

Faculté de santé publique

Modeling 2018-2020 North Kivu and Ituri Ebola Outbreak

Mémoire réalisé par
Caroline Defays

Promoteur(s)
Professeur Niko Speybroeck

Année académique 2019-2020
Master en sciences de la santé publique, finalité spécialisée

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Le plagiat

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Table of abbreviations

ABMs	Agent-based Models
ARDS	Acute Respiratory Distress Syndrome
BDBV	Bundibugyo ebolavirus
CIs	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disease
Covid-19	Corona Virus Disease 2019
DA-MCMC	Data-Augmented Markov Chain Monte Carlo
DRC	Democratic Republic of Congo
EBOV	Ebola virus
EBOVs	Ebolavirus
EMA	European Medicines Agency
EVD	Ebola Virus Disease
HCW	Health Care Workers
HDX	Humanitarian Data Exchange
HZ	Health Zone
IDPs :	Internally Displaced Persons
MCMC	Markov Chain Monte Carlo
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MEURI	Monitored Emergency Use of Unregistered Interventions
MLE	Maximum Likelihood Estimation
MoH	Ministry of Health of the Democratic Republic of Congo
mRNA	RiboNucleic Acid messenger
NLL	Negative Log-Likelihood
OCHA	Office for the Coordination of Humanitarian Affairs
ODEs	Ordinary Differential Equations
PIs	Prediction Intervals
RCT	Randomised Controlled Trial
RESTV	Reston ebolavirus
SAGE	Strategic Advisory Group of Experts
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SEIHFR	Susceptible – Exposed – Infectious - dead but who may transmit infection during the Funeral –Removed
SEIR	Susceptible – Exposed – Infectious – Removed or Recovered
SEIRD	Susceptible – Exposed – Infectious – Recovered – Deceased

SEIRSvrSvcM	Susceptible – Exposed – Infected – Refractory – Susceptible vaccinated by ring vaccination – Susceptible vaccinated by community vaccination – “in immune transition”, immune state M
SEI1I2I3CR	Susceptible – Exposed – Infectious, with three distinct phases of infection, corresponding to different stages of an Ebola infection – individuals that have been Controlled (detected and isolated) until the current time – Removed
SIHRD	Susceptible – Infected – Hospitalized – Recovered – Deceased
SIR	Susceptible – Infectious – Recovered
SVpVbE1E2IRD	Susceptible – prime Vaccinated – Boost vaccinated – Exposed 1 – Exposed2– Infectious – Recovered – Dead
SUDV	Sudan ebolavirus
TAFV	Tai Forest ebolavirus
WHO	World Health Organisation

1 Introduction

1.1 Ebola Virus Disease

Infections due to Ebola viruses may cause a severe disease in humans called Ebola virus disease (EVD) (1). EVD may result in acute haemorrhagic fever with an elevated case-fatality rate in humans (up to 90%) (2).

EVD caused by Ebolavirus (EBOVs) first appeared in 1976 in Zaire (Democratic Republic of Congo (DRC)) (3). Ebolavirus belong to the Filoviridae family from the order Mononegavirales, which includes three genera, Cuevavirus, Marburgvirus, and Ebolavirus (4). The genus Ebolavirus is composed of five strains, namely Ebola virus (EBOV, previously known as Zaire ebola virus), Sudan ebolavirus (SUDV), Tai Forest ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV) and Reston ebolavirus (RESTV) (5). Since 1976, over 20 known ebolavirus outbreaks have occurred, most of them in Central Africa (Sudan, Uganda, Democratic Republic of Congo, Gabon) and mainly due to the Ebola virus and Sudan ebolavirus (3). Ebola virus are emerging and re-emerging zoonotic pathogens (2).

Fruit bats are believed to be the Ebola virus' natural reservoir, however the virus has not been isolated until now from bats in natural conditions (6, 7). These bats may transmit EBOV (without being affected), to humans, apes and possibly other animals living in the forest. (6, 7). The first person becomes infected by handling infected animals (like fruit bats or primates), that is called a spillover event (1, 7). Secondly, a Human-to-Human transmission follows (1, 7). EVD is transmitted between humans through a direct or an indirect contact with a virus-infected fluid (blood, secretions, organs or other bodily fluids like breast milk) from infected humans or animals (dead or alive), or via EBOV-contaminated object (3, 7, 8). Eating affected bush meat, caring for the sick, or handling with Ebolavirus infected dead bodies (during traditional funerals, for example) are associated with high risk of EVD transmission (7). Before the medical community identifies the Ebola outbreak, nosocomial transmissions are common (7). Male survivors may still have the virus in their semen (up to 18 months after recovery from EVD) and transmit the disease if they have unprotected sexual intercourse (3, 9). Young age, age over 40 years, male sex, and pregnancy are considered poor prognostic factors (with a higher fatality rate) (10-13)

The incubation period of Ebolavirus ranges from 2 to 21 days (and 5.3–12.7 days for EBOV) (3, 14). The symptoms are: fever, fatigue, loss of appetite, vomiting, diarrhoea, muscle and head aches, stomach pain, body rash, tremors and, in some cases, internal and external bleedings (15, 16). A person becomes infectious once she develops EVD symptoms (15). Then, the patient can transmit the disease to susceptible individuals (15). The immediate family members of Ebola-infected people and health-care workers (HCW) who treat patients with suspected or confirmed EVD are at high risk of EBOV infection (3, 8). Infected people can recover from the disease (3, 8). However, an early diagnosis is important to improve chances of survival, which is challenging given that the disease shows similar symptoms as malaria and cholera (8).

1.2 Ebola Virus Disease outbreaks

The largest Ebola outbreak was the 2014-2016 epidemic that occurred in West Africa (mostly in Guinea, Liberia, and Sierra Leone), it killed 11 308 people and an extra 2 8612 got infected (3). The world's second largest EVD outbreak took place in North Kivu, and Ituri Provinces (in the Democratic Republic of Congo (DRC)) (17, 18). The start of the epidemic was announced on 1 August 2018 and was declared to be over on 25 June 2020 (19). The outbreak infected 3 481 people, and claimed 2 299 lives (20). Of the total number of cases, 56% were female, 28% were children (aged less than 18 years), and 5% were health care workers (HCW) (18). This was the tenth outbreak of Ebola in the DRC. Table 1 shows previous Ebola virus disease confirmed outbreaks which occurred in DRC.

Table 1. *Previous EVD confirmed outbreaks (3, 4, 21, 22)*

Years	Location	EVD	Cases	Deaths	Case fatality (%)
1976	Yambuku	EBOV	318	280	88
1977	Bonduni	EBOV	1	1	100
1995	Kikwit	EBOV	315	254	81
2007	Kampunku, Mweka	EBOV	264	187	71
2008	Mweka	EBOV	32	14	44
2012	Isiro	BDBV	57	29	51
2014	Boende	EBOV	68	49	72
2017	Bas Uele	EBOV	8	4	50
2018	Equateur	EBOV	54	33	61
2018-2020	North Kivu and Ituri	EBOV	3 481	2 299	66
2020	Equateur	EBOV	Ongoing		

This 2018-2020 EVD epidemic is highly complex (3). On the one hand, the risk that the EVD spreads to Uganda or Rwanda is high (23). Indeed, North Kivu, which has over eight million inhabitants including large number of displaced persons (IDPs), shares porous borders with these countries (23, 24). In a year, about 750 000 people from North Kivu and Ituri have fled conflicts (25). This situation allowed the virus to spread, through the displacement of potentially infected people into no-go zones (where armed groups operate) and neighbouring regions (25, 26). Besides, the EVD spilled over to South Kivu Province (DRC) and to Uganda (with 3 confirmed cases in the neighbouring country) (27). On the other hand, DRC has a well-functioning rapid response system that can contain an outbreak fairly quickly, it includes « an alert system that asks anyone with a mobile phone to report potential cases » (26). This allows to quickly implement the case detection, contact tracing and all other anti-Ebola measures. However, Eastern DRC is a region that has a long-standing experience of conflict and political instability (26). This context leads to a loss of community confidence in government institutions (28, 29). Political mistrust was also exacerbated by the postponing of the presidential elections to March 2019 (instead of December 2018) for the constituencies of Béni and Butembo: the anti-Ebola response was hindered (30-32). In addition, political distrust can lead to community reluctance to reporting cases which, as a result, prevents early isolation of sick patients, timely vaccination, and safe burials (31). Furthermore, attacks on health facilities and medical staff has coincided with the increase in the number of EVD cases (23). Some violent incidents targeting the anti-Ebola response centres having among others temporarily suspended their activities (29).

During the outbreak, new EVD therapeutics have been investigated (33, 34). Mulangu et al. conducted a randomised controlled trial (RCT) to test four experimental therapies for patients with EVD (34). The four investigational therapies were the triple monoclonal antibody Zmapp (administrated to the control group), the antiviral agent Remdesivir, the single monoclonal antibody MAb114, and the triple monoclonal antibody REGN-EB3 (34). At the beginning of the outbreak (and before the RCT), these four treatments were already used under the World Health Organisation ethical framework, known as the Monitored Emergency Use of Unregistered Interventions (MEURI) (35). During the RCT, patients were enrolled at Ebola treatment centres in Beni, Butembo, Katwa and Mangina (34). Other treatment centres continued to administer the therapeutics on a compassionate basis according to the MEURI's protocol (35). Although, according to Fedson, these agents are unlikely to change the course of the epidemic (36).

Several vaccines were also under study (37). Two vaccines were used during the 2018 North Kivu outbreak (38). The first is the rSVS-ZEBOV, a vesicular stomatitis virus-based vaccine expressing the glycoprotein of a Ebola virus (EBOV), and the second is the Ad26.ZEBOV/MVA-BN an adenovirus type 26-vectored vaccine encoding Ebola virus glycoprotein (Ad26.ZEBOV) (37-39). The latter being boosted by a modified vaccinia Ankara-vectored vaccine encoding glycoproteins from Ebola, Sudan ebola, and Marburg viruses and the nucleoprotein of Tai Forest virus (37-39). The rSVS-ZEBOV was approved for compassionate use by the Ethics Committee of the Democratic Republic of Congo during the early stage of the outbreak (39, 40). After which, the country licenses the vaccine for Ebola prevention (41). From 8 August 2018, the rVSV-ZEBOV vaccine has been administered to the contacts and contacts of contacts of confirmed cases (41). Preliminary results of rVSV-ZEBOV Ebola vaccine using the ring vaccination strategy in the North Kivu and Ituri Ebola outbreak have shown a 97.5% vaccine efficacy (42). In May 2019, the Strategic Advisory Group of Experts (SAGE) on Immunization recommended a third ring vaccination with the rVSV-ZEBOV vaccine at a lower dose (that is vaccinate people “who can potentially be involved in the tertiary generation of cases”) (43). Immunization of third level contacts will be slower (28 days instead of 10 days with the ring vaccination for first and second level contacts) (43, 44). In the same report, SAGE suggest the use of an alternative vaccine for individuals who are at lower risk of EBOV infection (person who lives in a “health zone” where there is a case of EVD or who lives in a zone close to the outbreak) (39, 43-46). Since mid-November 2019, the experimental vaccine Ad26.ZEBOV/MVA-BN-Filo has been introduced in the Democratic Republic of Congo epidemic (38, 45). This EVD outbreak is the first happening in a conflict zone, for which the adopted strategy was ring vaccination from the start (20, 47).

