the cluster level. Additionally, the model did not account for any logistical constraints that may affect the feasibility of the vaccination trial in the studied regions.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[39]	Improving the stepped-wedge cluster trial (SWCT) method.	The WHO district and county level case count data of Sierra Leone and Liberia. Geospatial data containing chiefdom boundaries were obtained from the database of Global Administrative Areas (GADM). Population densities of each of the chiefdoms of Sierra Leone, as well as the distance between them, were estimated.	An ordered SWCT (OSWCT) method was proposed in which clusters were ordered to increase the efficiency of the SWCT. This ordering was based on an observed EVD incidence data (data-OSWCT), a model projection about the order of the first incidence occurrence (first-OSWCT), and the districts with the highest model projection of weekly cases (peak-OSWCT). A metapopulation framework with a gravity type assumption was adapted to describe the movement of individuals among the chiefdoms.	All of the OSWCT trials showed a higher efficacy as compared to the SWCT. However, they all lost effectiveness when they were delayed. Furthermore, when the trials started ten weeks after the onset of the disease, the peak-OSWCT was more efficient.	This study linked the SWCT method with a gravity type metapopulation model. Further, it accounted for infected individuals with early dry and with late wet symptoms. Crucially, only the latter was assumed to transmit EVD.	The gravity type assumption used in the modelling does not account for factors that may affect the movement of individuals in Central and West African contexts. These include road closure resulting from rainfall and natural barriers such as rivers. Hence, the gravity assumption may overestimate the risk of the disease spread.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[64]	Improving the performance of cluster randomised trials.	Model parameter estimates were adapted from the literature.	A community-structured population was generated using a stochastic simulation with 20 clusters, each consisting of 200 individuals. The population was assumed to have six disease states (susceptible, exposed, infectious, hospitalised, funeral, removed). In order to provide a rapid epidemic control, a class of connectivity-informed designs was proposed for cluster randomised trials.	It was found that the connectivity-informed design interventions decrease the total infections by up to 20% in comparison with the traditional stepped wedge cluster randomised trial.	The proposed trial designs utilise connectivity information between clusters in intervention scenarios. Consequently, they cause a reduction in the number of infections more rapidly as compared to cluster randomised trials.	The approach requires information on connectivity concerning how epidemics spread (e.g., by close contact or through sexual partners). This information is usually hard to obtain accurately.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[119]	Characterising the spread of EVD and the impact of intervention measures.	Natural history parameters were adapted from the literature or assumed.	A stochastic model that describes the transition between the susceptible, exposed, infectious, deceased, hospitalised, and recovered individuals was proposed. In addition to the infectiousness from humans, susceptible individuals were assumed to be exposed to EVD spillover from animals. Various intervention measures were assessed, including quarantine and safe burials. Monte Carol simulation was used to simulate the model.	Outbreak vulnerability was simulated as a function of the reservoir transmission rate, and a range of values for these rates that cause isolated and endemic outbreaks was determined. Increasing the safe burial rate and reducing the contact rate was found to control the outbreaks ultimately.	The model accounted for inherited randomness of the spillover event of EVD.	The study did not account for a metapopulation spread. This consideration is, in particular, important since EVD spillover usually happens in remote areas and expands to urban regions with the movement of people.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[76]	Determining key elements that help in preventing the spread of EVD among health care workers (HCWs) during EVD outbreaks.	Model parameters were either assumed or adapted from the literature.	Agent-based modelling and simulation were used. The modelling included the initial educational state about the disease, followed by training to avoid EVD. The study had further accounted for how well health care workers performed in avoiding infection. Additionally, the study considered conditions and parameters that were important in hindering EVD infection.	Increasing the probability of seeking intensive training and practising appropriate care procedures was found to have caused a significant decline in EVD infection. On the other hand, increasing the percentage of HCWs who initially had knowledge about the disease or those who attended some training during the outbreak was less significant.	The study explored how EVD training workshops could protect healthcare workers and showed the value of effective preparedness and the right attitude towards the profession to fight EVD infection among HCWs.	The model did not account for any actual geographical distributions of HCWs. It also did not account for delays in establishing EVD training academies for HCWs.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[57]	Estimating the public health response and behavioural changes that contributed to ending EVD outbreak.	Detailed epidemic data about Lofa county of Liberia. The data were extracted from the records of the ministry of health and social welfare of Liberia.	Two transmission routes were considered: within Ebola treatment centres (ETCs) and in the community. Transmission from the deceased was assumed to occur only in the community. Super-spreading was implicitly considered by assuming the time-varying EVD transmission rate to have a normal distribution.	The basic reproduction number was found to have generally decreased from early August with the expansion of the number of ETCs. The healthcare-seeking rate was doubled during the outbreak. Isolation of EVD patients at ETCs reduced the basic reproduction number to about two-thirds of its original estimate.	The population was structured into a general community and individuals within healthcare centres. The study highlighted the importance of community engagement in alleviating the disease.	The study did not account for unreported EVD cases in the community that were common during the 2014 WA EVD [35].