The goal of anti-Ebola control efforts is to minimize the contact with infected bodily fluids (4). Therefore, it is all about early case detection, rapid laboratory diagnostic tests, the wearing of protective equipment by HCW, quarantine of suspected cases, isolation of symptomatic cases, safe burial and health education, and vaccination (46, 48, 49).

1.3 History of infectious disease model

Some researchers greatly contributed to a better understanding of infectious diseases thus enabling the subsequent development of mathematical models on the spread of communicable disease (50). More specifically, Daniel Bernoulli's work on the inoculation against smallpox is remarkable (50, 51). Published in the 1760s, his study focused on the increase in life expectancy if smallpox could be eliminated as a cause of death using variolation (inoculation with a mild strain) (50, 51). John Snow's work is also to be point out. (50, 52). During the 1855 cholera epidemic in London, Snow studied the temporal and spatial patterns of cases, allowing to pinpoint the source of infection (namely, the Brad Street water pump) (50, 52).

Public health physicians such as Hamer, Ross, Kermack and McKendrick initiated the development of mathematical model on infectious disease (50, 53-57). In the early 1900s, Harmer introduced the law of mass action to determine the rate of new infections (50, 53). According to this law, the spread of infection depends on the number of susceptible individuals and the number of infective individuals (50, 53). Since that time, this concept has been at the heart of compartmental models (50). At the same period, Dr. Ross came up with a simple compartmental model that describes the dynamics of the transmission of malaria between mosquitoes and humans (50, 57). He was the first to introduce the concept of the basic reproduction number (50). In 1927, 1932, and 1933, Kermack and McKendrick published a series of three papers to describe the transmission of communicable diseases using basic compartmental models (50, 54-56). The general model included: a threshold quantity (the basic reproduction number), and the age of infection (the time since becoming infected). It can be used to derive a final size relation (50). However, although the concept of basic reproduction number was introduced by the latter, none of them identified this threshold quantity (50). It was not until the work on malaria of MacDonald, that the threshold quantity was explicitly named (50, 58). This threshold, the basic reproduction number (R_0), "is the expected number of disease cases produced by a typical infected individual in a wholly susceptible population over the full course of the infectious period" (50).

According to Brauer, various disease outbreaks, including the 2002-2003 SARS (Severe Acute Respiratory Syndrome) epidemic, the 2009 H1N1 influenza pandemic, and the 2014 Ebola outbreak have" re-ignited interest in epidemic models" (50).

1.4 Ebola models

Regarding Ebola outbreaks, modeling studies were initiated by Chowell et al. (59), Lekone et al. (60) and Legrand et al. (61), among others. These authors have used SEIR-type compartmental models (Susceptible – Exposed – Infectious – Removed or Recovered) to analyze the effects of control interventions on the dynamics of the 1995 DRC and 2000 Uganda Ebola outbreaks. Legrand et al. added compartments for hospitalized individuals and dead Ebola patients (who have not been buried yet) to the initial model framework which gave birth to the so-called SEIHFR (Susceptible – Exposed – Infectious – Hospitalized – dead but who may transmit infection during the Funeral – Removed) model (61).

To better understand the Ebola transmission dynamics during the West Africa outbreak, a large number of Ebola models have been analyzed. Some researchers have used the SEIR-type model to study: the basic or effective reproduction number (8, 62-66), the impact of traditional beliefs and customs (8) as well as the impact of targeted control strategies (63, 64) on the EVD transmission. Weitz et al. used the SEIRD model (Susceptible – Exposed – Infectious – Recovered – Deceased) and added for their part, the “deceased compartment” to take into account the post-death transmission of Ebola (66). Others have employed the SEIHFR model of Legrand et al. to also estimate the basic or the effective reproduction number (67-70), make short term projections of the outbreak (71), and measure some control interventions, such as safe burial procedures, isolation of infectious Ebola patients, contact-tracing with follow-up and quarantine, Ebola treatment units, household protection kits, and ring vaccination (67-71). Merler et al. and Ajelli et al. (67, 69, 72) have used the SEIHFR framework in an agent-based model to project the spatiotemporal spreading of the disease. Additional models have been developed for the same purpose, either compartmental model (73-92) or agent-based model (93, 94). In their research, some authors have taken into account: the age of the infection (92), the relapse, and the reinfection to the disease (73), the vaccination constraints (75), the indirect environmental route of infection (77, 88, 91), the level of education of the population (86), or the cost effectiveness of control measures (90). Finally, sexual and superspreading transmission have also been studied by Lee et al., and Lau et al. respectively (95, 96).

Ebola epidemics in DRC have also led to the development of transmission models ([21](#), [47](#), [97-116](#)). [Table 2](#) is a list of models of Ebola epidemics that have occurred in DRC, published over the last five years in Pubmed, Embase and Scopus. These models either project the trajectory of disease outbreaks or provide epidemiological parameters estimation of Ebola (including basic reproduction number (R_0), serial interval, latent period, infectious period and case fatality rate).

Table 2. An overview of modeling studies of Ebola outbreaks in DRC over the last five years (page 1/6)

References	Outbreaks	Description of modeling approaches	Compartments and parameters estimation, if applicable
Robert et al., 2019 (111)	1995 Congo	Transmission model allowing to explore the relative contribution of Health Care Workers (HCW) and the community to transmission. Measurement of the impact of ahead-of-time HCW-targeted strategies, and reactive HCW and community vaccination. Population were stratified by occupation, HCW (h) or community members (c).	SVpVbE1E2IRD model: Susceptible – prime Vaccinated – Boost vaccinated – Exposed 1 – Exposed 2– Infectious – Recovered – Dead “Exposed compartments” (are Erlang-distributed) . When vaccination campaigns were implemented, susceptible individuals entered the prime (Vp,i) and boost (Vb,i) compartments and were subject to a lower force of infection than susceptible class.
Choi et al., 2019 (99)	2012 DRC	Two modeling’s approaches based on a branching process approximation and direct analysis of the transmission network and based on a survival model derived from the classical SIR equations with no explicit transmission information.	SIR equations: Susceptible – Infectious – Recovered
Althaus, 2015 (98)	2014 DRC	SEIRD compartmental model used to quantify the transmission rate during this outbreak, it provides an estimate of the basic reproduction number (R_0), and calculates the date at which the net reproduction number (R_t) fell below one.	SEIRD model: Susceptible – Exposed – Infectious – Recovered – Dead
Kelly et al., 2019 (106)	2018 Equateur, DRC	Stochastic branching process model that included reproduction numbers from past Ebola outbreaks to generate a probabilistic projection of the outbreak size and duration using high (62%), low (44%), and zero (0%) estimates of vaccination coverage (after deployment).	Not Available

Table 2. An overview of modeling studies of Ebola outbreaks in DRC over the last five years (page 2/6)

References	Outbreaks	Description of modeling approaches	Compartments and parameters estimation, if applicable
Meakin et al., 2019 (109)	2018 Equateur, DRC	Simple stochastic metapopulation model used to describe the spatial dynamics of EVD transmission in three affected health zones: Bikoro, Iboko and Wangata. This model allowed to capture possible changes in transmission rate after the implementation of control measures.	SEIHFR model: Susceptible – Exposed – Infectious – Hospitalized – Dead individuals who are still infectious and may transmit infection during the Funeral – Removed
Wells et al., 2019 (116)	2018 Equateur, DRC	Spatial logistic model that accounts for human mobility, geographic distance, poverty, and population density, as covariates Goal: to evaluate the spatial dynamics of Ebola transmission and quantify the impact of vaccination.	Not Available
Akhmetzhano v et al., 2019 (97)	2018 North Kivu and Ituri, DRC	Mathematical model that adjusts the reporting delay to appropriately estimate the latest incidence and obtain short-term forecasts from weekly reporting data of EVD in North Kivu.	Not Available
Chowell et al., 2019 (100)	2018 North Kivu and Ituri, DRC	Individual-based stochastic transmission model. Evaluation of ring and community vaccination strategies for containing Ebola epidemics in the context of varying levels of community accessibility to public health intervention.	SEIRSVrSvcM model: Susceptible – Exposed – Infected – Refractory – Susceptible vaccinated by ring vaccination – Susceptible vaccinated by community vaccination – “in immune transition”, immune state M

Table 2. An overview of modeling studies of Ebola outbreaks in DRC over the last five years (page 3/6)

References	Outbreaks	Description of modeling approaches	Compartments and parameters estimation, if applicable
Hart et al., 2019 (101)	2018 North Kivu and Ituri, DRC	Comparison predictions of a compartmental model in which a constant symptoms level is assumed to another one that accounts for varying symptoms during infection.	SEI1I2I3CR model: Susceptible – Exposed – Infectious, with three distinct phases of infection, corresponding to different stages of an Ebola infection – individuals that have been Controlled (detected and isolated) until the current time – Removed
Jombart et al., 2020 (102)	2018 North Kivu and Ituri, DRC	Transmission model used to quantify the impact of major security incidents and strategic changes of the response, on EVD dynamics. Estimation of effective reproduction number.	Not Available
Juga et al., 2020 (103)	2018 North Kivu and Ituri, DRC	Deterministic model with demographics that allowed to analyze EVD dynamics in the presence of interfered control (due of war). Estimation of effective reproduction number depending on the proportion of the infected population that was not being hospitalized as a result of war.	SIHRD model: Susceptible – Infected – Hospitalized – Recovered – Deceased
Kelly et al., 2019 (104)	2018 North Kivu and Ituri, DRC	Model used to estimate the expected cumulative case counts, using non-parametrically estimated Hawkes.	Not Available

Table 2. An overview of modeling studies of Ebola outbreaks in DRC over the last five years (page 4/6)

References	Outbreaks	Description of modeling approaches	Compartments and parameters estimation, if applicable
Kelly et al., 2020 (105)	2018 North Kivu and Ituri, DRC	Mathematical model used to identify the different effects of Ebola-targeted versus Ebola-untargeted violence on subsequent EBOV transmission. Estimation of the daily estimated reproduction number (R_t) for the overall outbreak and by health zone.	Not Available
Kraemer et al., 2020 (107)	2018 North Kivu and Ituri, DRC	Mathematical model used to understand the association between conflicts and EVD transmission dynamics. Estimation of bi-weekly temporal trends in the instantaneous reproduction number for each time period of substantial uninterrupted transmission. Correlation analysis between the incidence of conflict and the incidence of disease.	Not Available
Mizumoto et al., 2019 (110)	2018 North Kivu and Ituri, DRC	Transmission model which allowed to quantify effective reproduction number (R_t) at national and regional levels, and to generate short-term forecasts at the national and health zone (HZ) levels.	Not Available
Roosa et al., 2020 (112)	2018 North Kivu and Ituri, DRC	Comparison of real-time forecasts (one to four weeks ahead) for the Ebola epidemic using seven dynamic models of variable complexity. These models included a simple logistic model, a Richards model, an endemic Richards model, a double logistic growth model, a multi-model approach and two sub-epidemic models.	Not Available