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[44]	Resource planning to control the spread of EVD.	Model parameter estimates used were either documented in the literature or assumed.	A compartment model of $SEIR$ type with further hospitalisation, quarantine, and vaccination components was introduced. Optimal control and sensitivity analysis methods were used to assess resource utilisation and vaccination effectiveness. They were also used to identify parameters that were the most influential in the model dynamics.	If the transmission rate of isolated individuals was less than one-fourth of the non-isolated, the basic reproduction number was less than one. Further, it was found that the time-varying optimal quarantine was more effective as compared to a high but fixed level of quarantine.	The model accounted for transmission from people at high risk, including healthcare workers, family members, and persons who are involved in the burial of EVD deceased. It also accounted for transmission from the general population.	The study assumed transmission only from living infectious individuals (in the community or at hospitals) and did not consider a transmission from the deceased or an unclean environment.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[184]	Eradicating the spread of EVD using a dynamic programming approach.	The WHO reported data for Guinea, Liberia, and Sierra Leone from 27 May to 28 November 2014.	A compartment model was proposed. EVD drugs and vaccines were assumed to be distributed according to the number of infected and susceptible cases in each district. Optimisation methods were used to calculate the fastest road for drug and vaccine distributions and to find the storage solution that results in the minimum total cost.	The basic reproduction number ($\mathcal{R}_0$) was calculated. It indicated that speeding up drug production and distributing drugs and vaccines systematically to be a powerful method of controlling EVD. Further, the study identified the fastest road and the minimum total storage.	The study used a disease compartment structure and motivated the impact of studying drugs and vaccines delivery. It helped in planning the cost of storing and distributing drugs and vaccines.	The model did not account for heterogeneity regarding the cost of vaccines depending on the type of vaccine stored. For example, the two widely used vaccines, the Merck rVSV-ZEBOV and the Johnson & Johnson Ad26.ZEBOV/MVA-BN have different storage temperatures which creates different logistical costs [77, 22].

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[75]	Studying the optimal strategy for eradicating EVD.	The WHO total EVD cases for Liberia during the 2014 WA EVD. This data were recorded for the period of 2 July 2014 to 28 August 2014.	An $SEIR$ type model was considered. The model incorporated for early and advanced stages of infectiousness, hospital isolation, EVD therapy, and vaccination. The model was fitted to the Liberian data, and EVD transmission rate was estimated. Further, the impact of different types of intervention measures, and regional transmission were studied.	The study predicted the outbreak would reach its second peak at the end of February 2015 and terminate in September 2015. To control the spread, the study suggested controlling regional transmission, practising effective hospitalisation, and vaccination.	The study described a detailed regional EVD spread and made a systematic evaluation for different intervention strategies.	The study did not explore the optimal vaccination strategy between two types of vaccines (the rVSV-ZEBOV and Ad26.ZEBOV/MVA-BN) in the context of the 2018-2020 DR Congo outbreak.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[94]	Assessing the effect of public health education on the dynamics of EVD in Sudan.	The 1976 and the 1979 EVD data of the Nzara area in Sudan. These data were adapted from the literature.	A deterministic compartment model was used. Some individuals were assumed to be educated about EVD and took necessary measures to avoid infection. Individuals who did not take these measures were recruited to become educated about disease transmission. The impact of this recruitment was studied. An optimisation method was used to estimate model parameters.	The analysis of the full model, with educated and uneducated persons, revealed that the initial proportion of educated and non-educated susceptible individuals and the timing of the behavioural changes (seeking hospitalisation) played an important role in determining the magnitude of the outbreak.	Some crucial assumptions were made in the study. It was considered EVD transmission in the community to be different from healthcare centres. Further, the study accounted for environmental spread. The results obtained in the modelling showed the importance of public health education in controlling the disease.	The study assumed transmission in the community as one unit and did not account for having a higher chance of transmission from household members, relatives and friends.

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[110]	Assessing the effectiveness of contact tracing in the early phase of an outbreak.	The EVD natural history and the network parameters were adapted from the literature.	An activity-driven network method was employed in which the activity potential of an individual was assigned according to some probability distribution. The contacts of an infectious person were observed for 21 days, but sometimes this observation was implemented after some delay. The effects of this delay were assessed.	It was found that contact tracing to be more effective if the identification of the traced persons was not delayed for more than ten days.	The study has relevantly adapted an activity-driven modelling or temporal social networks to record contacts of an infected individual and conducted extensive simulation using a different range of delays.	The study did not account for the frequency of contact with infectious persons. However, nurses and people who frequently care for patients have a higher chance of infection compared to others. Further, the study did not account for infectiousness from the deceased.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[122]	Assessing the relationship between EVD natural history and different control intervention strategies.	Model parameters were adapted from the literature or estimated.	An agent-based model of $SEIR$ type was proposed. The model focused on understanding the dynamics in the early epidemic phase of the outbreak. The impact of quarantine, symptom monitoring, and contact tracing was evaluated. The most crucial intervention measures on the dynamics of the disease were identified via the Partial Rank Correlation Coefficient method.	It was found that the effects of control interventions, including quarantine and symptom monitoring to be influenced by the natural history of EVD and the containment feasibility within healthcare settings. Further, symptom monitoring was found to be the most effective measure in containing EVD compared to quarantine.	The model findings were in line with the WHO emphasis on not recommending quarantine since it restricts personal liberty and creates stigmatisation [177].	The study did not assess the impact of vaccination in controlling the spread of EVD as compared to the other non-pharmaceutical measures.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[107]	Providing a quantitative estimate for the effectiveness of ring vaccination trials.	The datasets used included the distribution of household sizes in Pujehun, Sierra Leone. Additionally, they included household distribution in villages in the district and town of Pujehun. These datasets were obtained from demographic and health surveys and analysis of aerial images.	The model used was an individual-based compartment model. It was used to simulate the spread of EVD within-households, extended families, and the general community. The within-household and extended family transmission represented the contacts and contacts of contacts used in the ring vaccination.	It was found that ring vaccination was efficient in containing EVD up to the value of 1.6 for the effective reproductive number (R_t). Further, if the period from EVD onset to hospitalisation became between two and three days, two kilometres were added to the area covered by the ring vaccination, and improved quarantine was practised, the disease could have been contained for up to $R_t = 2.6$.	The study was used to integrate transmission within households and extended families. Further, it was used to simultaneously assess the effect of ring vaccination and other non-pharmaceutical measures.	The model did not account for different possible immunity periods that the Merck rVSV-ZEBOV, assumed in the study, might have [52].