Table 2. An overview of modeling studies of Ebola outbreaks in DRC over the last five years (page 5/6)

References	Outbreaks	Description of modeling approaches	Compartments and parameters estimation, if applicable
Tariq et al., 2019 (113)	2018 North Kivu and Ituri, DRC	Real-time analysis of the Ebola outbreak to assess the impact of reporting delays. Analyzes of temporal trends in reporting delays, epidemic curves of crude and reporting-delay adjusted incidences and changes in the effective reproduction number, R_t .	Not Available
Wannier et al., 2019 (114)	2018 North Kivu and Ituri, DRC	Transmission model used to estimate the reproduction number R_t by day per zone on the presence of recently reported violent events.	Not Available
Wells et al., 2019 (115)	2018 North Kivu and Ituri, DRC	Informed by temporal incidence and conflict data, authors developed a model of Ebola transmission and control to assess the impact of conflict on the epidemic.	Modified SEIR model: Susceptible – Exposed – Infectious – Removed Latently infected (E) and infectious (I) populations were subdivided into nE and nI classes, respectively, based on Erlang distribution
Worden et al., 2019 (47)	2018 North Kivu and Ituri, DRC	Transmission model using a stochastic branching process to make short- and long-term projections of the epidemic. High and low estimates of vaccination coverage were integrated into the model.	Not Available

1.5 Model presentation

The aforementioned studies do not use a compartmental model of type SEIRD (Susceptible – Exposed – Infectious – Recovered – Dead) to model the 2018-2020 DRC Ebola epidemic. EVD involves an incubation period of up to 13 days for EBOV (14). That includes the exposed class which is of great importance. As pointed out by Ndanguza et al. (21), it were mainly onset data that were used to estimate model parameters. The purpose of this current study is therefore to model the course of the North Kivu and Ituri Ebola outbreak using a modified SEIR (Susceptible – Exposed – Infectious – Removed) epidemic model that captures the Ebola dynamics by splitting the removed class into recovered and dead compartments. The deterministic and continuous-time model includes a transition in the transmission rate after the implementation of control interventions. Moreover, estimates of the reproduction numbers of EBOV in absence and presence of control measures are provided by fitting the model to the daily observations of reported cases and deaths. Finally, the critical immunization coverage is calculated by using the basic reproduction estimate.

2 Methods

2.1 Epidemic Model

Compartmental models are models in which the population under study is divided into compartments with assumptions about nature and time transfer rate from one compartment to another (117). The number of individuals in a compartment is a differentiable function of time (117). Inspired by Ndanguza and Althaus papers (21, 62), I divided the population studied into five classes labeled SEIRD (Susceptible – Exposed – Infectious – Recovered – Dead) (see Figure 1). S refers to the number of people who are susceptible to the disease (who had not (yet) been infected) at time t . E represents the number of exposed individuals, who were infected but not infectious (not able to transmit the disease) at time t . I refers to the number of infected individuals, infectious and able to communicate the disease by contact with susceptible people, at time t . R concerns the number of people who have been infected and recovered, so removed from the possibility of transmitting infection at time t . Finally, D represents the number of people who died from the disease (therefore also removed) at time t . An individual can be removed via recovery from the disease with immunity against reinfection (R), via death (caused by Ebola Virus Disease) (D), or via immunization against infection (with vaccination for example) (117).

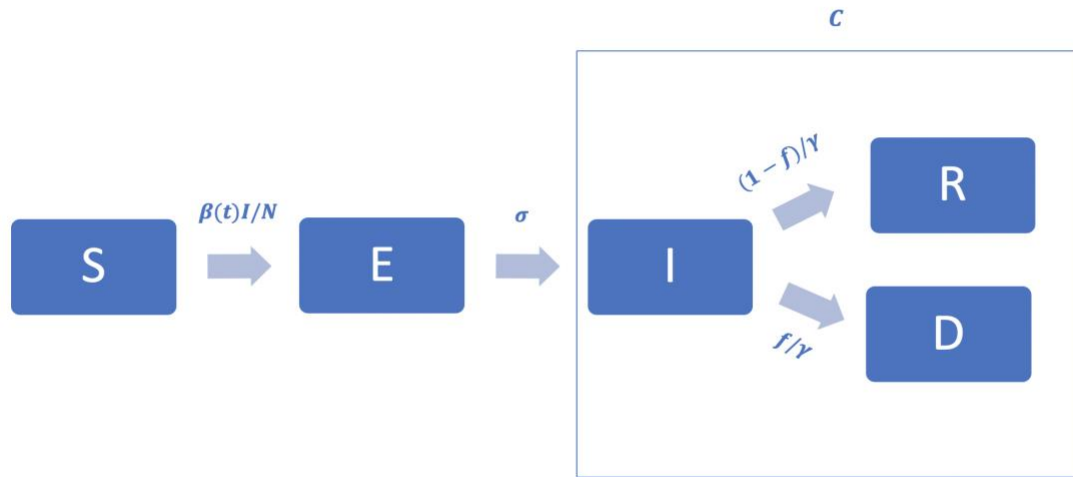


Figure 1. Flow diagram SEIRD. Schematic representation of the EVD transmission model. Susceptible individuals S become exposed by infectious individuals I at rate $\frac{\beta(t)I}{N}$. Exposed individuals move through an incubation period at rate σ before becoming infectious individuals I . Then, infectious individuals I recover at rate $\frac{(1-f)}{\gamma}$ and die at rate $\frac{f}{\gamma}$. The case fatality rate is given by f and C is the cumulative number of infectious individuals.

The transmission process is modeled using the system of nonlinear differential equations:

$$\frac{dS}{dt} = -\frac{\beta(t)SI}{N}$$

$$\frac{dE}{dt} = \frac{\beta(t)SI}{N} - \sigma E$$

$$\frac{dI}{dt} = \sigma E - \gamma I$$

$$\frac{dR}{dt} = (1-f) \gamma I$$

$$\frac{dD}{dt} = f \gamma I$$

$$\frac{dC}{dt} = \sigma E$$

Susceptible individuals, S , in contact with the Ebola virus enter the exposed class, E , at the rate, $\frac{\beta(t)I}{N}$:

- $\beta(t)$ being the transmission rate at time t ,
- I being the number of infectious individuals,
- $N = S + E + I + R + D$ being the total population.

$\frac{1}{\sigma}$ and $\frac{1}{\gamma}$ are the mean incubation period and the average duration of infectiousness, respectively. Recovered individuals R are assumed to have acquired immunity against reinfection for the duration of the outbreak. f is the case fatality rate, while C is the cumulative number of infectious people at time t (and is not an epidemiological state).

I assumed that the epidemic started with a single infected case. Therefore, at the beginning of the outbreak, the entire population was assumed to be susceptible, $N(0) \approx S(0)$. I assumed that homogeneous individuals mix (random mixing): $\frac{I}{N}$ being the probability of a random contact with an infectious individual in a total population (N).

Finally, I assumed that the course of the Ebola outbreak was rapid enough so that there were not significant demographic effects (births, natural deaths, recruitment) on the studied population, therefore, background demographic processes were not included in the model. The model is characterized by a constant population size, $N(0)$.

2.2 The transmission rate and the impact of interventions

The control strategies of EVD include early case detection, rapid laboratory diagnostic tests, the wearing of protective equipment by HCW, quarantine of suspected cases, isolation of symptomatic cases, safe burials, health education and vaccination (48, 118).

In this model, their net effect is to reduce the transmission rate β . In absence of control measures, the initial transmission rate stays constant: $\beta(t) = \beta$. As in Lekone et al. (60), and Althaus (62), once the control interventions were implemented at time point τ , the transmission rate was thought to decay exponentially at rate k : $\beta(t) = \beta e^{-k(t-\tau)}$, where $k > 0$ is the control rate at which $\beta(t)$ decays for $t > \tau$.

2.3 Parameters estimation of the epidemic model

The total population size $N = S + E + I + R + D$ in the two Provinces (North Kivu and Ituri) was rounded to be 12 million individuals (24, 119).

I used the program RStudio Version 1.3.959 for statistical computing and I adapted Althaus R-codes, which are freely accessible on GitHub (120). I used the function *ode* from the package *deSolve* to solve the ordinary differential equations (121).

Always following the logic of Althaus methodology (62), the model parameters ($\beta(t)$, k , T) were fitted to EVD outbreak of the eastern DRC data by maximum likelihood estimation (MLE), assuming the cumulative numbers of cases and deaths were Poisson distributed (62, 122). T refers to the date of appearance of primary case. The average durations of incubation ($\frac{1}{\sigma}$) and infectiousness ($\frac{1}{\gamma}$) were set and retrieved from Meakin et al. and were used also in Hart et al. (101, 109). I set the time point τ at 90 days as the implementation of control measures began about 3 months after the first cases have been registered (19).

MLE is a standard approach to parameter estimation that allows to find the “best” estimates of the parameters for such a dataset (123, 124). The estimated parameters from the MLE are the parameters values that make the observed data the most likely to have happened (123, 124). To find the maximum likelihood estimates, I defined the likelihood as followed. The likelihood of cumulative numbers of cases and deaths is based on the probability density function for the Poisson distribution. Then, I used the log-likelihood (the log of a product being equal to the sum of the logs (124)). Finally, I used the negative log-likelihood (NLL) to find the best estimates of my model parameters, by minimizing measure of lack of fit (124).

In order to calibrate the model to improve its prediction ability, I used the algorithm “Nelder & Mead” that was implemented in the function *optim* (for optimization). It is a local algorithm, which by local iterative procedure looks for the minimum of the objective function (NLL, here) approximating its previous values (125, 126). The likelihood profile allowed to calculate the 95% confidence intervals (CIs).