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Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[87]	Assessing the effectiveness of EVD vaccination.	An individual-level EVD spread data for Guinea. The data were obtained during the 2014 WA EVD by the WHO and the Guinean Ministry of Health.	Individuals who could not be associated with any recognised transmission chain were assumed to have a basic reproduction number ($\mathcal{R}_0$) of seven. Cases within the known transmission chain had $\mathcal{R}_0 = 0.66$. A ring was defined to be all individuals who could be part of the identified transmission chains. A branching process and binomial distribution were used to assess the impact of ring vaccination.	It was found at the starting of the 2014 WA EVD that ring vaccination would not have been enough to contain the outbreak. However, later when the epidemic was less severe, this policy was more significant.	The study accounted for EVD transmission from cases that were not recorded in any transmission chain and explored the circumstance under which ring vaccination could control the spread of EVD.	Similar to [107], this model did not account for the vaccination immunity period. This consideration is important when outbreaks continue for a long period.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[12]	Evaluating the impact of the rVSV-ZEBOV EVD ring vaccination.	The data used was the 2014 WA EVD cumulative cases and deaths in Sierra Leone. Additionally, EVD natural history parameters were adapted from the literature.	A compartment model was utilised. The model accounted for various risks of infection, and for improved survival rate resulting from an increase in the number of trained healthcare workers. Latin Hypercube Sampling (LHS) over the uniform distributions for the set of model parameters and the least square methods were used to estimate model parameters.	The basic reproduction number ($\mathcal{R}_0$) was estimated to be 1.33. Additionally, it was found that to stop the outbreak, 40% of the total population and 95% of healthcare workers should have been vaccinated.	The model assumed the general population to either have a high or low risk of infection. Crucially, the ring vaccination was applied to those of high risk. Further, the model assumed different vaccination strategies and predicted an array of vaccination coverages.	The study considered EVD trajectories in Sierra Leone as one unit and did not account for the high variation in EVD trajectories among the different districts.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[65]	Using simulation to assess a ring vaccination trial design.	Model parameters were either adapted from the literature or assumed.	A compartment model structure was used. Individuals in rings of infected individuals were enrolled in the trial and either immediately vaccinated or after some delay. The cumulative incidences in the immediate and delayed vaccinated groups were recorded and used to estimate vaccination efficacy and calculate the sample size required to achieve the efficacy.	It was estimated that $7,100$ participants were needed in order to reach 80% of the power of detecting the difference between the immediately vaccinated and the delayed groups. These figures, however, were sensitive to the settings of the parameters and the properties of the vaccine.	The model incorporated simulation into the process of designing a vaccination trial. It allowed understanding how the sample size and the expected outcome of a trial are influenced by the population characteristics and the vaccine efficacy.	The population in each ring of contacts and contact of contacts was assumed to have the same rate of transmission. However, people who closely care for patients have a higher chance of transmission compared to others. Further, contacts have a higher transmission rate compared to the contacts of contacts.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[15]	Evaluating a voluntary vaccination strategy of EVD.	EVD natural history parameters, vitality rates, and other model parameters were either adapted from the literature or assumed.	The study utilised a compartment modelling structure and accounted for vaccination by adding a new compartment for this purpose. The basic reproduction number and the vaccination threshold of reaching herd immunity were derived. A game-theoretic concept was introduced to model the voluntary vaccination, and the Nash equilibrium was derived.	As a result of the high risk of EVD infection, a voluntary vaccination was found to be very close to the herd immunity level. Consequently, it might eradicate EVD, particularly when added to other control measures.	The study assessed a novel strategy of Ebola vaccination (voluntary vaccination) using a game-theoretic approach.	The study assumed the population to be rational enough to decide to be vaccinated voluntarily and to be well informed about the risk of the disease and the direct and indirect cost of vaccination.