I derived simulation based on 95% confidence intervals (CIs), for the model curve of the cumulative number of cases and deaths, making use of the asymptotic normality of MLEs and I also constructed 95% prediction intervals (PIs) for cumulative reported cases and deaths (127, 128). The algorithm, used by Althaus et al. (127), included the following steps:

- Using the function *rmvnorm* from the package *mvtnorm*, simulate $n = 10\,000$ values, $\theta_1, \dots, \theta_n \sim N(\hat{\theta}, \Sigma)$, where $\hat{\theta}$ is the MLE of the unknown model parameters with associated variance-covariance matrix Σ . (According to the “help” tab of RStudio, *mvtnorm* it is the “Multivariate Normal Density and Random Deviates: these functions provide the density function and a random number generator for multivariate normal distribution with mean equal to mean and covariance matrix sigma”).
- The system of Ordinary Differential Equations (ODEs) is solved for each θ_i to obtain the model curves. For each time-point t , the pointwise 95% CIs are built with the use of 5% and 95% quantiles from the bootstrap samples.
- For each outbreak trajectory, creation of a simulate vector of daily incident cases from the sampling model. For each time-point t , the 95% PIs are constructed using the bootstrap sample of the cumulative number of cases. The same procedure was applied for the number of deaths.

2.4 The reproduction numbers

As a reminder, “The definition of the basic reproduction number R_0 is that the basic reproduction number is the number of secondary infections caused by a single infective introduced into a wholly susceptible population of size $N(0) \approx S(0)$ over the course of the infection of this single infective” (117).

If there are no significant demographic effects on the population during the course of the Ebola outbreak, and if all infected individuals recover with full immunity against re-infection, then the disease will die out if the basic reproduction number is less than one. Inversely, if R_0 exceeds one, there will be an epidemic (50, 117). In other words, “the threshold $R_0 = 1$ is the dividing line between the infection dying out and the onset of an epidemic” (50). If the number of cases is small compared to the total population size, the exact population size does not need to be known to estimate the model parameters (59, 62). The basic reproduction number of this system is given by the product of the mean transmission rate and the mean infectious period, $R_0 = \frac{\beta}{\gamma}$ (59, 62). As long as the number of cases remains well below S , the effective reproduction number is given by $R_e = \frac{\beta(t)S}{\gamma N} \approx \frac{\beta(t)}{\gamma}$ (62). The effective reproduction number is defined by the “average number of secondary cases arising from a primary case in population with susceptible and immune individuals” (129).

In this paper, I focus on the estimation of the basic reproduction number from an inverse problem perspective using compartmental epidemic models based on systems of ordinary differential equations. I used the estimated parameter of the transmission rate to calculate the basic reproduction number (R_0), the effective reproduction number (R_e), and the time at which R_e dropped below unity.

2.5 Data

Data for the North Kivu and Ituri EVD outbreak includes daily incidence of symptom onset and daily number of deaths that were derived from Tariq et al. publication ([113](#)), from WHO (World Health Organisation) situation reports and from DRC Ministry of Health (MoH) reports. Data from situation reports (from WHO and MoH), which include data covering the period from 4 August 2018 to the end of the epidemic, can be downloaded directly from the Humanitarian Data Exchange (HDX) website (a platform related of the United Nations Office for the Coordination of Humanitarian Affairs (OCHA) Services) ([130](#)). Data covers the period from April 30, 2018 to June 25, 2020 (See [Figure 2](#)).

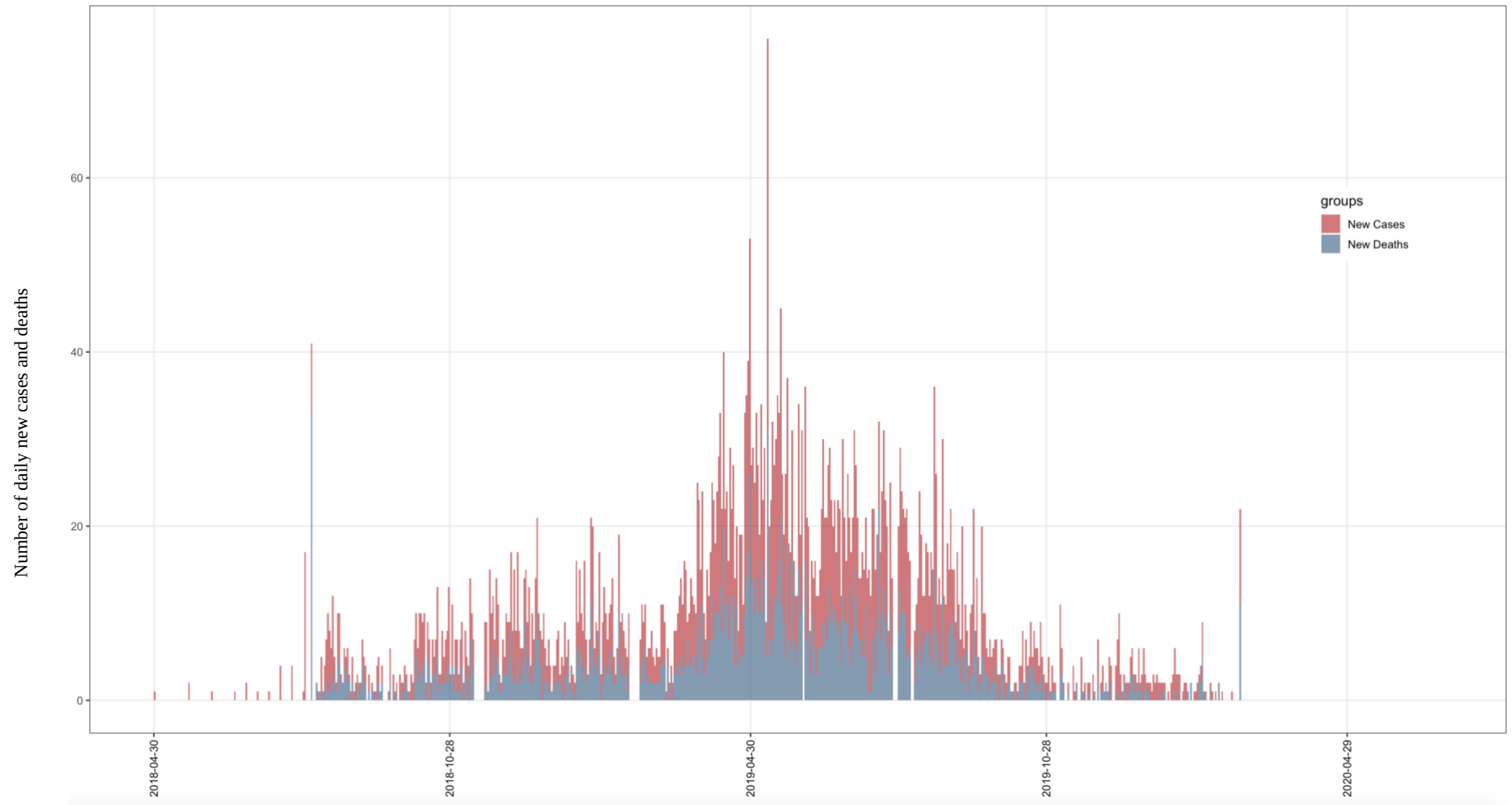


Figure 2. Graphic representation of daily EVD new cases and deaths observations during the North Kivu and Ituri Ebola outbreak (from April 30, 2018 to June 25, 2020).

3 Results

The maximum likelihood estimate (MLE) of the transmission rate β_0 was 0.162 per day and 1.351×10^{-8} per individual per day. This corresponds to a basic reproduction number $R_0 = 1.59$. The rate at which control measures reduce transmission was estimated at $k = 0.0025$ per day. [Table 3](#) shows all parameter values used or estimated in the analysis of data from the 2018-2020 North Kivu and Ituri Ebola outbreak.

Table 3. *Parameter values*

Parameter	Definition	Values (IC95%)	Justification
R_0	Basic reproduction number	1.589 (1.588 – 1.590)	Fitted to data
β_0	Transmission rate per day	0.162 (0.162 – 0.162)	Fitted to data
	Transmission rate per individual	1.351×10^{-8} ($1.351 \times 10^{-8} - 1.352 \times 10^{-8}$)	Fitted to data
k	Rate at which control measures reduce transmission, k (per day)	0.0025 (0.0025 – 0.0025)	Fitted to data
T	Date at which the first case appears	April 30, 2018 (-)	Fitted to data
τ	Time at which control measures begins once the first case appeared	90 days	(19)
$\frac{1}{\sigma}$	Mean incubation period	7 days	(109)
$\frac{1}{\gamma}$	Mean infectious period	9.8 days	(109)
f	Case fatality rate	0.66	(20)

With fixed and estimated parameters, I constructed the SEIRD graph (see [Figure 3](#)). [Figure 3](#) illustrates the magnitude of the epidemic, if nothing is done to reduce the basic reproduction number. The graph displays the curves representing the number of people in the different classes of the model (Susceptible, Exposed, Infectious, Recovered, Dead) with a constant transmission rate (without the transition of this transmission rate linked to the implementation of the intervention).

The graph indicates that with such a rate of transmission, almost two thirds of the population would have been affected by the virus, which means that the number of susceptible people would stabilize at the end of the epidemic. The epidemic would have ended approximately 600 days after the first EVD case. A very high number of deaths would have been expected given the high mortality rate of 66%. This roughly is twice the number of recovered people.

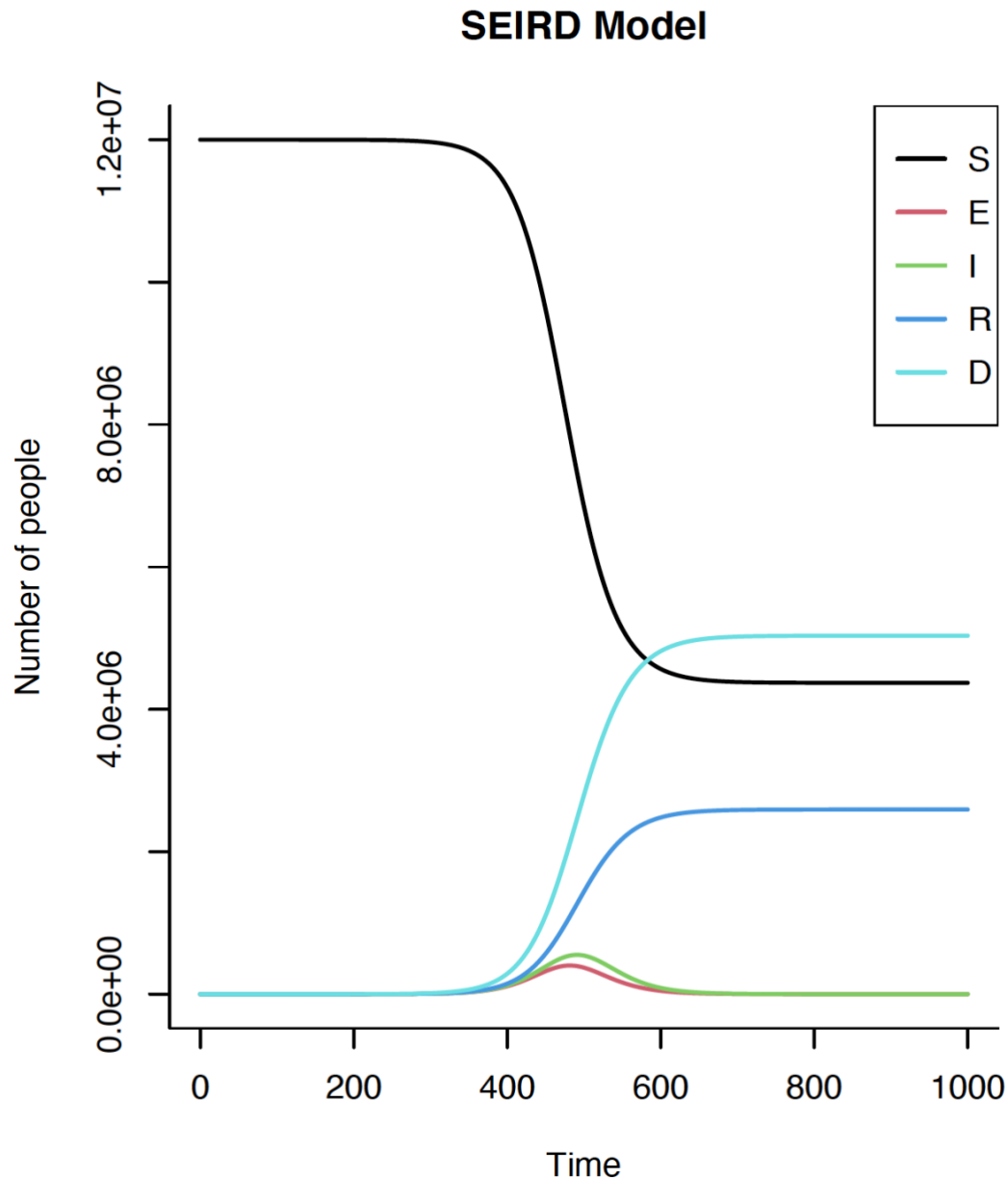


Figure 3. Graph of the SEIRD model without transition in the transmission rate β . Colored lines (dark, red, green, dark blue and sky blue) represent the number of people in the respective S, E, I, R, D classes, according to time.

The model provides a quite good description of the cumulative number of cases and deaths (See [Figure 4](#) and [Figure 5](#)). However, between the onset of the epidemic (30 April 2018) and end of July 2018, the model shows a slower increase in the cumulative number of cases and deaths, compared to the rapid rise in cases that was observed after the index case. From July on, the increase in the model's cumulative cases and deaths is steeper, while the increase in the observed data is more gradual. As in Althaus ([127](#)), stochastic effects could explain this gap at the beginning of the outbreak (see in Section 4: [Discussion](#)). The curves converge at the end of December 2018. As for the cumulative case curves (observed and generated by the model), they deviate very slightly from January 2019, but are almost "stuck" and merge again in August 2019. On the other hand, the cumulative death curves merge as of December 2018.

I illustrated the decrease in the effective reproduction number (R_e) following the introduction of control measures (with estimated parameters of the transmission rate β_0 and the rate k at which control interventions reduce transmission). [Figure 6](#) illustrate the evolution of R_e during the outbreak, as well as the time at which R_e dropped below unity. R_e dropped below unity the January 29, 2019, around 9 months after the arrival of the index case, that is, around 6 months after control measures were implemented.

The relation between the basic reproduction number R_0 and the critical immunization coverage P_c is given by $P_c = 1 - \frac{1}{R_0}$ ([129](#)). In order to control an infectious disease by vaccination, it is necessary to achieve a certain level of immunization coverage, which depends on the transmissibility of the disease ([131](#)). According to Duijzer, critical immunization coverages are vaccination allocations involving a reproduction number of one ([132](#)). Using the estimated value of R_0 of the North Kivu and Ituri Ebola outbreak, I calculated that the critical immunization coverage P_c was 37% (95% CI: 37-37%) (See [Figure 7](#)).

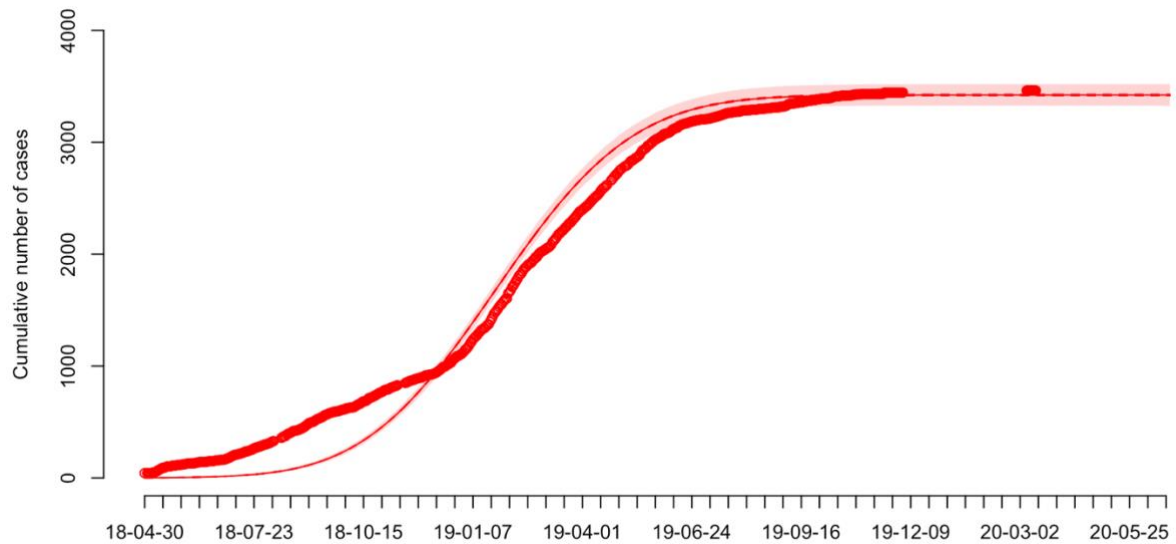


Figure 4. Cumulative number of cases. Red curbs represent cases. The solid line corresponds to the best-fit model, it is surrounded by the 95% confidence intervals in dashed lines while the shaded area illustrates the 95% prediction intervals.

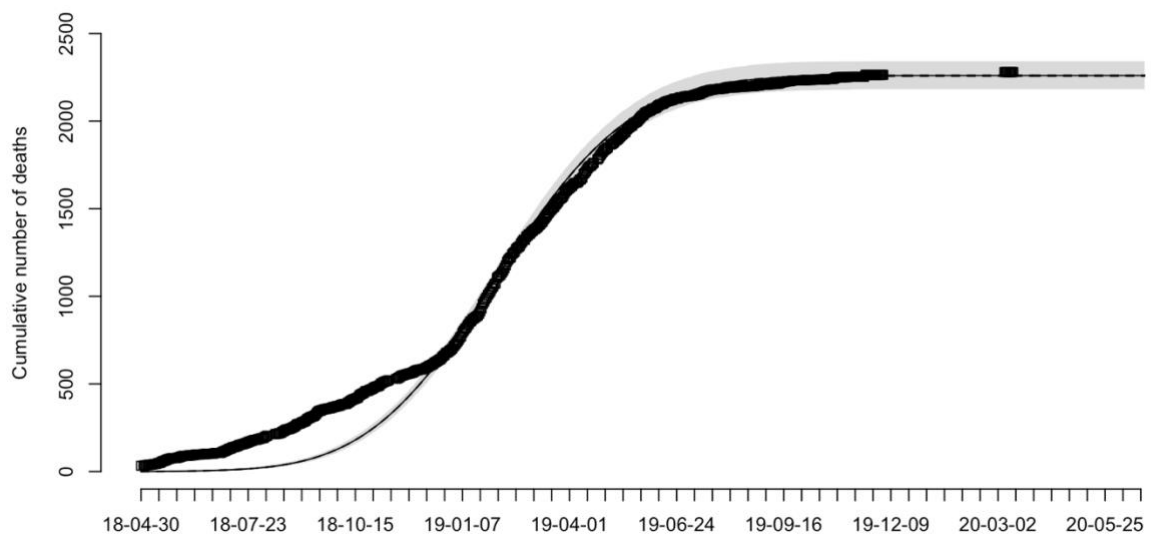


Figure 5. Cumulative number of deaths. Dark curbs represent deaths. The solid line corresponds to the best-fit model, it is surrounded by the 95% confidence intervals in dashed lines while the shaded area illustrates the 95% prediction intervals.

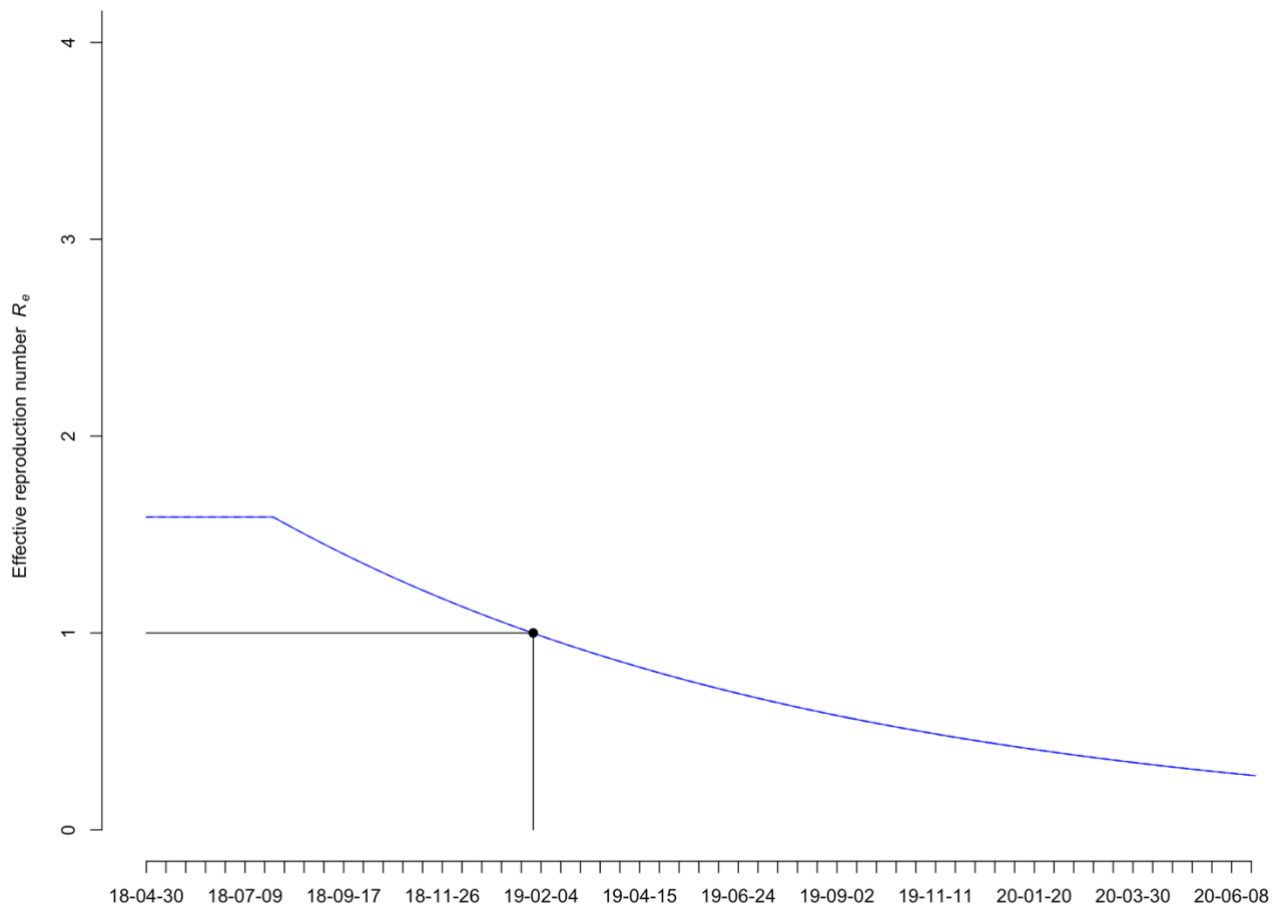


Figure 6. Effective reproduction number R_e during the EVD outbreak in North Kivu and Ituri. MLE of the effective reproduction number R_e (solid line) is illustrated. The black dot indicates the time at which R_e dropped below unity.