Table A.1 – *Continued from previous page*

Ref.	Research question	Data	Methodology	Conclusions	Advantages	Limitations/gaps
[71]	Understanding the impact of convalescent blood transfusion therapy.	Model parameters were either adapted from the literature or estimated.	A treatment-donation-stockpiles compartment model was used. It was assumed that infected individuals to be efficiently hospitalised and safely buried when deceased.	The convalescent plasma treatment was found to be significant in reducing the case fatality rate and increasing the blood bank storage. Further, when more blood donors were recruited, and the right track of their contact was kept for re-donation, more reduction in the case fatality rate occurred.	The study provided a novel methodology in assessing convalescent blood transfusion therapy and found vital factors that strengthen this treatment.	The studied population was assumed to be homogeneously mixed in a perfect context of EVD hospitalisation and safe burials. However, these assumptions are not realistic with most of EVD outbreaks that occurred during the last decade.

Appendix B

Standard proofs for theorems

Proof of Proposition 3.3.1. The first and the second equations of System (3.2) can be rewritten as

$$\frac{dS_H}{dt} = \sigma\Pi - A_1(t)S_H \tag{B.1}$$

and

$$\frac{dS_L}{dt} = (1-\sigma)\,\Pi - B_1(t)S_L, \tag{B.2}$$

where

$$A_1(t) = \lambda_1 + \lambda_2 + g_1 + m_1 + \mu$$

and

$$B_1(t) = \lambda_1\tau_1 + \tau_2\lambda_2 + g_2 + m_2 + \mu.$$

Equations (B.1) and (B.2) are linear first order equations in S_H and S_L, respectively, and have the solutions:

$$S_H(t) = S_H(0)e^{-\int_0^t A_1(s)ds} + e^{-\int_0^t A_1(s)ds} \times \int_0^t \sigma\Pi e^{-\int_0^u A_1(w)dw} du \geq 0;$$

and

$$S_L(t) = S_L(0)e^{-\int_0^t B_1(s)ds} + e^{-\int_0^t B_1(s)ds} \times \int_0^t (1-\sigma)\Pi e^{-\int_0^u B_1(w)dw} du \geq 0$$

for all t. Remark that the non-negativity of $V_1(t)$, $V_2(t)$, $V_3(t)$, $V_4(t)$, $V_5(t), V_6(t)$ $E(t)$, $I(t)$, $H(t)$, $D(t)$, and $R(t)$ depends on the non-negativity of $S_H(t)$ and $S_L(t)$. In fact, similar to proving the non-negativity of $S_H(t)$ and $S_L(t)$, it is straightforward to show that these state variables are non-negative for all time t. This completes the proof of the proposition. □

Proof of Proposition 3.3.2. From Equation (3.1), it follows that if N is bounded, all state

variables that compose N will be bounded. Thus, it suffices to show that N is bounded. From (3.2),

$$\frac{dN}{dt} = \Pi - \mu N + (\mu - b)D - \eta f_2 H \tag{B.3}$$

Note that the disease-induced death rate b is much larger than the natural death rate μ. Thus, $\mu - b < 0$. Hence

$$\frac{dN}{dt} \leq \Pi - \mu N. \tag{B.4}$$

Application of the Gronwall inequality yields

$$N(t) \leq \frac{\Pi}{\mu} + \left(N(0) - \frac{\Pi}{\mu} \right) e^{-\mu t}. \tag{B.5}$$

We can see from (B.5) that if $N(0) < \frac{\Pi}{\mu}$,

$$0 \leq N(t) < \frac{\Pi}{\mu}.$$

On the other hand, $N(0) \geq \frac{\Pi}{\mu}$ implies that

$$N(t) \leq \frac{\Pi}{\mu} + \left(N(0) - \frac{\Pi}{\mu} \right) e^{-\mu t} \leq \frac{\Pi}{\mu} + N(0) - \frac{\Pi}{\mu} = N(0).$$

Thus, $N(t)$ is bounded for all $t > 0$. □