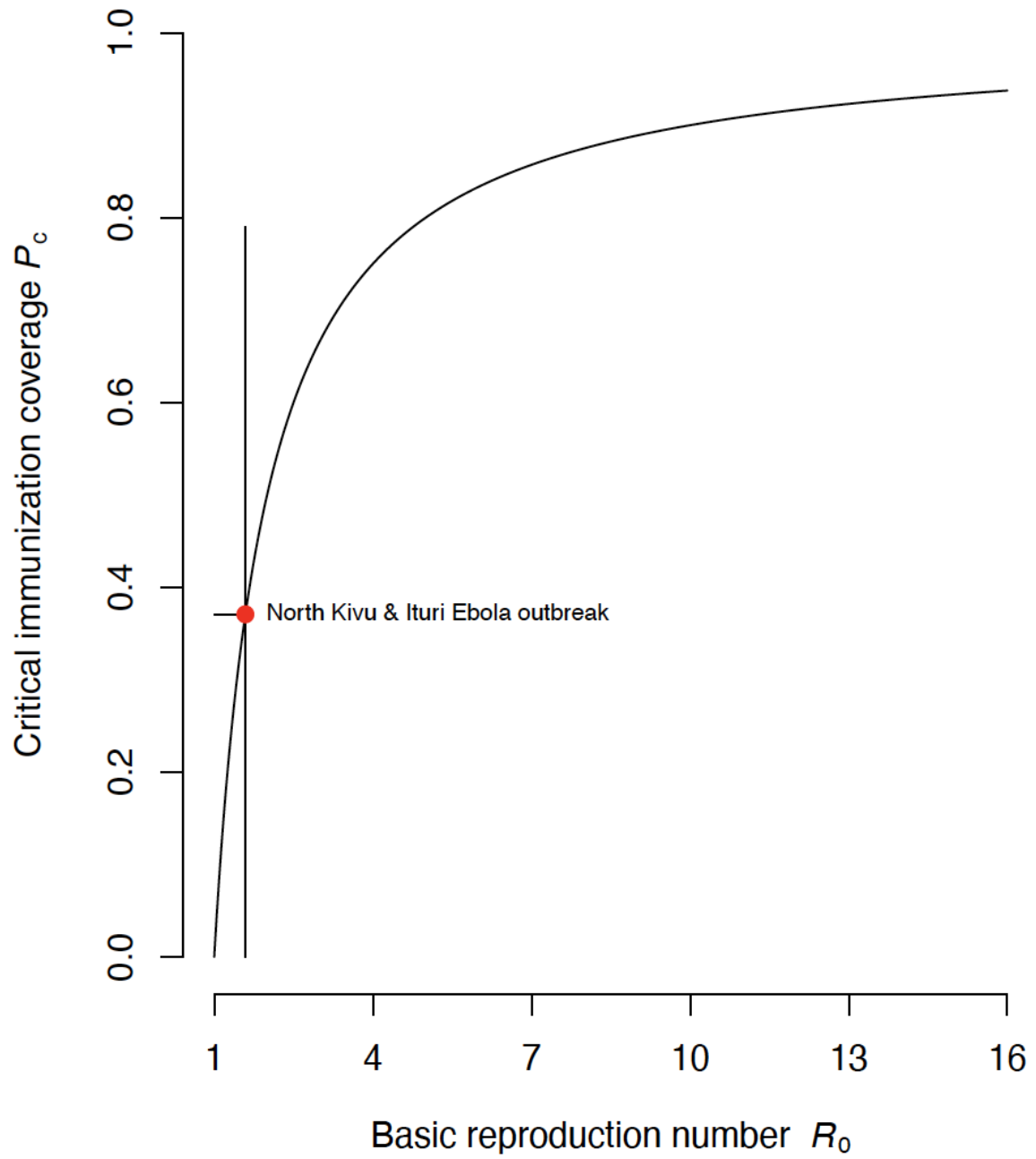


Figure 7. Critical immunization coverage (P_c) for the North Kivu and Ituri Ebola outbreak (represented by the red dot). The curve illustrates the relation between the basic reproduction number R_0 (red dot) and P_c .

4 Discussion

4.1 Results discussion

I fitted a deterministic SEIRD (Susceptible – Exposed – Infectious – Recovered – Dead) transmission model to the data related to reported cumulative cases and deaths of EVD during the 2018-2020 North Kivu and Ituri outbreak. I estimated that the basic reproduction number R_0 was 1.59. The implementation of control measures reduced greatly the magnitude of the epidemic. This could be observed by comparing the predicted number of deaths regarding the model without intervention measures, which amounts to more than 5 million deaths at the end of the outbreak (see [Figure 3](#)), with the real number of deaths or the one predicted by the model with intervention measures, which amounts to about 2 300 deaths (see [Figure 5](#)). I also pointed that introduction of control interventions reduced the effective reproduction number R_e below unity 275 days after the arrival of the index case. Finally, I assessed that the critical immunization coverage P_c was 37%.

This study adds to the epidemiological descriptions of the 2018-2020 North Kivu and Ituri epidemic and gives estimations of the number of secondary cases generated by an infected index case in absence and presence of control measures. Hart et al., Juga et al. and Wells et al. have also been searching for the basic reproduction number of this outbreak ([101](#), [103](#), [115](#)). With their SEI1I2I3CR model (Susceptible – Exposed – Infectious, with three distinct phases of infection, corresponding to different stages of an Ebola infection – individuals that have been Controlled (detected and isolated) until the current time – Removed), Hart et al. found a R_0 at 1.83 for the variable symptoms model and at 1.90 for the constant symptoms model ([101](#)). Juga et al. estimated a R_0 at 2.49 with their SIHRD model (Susceptible – Infected – Hospitalized – Recovered – Deceased) ([103](#)). Finally, Wells et al. obtained a R_0 at 1.66 using their SEIR model (Susceptible – Exposed – Infectious – Removed) ([115](#)).

The basic reproduction number and the transmission rate that I have estimated are lower than previously estimated. This can be explained by the differences between models (see [Table 4](#)). I would like to underline the fact that I started my analysis from April 30, 2018 date of symptoms onset of the first index case. Wells et al., which found a R_0 closer to the one estimated in this paper, begun also their analysis at this time ([115](#)). As for Hart et al. and Juga et al., they started their analysis form early August ([101](#), [103](#)).

Table 4. Main differences between previous 2018-2020 DRC Ebola outbreak model, which give R_0 estimates

References	Hart et al. (101)	Juga et al. (103)	Wells et al. (115)
R_0 estimates	1.83 (constant symptoms model) 1.90 (variable symptoms model)	2.49	1.66
Transmission parameters number	2 (preintervention decays to postintervention)	1	1
Transmission rates per individual per day estimates	Early in epidemic: 8.43×10^{-7} (constant symptoms model) or 8.1×10^{-7} (variable symptoms model) Late in epidemic: 3.67×10^{-7} (constant symptoms model) 3.59×10^{-7} (variable symptoms model)	10^{-6}	-
Model fitting	Least square method	Least square method	Maximum likelihood estimate
Data	Weekly number of cases from city of Beni and Kalunguta Health zone between August 4, 2018 and January 10, 2019	Bimonthly number of cases from North Kivu Province between August 5, 2018 and July 27, 2019	Weekly number of cases from North Kivu and Ituri Provinces between April 30, 2018 and June 23, 2019
Considered: Exposed class, Variable symptoms Nosocomial transmission Burial transmission Demographic effects	Yes Yes No No No	No No Yes Yes Yes	Yes No No No No

Using the estimated value of R_0 , I calculated that the critical immunization coverage was 37%. The critical immunization coverage represents the proportion of the population to be immunized in order to indirectly protect susceptible individuals ([129](#)). This immunization coverage allows the decrease of the infection incidence (which leads to a reproduction number below one). This is called herd immunity ([129](#)). Given that the efficacy of the rSVS-ZEBOV vaccine is 97.5% ([42](#)), 38% of the population should be vaccinated with this vaccine. However, during the EVD outbreak, 301 785 people were vaccinated with the rVSV-ZEBOV Ebola vaccine, and 20 339 people received the Ad. SEBOV/MVA-BN-Filo vaccine in health areas near Goma ([38](#)). Therefore, 27% of population members were vaccinated if we consider the population of North Kivu and Ituri Provinces. The strategy was a ring vaccination (up to 3 levels) with the rSVS-ZEBOV vaccine, and a program vaccination with the Ad26.ZEBOV/MVA-BN vaccine for individuals who live in a “health zone” at high risk of EVD or where there is an EVD case ([39](#), [43](#)).

4.2 Model discussion

Although the incubation period and disease-related mortality have been taken into account, the model has several limitations.

First, at the beginning of the epidemic (until December 2018), my model does not quite fit the reality (see [Figure 4](#) and [Figure 5](#)). Maybe it is due to the fact that I assumed that the sizes of the compartments were large enough for the mixing of members to be homogeneous, while for small populations or at the beginning of a disease outbreak, the transmission of infection is a stochastic event because of a small number of infectious individuals ([50](#)). Use of stochastic model allows to best describe the onset of an epidemic (or an epidemic affecting a small number of people) ([50](#)). Two approaches can be used to take into account the stochastic nature of the beginning of an epidemic ([50](#)). The first one is to initially use a stochastic branching process model and then turn to a compartmental model when the number of infectives individuals is sufficient for the homogeneous mixing of population members ([50](#)). The second one consists in using a stochastic model throughout the course of the outbreak ([50](#)). There are many types of stochastic epidemic models ([133](#)). Stochastic branching process in compartmental model was used many times to model the Ebola outbreak ([21](#), [59-61](#), [67](#), [70](#), [72](#), [85](#), [99](#), [108](#), [109](#)). Another type of infectious disease model that captures stochasticity is the agent-based model. Agent-based models (ABMs) are “a type of computer simulation composed of agents that can interact with each other and with an environment” ([134](#)). That means that, an agent can represent an individual as well as an organization, a body, or a nation state,... ([134](#)). ABMs can capture the spatial and social heterogeneity ([134](#), [135](#)), such as those used by Chowell ([100](#)), Merler et al. or Ajelli et al. ([67](#), [69](#), [72](#)). Finally, other transmission models, also using stochastic branching process, was used in the modeling of the Ebola ([47](#), [106](#)).

Secondly, the model gives January 29, 2019 as the date of which R_e dropped below unity. However, [Figure 2](#) shows a further increase in the number of cases and deaths from end of March 2019 and illustrates that the peak of the epidemic was reached on May 10, 2019. That implies that the transmission rate increased further between the end of March and the beginning of May 2019. This increase in April 2019 in the transmission rate and potentially in the effective reproduction number was not illustrated by the model given that, once the control interventions had been put in place, the transmission rate decreased exponentially (in particular according to the constant control rate). It is also worth mentioning that the effective reproduction number is directly influenced by the transmission rate. Therefore, the model does not take into account variability of the control rate. This increased transmission rate in April 2019 can be explained by the context of conflict and political instability in the provinces of North Kivu and Ituri. Moreover, according to Jombart et al. the period during which the increase in transmission took place (late March to early May 2019), is defined as the “disrupted phase” and is characterised by an effective reproduction number at 1.22 ([102](#)).

Then, as in Althaus et al. ([127](#)), I did not make a distinction between transmission in health-care settings and within the community, and I did not take into account post-death transmission (as in Legrand et al. paper ([61](#)) and other studies ([67-72](#))). As a result, I was unable to examine their separate effects.

Moreover, I did not make any difference between different interventions such as contact tracing, early detection and isolation of symptomatic cases, safe burials, health education and vaccination ([49](#)). I considered all control measures as a whole and assumed that their indiscriminate implementation would lead to an exponential reduction in the transmission rate.

Finally, I also did not take into account the increase in transmission with disease progression due to higher viral loads ([136](#)), an element that was considered in the paper of Hart et al. ([101](#)).

This SEIRD model allowed me, among others: to calculate the basic reproduction number, to illustrate the magnitude of the epidemic in absence of control measures, as well as to determine the critical immunization coverage. It would be interesting to use this compartmental model to study the impact of the conflict and of the different control interventions (such as vaccination, contact tracing, isolation of symptomatic cases), as did Wells et al. with their SEIR model (116). In my opinion, it would also be important to include the impact of community involvement in the analysis. Indeed, a study found that 72% of 630 respondents were dissatisfied with the EVD response, 12% of respondents believing that the Ebola outbreak was not real and 9% having sympathized with people behind enemy lines (31). Further on, 15% of them expressed non-compliant intentions on anti-Ebola activities (for example by hiding the EVD family member from the health authorities, by touching the body, or by refusing to welcome a burial team) (31). As a reminder, the context of long-stand experienced conflict and political instability leads to a loss of community trust in government institutions (28, 29). Thus mistrust can lead to less community involvement (31). It might also be worthwhile to use an agent-based model to capture dynamics of EVD with spatial and social heterogeneity (it is worth remembering that conflicts and these impacts on community involvement for example, reach some places more than others).

More broadly, the use of a compartmental model (of type SEIRD) enables to: understand the mechanisms of propagation of an infectious disease, highlight the significance of the reproduction numbers, estimate the number of people in each class in order to influence decision-making regarding control measures, and also compare the characteristics of different epidemics (129, 137). Seeking to explain the mechanism of the spread of an outbreak *a posteriori* provides a better understanding of the phenomenon so as to be able to act more effectively in the event of a similar situation (a situation where the model seems to be applicable).

Besides, the SEIRD type framework was also used to model the Covid-19 (Corona Virus Disease 2019) outbreak in different areas (California ([138](#)), Bangladesh ([139](#)), Belgium ([140](#)), Italy ([141](#)), Japan ([138](#)), Korea ([142](#)), Spain ([142](#)), and United States of America ([138](#))).

More precisely, Alleman et al. built a deterministic, age-stratified-SEIRD model with detailed hospital dynamics to analyze the Covid-19 transmission in Belgium ([140](#)). They found a basic reproduction number during March 2020 at 2.83 ([140](#)). Then, they recomputed the reproduction number during lockdown (from May 5, 2020 until July 10, 2020) at 0.73 ([140](#)). In the conclusion of their study, they stated that the protection of the elderly may be the most efficient way to reduce strain on the public health system ([140](#)).

4.3 Ebola Virus Disease and Corona Virus Disease

The ongoing Covid-19 outbreak is a new coronavirus pneumonia epidemic caused by the virus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) which killed more than 1.5 million and infected over 72 million individuals (as of December 18, 2020) ([143-145](#)). Two other viruses belonging to the coronavirus family also caused severe human diseases. The SARS-CoV-1 (Severe Acute Respiratory Syndrome Coronavirus 1) caused acute respiratory distress syndrome (ARDS), the same applies to the MERS-CoV (Middle East Respiratory Syndrome Coronavirus) ([143, 144](#)). The first one emerged in 2003 in Guangdong (China) before causing an epidemic of 8 000 infected cases and 776 deaths around the globe ([144](#)). In 2012 appeared the second one, the MERS-CoV, which caused mild upper respiratory injury before turning into severe respiratory disease, infecting more than 2 428 individuals and killing 838 people ([144](#)). At the end of 2019, the Covid-19 outbreak emerged in the mega city of Wuhan, located in the Hubei Province in China, before globally spreading ([140, 143, 144](#)). The epidemic is thought to have started in the Hunan seafood market of Wuhan and rapidly infected more than 50 people ([143, 144](#)). The SARS-CoV-2 is likely to have zoonotic origins and is capable of human-to-human transmission through close contact with an infected person – even pre-symptomatic – when one is exposed to coughing, sneezing, respiratory droplets or aerosols ([140, 144](#)). The disease is severe, especially in older individuals ([140](#)).

[Table 5](#) includes the main characteristics of Coronavirus Disease 2019 and the Ebola Virus Disease to highlight their similarities and differences while [Table 6](#) summarizes the differences between the current Covid-19 and the North Kivu and Ituri Ebola epidemics.

Table 5. Comparison of the main characteristics of Covid-19 and EVD (page 1/2)

Disease	Covid-19	EVD
Virology (taxonomy)	Covid-19 is caused by the SARS-CoV-2 belonging to the Coronaviridae family in the Nidovirales order (146). Subgroups of coronavirus family are: alpha (α), beta (β), gamma (γ), and delta (δ). SARS-CoV-2, as well as SARS-CoV and MERS-CoV are β-coronaviruses. (146)	EVD is caused by Ebolavirus (EBOVs) belonging to the Filoviridae family in the Mononegavirales order (4). Subgroups of EBOVs are: Ebola virus (EBOV), Sudan ebolavirus (SUDV), Tai Forest ebolavirus (TAFV), Bundibugyo ebolavirus (BDBV) and Reston ebolavirus (RESTV) (4, 5, 22).
Reservoir of the virus	SARS-CoV-2 is believed to have a zoonotic origin (possibly bats) (146, 147). Pangolin, snakes, turtles, and various wild mammals (cats, dogs for example) could be potential intermediated hosts (146, 148).	EBOV is believed to have a zoonotic origin (possibly African fruit bats, as Rousettus aegyptiacus) (4). Apes, monkeys and species such as antelopes that live in forest areas could be potential intermediated hosts (4).
Mode of transmission	SARS-CoV-2 is transmitted from human to human by infectious droplets (146, 149). Transmission may also occur indirectly through infected surfaces or fomites (146, 150) Faeco-oral transmission and long-range airborne transmission are also possible (146).	Interhuman transmissions take place through a direct or an indirect contact with a virus-infected fluid (blood, secretions, organs or other bodily fluids like breast milk) from infected humans or animals (dead or alive), or via EBOV-contaminated object (3, 7, 8). Male survivors may still have the virus in their semen (up to 18 months after recovery from EVD) and transmit the disease if they have unprotected sexual intercourse (3, 9).

Table 5. *Comparison of the main characteristics of Covid-19 and EVD (page 2/2)*

Disease	Covid-19	EVD
Incubation period	The average incubation period is about 4-6 days with about 95% of individuals developing symptoms within 14 days (146 , 151-153).	The incubation period of Ebola viruses ranges from 2 to 21 days (and 5.3–12.7 days for EBOV) (3 , 14).
Contagious period	Contagious period can start a few days before symptoms onset, however uncertainty about the weight of pre-symptomatic transmission remains (146). Infectiousness peaks around the time of symptoms onset (146 , 154). Probability of successfully culturing virus seems limited (<5%) 8-10 days after symptom onset in mild-moderate cases and 14-20 days (or more) in severe cases (146 , 155)	During symptoms period, between the 2nd and 21st day of the disease (4).
Symptoms	Most frequent symptoms are: fever, cough, and shortness of breath (146). Other common symptoms are: myalgia or fatigue, dyspnea, expectoration, and chest distress such as gastrointestinal symptoms combined with diarrhea, nausea or vomiting, abdominal discomfort/pain, or loss of appetite (146 , 156).	The symptoms are: fever, fatigue, loss of appetite, vomiting, diarrhoea, muscle and head aches, stomach pain, body rash, tremors and, in some cases, internal and external bleedings (15 , 16).
Groups at risk	The elderly, males, smokers, and patients with comorbidities, such as hypertension, cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD), malignancy, and chronic kidney disease (146 , 157 , 158)	Young age, age over 40 years, male sex, and pregnancy are considered poor prognostic factors (with a higher fatality rate) (10-13).

Table 6. Comparison of the main characteristics of Covid-19 and 2018-2020 DRC EVD outbreaks (page 1/2)

Outbreak	Covid-19	2018-2020 DRC EVD
Emergence date	End of December 2019 (143)	April 30, 2018 (113)
Area of Emergence	Wuhan, a city of around 11 million residents located in the Hubei Province, China (159)	Mangina, a small rural town of Mabalako in North Kivu Province, DRC (160)
Date of fully controlled	Not controlled yet	June 25, 2020 (19)
Number of infectious cases	73 275 943 (as of December 18, 2020) (145)	3 481 (20)
Number of deaths related to the disease	1 650 348 (as of December 18, 2020) (145)	2 299 (20)
Fatality case rate of the disease	2.25%	66.04%
Affected countries	Only 15 countries in the world did not report any cases according to WHO: Tuvalu, Turkmenistan, Tonga, Tokelau, Samoa, Saint Helena, Pitcairn Islands, Palau, Niue, Nauru, Micronesia, Kiribati, Democratic People's Republic of Korea, Cook Islands, and American Samoa (145)	Democratic Republic of Congo and Uganda (27)
Basic reproduction number	From 2 to 4 (before lockdown) (146 , 161)	From 1.59 to 2.49 (101 , 103 , 115)

Table 6. Comparison of the main characteristics of Covid-19 and 2018-2020 DRC EVD outbreaks (page 2/2)

Outbreak	Covid-19	2018-2020 DRC EVD
Non-pharmaceutical interventions	Handwashing, social distancing, wearing a face mask, wearing of protective equipment by HCW, quarantine of suspected cases, health education (146)	Early case detection (with contact tracing), rapid laboratory diagnostic tests, wearing of protective equipment by HCW, quarantine of suspected cases, isolation of symptomatic cases, safe burials, health campaigns and educational activities (4, 49)
Pharmaceutical interventions	Vaccines are not yet available in Belgium, but the country ordered vaccines from: BioNtech-Pfizer (mRNA vaccine), Moderna (mRNA vaccine), AstraZeneca/Oxford (non-replicating viral vector vaccine ChAdOx1), Johnson & Johnson (non-replicating viral vector, Ad26), and Curevac (mRNA vaccine) If authorization is granted by the European Medicines Agency (EMA), they will be the first vaccine brands to be available in Belgium (146) Current therapeutics recommendations for confirmed Covid-19 critical disease are the use of Dexamethasone, and Remdesivir Other treatments such as Interferon, Favipiravir, convalescent plasma, Hydroxy-chloroquine, Chloroquine-phosphate are still in clinical trials (162) Supportive treatment	Vaccination program (ring and community vaccination): Ring vaccination (until 3rd level) with rSVS-ZEBOV, a vesicular stomatitis virus-based vaccine expressing the glycoprotein of a Zaire Ebolavirus, and Community vaccination (for individuals at lower risk to EVD) with Ad26.ZEBOV/MVA-BN an adenovirus type 26-vectored vaccine encoding Ebola virus glycoprotein (Ad26.ZEBOV) (37-39) Agents such as the triple monoclonal antibody Zmapp, the antiviral agent Remdesivir, the single monoclonal antibody MAb114, and the triple monoclonal antibody REGN-EB3 were studied in the framework of a clinical trial (34) Supportive treatment

To summarize, Table 5 and Table 6 show that the mode of transmission and the main symptoms of the two diseases are different. Unlike Covid-19, young age presents a risk factor for EVD. For Covid-19, transmission may occur during the pre-symptomatic period, which is not the case for EVD. However, incubation periods are more or less similar when comparing Covid-19 to EBOV. The Covid-19 outbreak takes its starting point in Wuhan, a mega city of around 11 million residents, unlike the Ebola epidemic which emerged from a rather rural area. In addition, Covid-19 is transmitted more rapidly when comparing the reproduction numbers of the diseases. Moreover, Covid-19 epidemic spread around the world to affect tens of millions of people, unlike the Ebola epidemic which remained localized. Furthermore, the fatality cases rates of the two diseases during these epidemics are as for very different. Pharmaceutical intervention measures in the management of these two epidemics are relatively similar (with vaccination and the use of antivirals such as Remdesivir). Both viral (SARS-CoV-2 and EBOV) diseases were found to be of zoonotic origin. The bat seems to be common reservoir and seems to be able to transmit the infection to other animals (which can be considered as intermediate hosts) and/or to humans (inter-species transmission). Subsequently, human-to-human transmission occurs.

4.4 Zoonotic Diseases

The emergence of these outbreaks linked to zoonotic diseases (such as EVD, Covid-19, MERS (Middle East Respiratory Syndrome), SARS (Severe Acute Respiratory Syndrome)) alert us regarding some of our human behaviors. Indeed, according to the report of the United Nations Environment Programme and International Livestock Research Institute, the emergence of zoonotic diseases is caused by seven main drivers, and these are related to human activities (anthropogenic) (163). These drivers are: an increasing demand for animal protein (which is accompanied by significant growths in population), the unsustainable agricultural intensification (linked to the increase of animal protein demand and which results in a large numbers of genetically similar animals, thus resulting in a greater vulnerability to infections compared with genetically diverse populations), an increasing use and exploitation of wildlife (including the consumption of wild meat), the unsustainable utilization of natural resources accelerated by urbanization, land use change and extractive industries (for example through deforestation and the creation of irrigation systems), travel and transportation (diseases can move around the world in shorter period of time than their incubation periods), changes in food supply chains (including: an increased demand for animal-based food, new markets for wild foods, and poorly regulated agricultural intensification), and climate change (many zoonoses are climate sensitive, and the extinction of some host animals results in the loss of their population-moderating effects or in the establishment of other species) (163).

In order to reduce the risk of the emergence of future epidemics, it is therefore necessary to act on these seven aspects on an individual, societal, and global level. To achieve this, it would be interesting to consider in our policies and behavior that our health depends on the health of the environment in which we live (including the health of animal and plant species) (163). It is now high time to enhance awareness, empowerment, capacity buildings, mutual aid, solidarity, good (environmental) governance, but also resilience (allowing to withstand future epidemics impacts), in order to protect ourselves and above all, to best protect our environment (inhabited by the plant and animal world).

5 Conclusion

Ebola virus disease may result in acute haemorrhagic fever with an elevated case-fatality rate in humans (up to 90%). The world's second largest Ebola Virus Disease (EVD) outbreak took place in North Kivu, and Ituri Provinces (in the Democratic Republic of Congo (DRC)). This EVD outbreak is the first happening in a conflict zone, for which the adopted strategy was ring vaccination from the start. Mathematical models on infectious disease allow for a better understanding of the communicable diseases spread. This is why, I modelled the 2018-2020 North Kivu and Ituri outbreak, and found that the implementation of control measures reduced greatly the magnitude of the epidemic. Ebola virus disease, such as Corona virus disease 2019 are zoonotic disease. The emergence of zoonotic diseases outbreaks is strongly influenced by human activity. As the emergence and the spread of zoonotic diseases epidemics are strongly influenced by human behaviour, it is all the more interesting to study them from the perspective of mathematical models in order to better understand their spread and to define the necessary actions to put in place as a way to better prevent and control them.

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Annexe

R-Codes

Model R-Codes

Model R-codes were adapted from the Alhtaus' R-codes which can be directly downloaded from GitHub (<https://github.com/calthaus/Ebola>)

Necessary libraries

```
library(deSolve)
library(chron)
library(bbmle)
library(stats4)
library(MASS)
library(mvtnorm)
library(tidyverse)
```

Read the data file

```
Data_Base_Ebola_NK_2018_2020$Date<-
chron(as.character(Data_Base_Ebola_NK_2018_2020$Date),format=c(dates = "y-m-
d"))
```

Definition of the intervention function

```
exponential <- function(t,beta0,k,tau1) {
  if(t < tau1) {
    beta <- beta0
  } else {
    beta <- beta0*exp(-k*(t-tau1))
  }
  return(beta)
}
Exponential <- Vectorize(exponential, vectorize.args = 't')
```

Definition of the SEIR model

```
SEIR <- function(t, x, parms){
  with(as.list(c(parms,x)),{
    beta<- exponential(t,beta0,k,tau1)
    N <- S + E + I + R
    dS <- - beta*S*I/N
    dE <- beta*S*I/N - sigma*E
    dI <- sigma*E - gamma*I
    dR <- (1-f)*gamma*I
    dD <- f*gamma*I
    dC <- sigma*E
    der <- c(dS,dE,dI,dR,dD,dC)
    list(der)
  })
}
```

```

# Negative log-likelihood
nll <- function(beta0,k,f,tau0,tau1,sigma,gamma) {
  pars <- c(beta0=beta0,k=k,f=f,tau0=tau0,tau1=tau1,sigma=sigma,gamma=gamma)
  pars <- trans(pars)
  times <- c(0,data$times+pars["tau0"])
  simulation <- as.data.frame(ode(init,times,SEIR,parms=pars))
  simulation <- simulation[-1,]
  ll <- sum(dpois(data$cases,simulation$C,log=TRUE)) +
  sum(dpois(data$deaths,simulation$D,log=TRUE))
  return(-ll)
}

# Parameter transformation
trans <- function(pars) {
  pars["beta0"] <- exp(pars["beta0"])
  pars["f"] <- plogis(pars["f"])
  pars["k"] <- exp(pars["k"])
  pars["tau0"] <- exp(pars["tau0"])
  return(pars)
}

# North Kivu and Ituri: Prepare the data, set the initial values and fit the model
data <-
na.omit(Data_Base_Ebola_NK_2018_2020[c("Date","total_cases","total_deaths")])
names(data) <- c("times","cases","deaths")
begin <- chron("18-04-30", format=c(dates = "y-m-d"))
delay <- as.numeric(data$times[1] - begin)
data$times <- data$times - data$times[1]
N <- 12000000
init <- c(S = N - 1, E = 0, I = 1, R = 0, D = 0, C = 1)
fixed <- c( sigma = 1/7, gamma = 1/9.8,f = qlogis(2319/3512), tau1=90)
free<- c(beta0 = log(0.6),k=log(0.001), tau0=log(0.1))
fit <- mle2(nll,start=as.list(free),fixed=as.list(fixed),method="Nelder-
Mead",control=list(maxit=1e3))
fit
trans(coef(fit))
as.list(trans(coef(fit)))$beta0/ as.list(trans(coef(fit)))$gamma
stdEr(fit)

# Parameter sampling (for CIs and prediction interval)
n_sim <- 1e4
m <- coef(fit,exclude.fixed=TRUE)
sigma <- vcov(fit)
sim_coef <- data.frame(rmvnorm(n_sim, mean = m, sigma = sigma))
sim_coef

```

```

# Timepoints
pars <- trans(coef(fit))
end <- chron("20-06-25", format=c(dates = "y-m-d"))
months <- chron(c("18-06-15", "18-09-15", "18-12-15", "19-03-15", "19-06-15", "19-
09-15", "19-12-15", "20-03-15", "20-06-15"), format=c(dates = "y-m-d"))
weeks <- seq.dates(from = chron("18-04-30", format = c(dates = "y-m-d")), to =
chron("20-06-25", format = c(dates = "y-m-d")), by = 14)
timepoints <- seq(0,end-begin,1)

# Plot the daily incidence and cumulative number of new cases and deaths
par(mfrow=c(2,2))

# Simulations
mod_sim_C_Cum <- numeric()
mod_sim_D_Cum <- numeric()
obs_sim_C_Cum <- numeric()
obs_sim_D_Cum <- numeric()
for(i in 1:n_sim) {
  pars <- trans(c(unlist(sim_coef[i,]),fixed))
  simulation <- as.data.frame(ode(init,timepoints,SEIR,parms=pars))
  mod_sim_C_Cum <- cbind(mod_sim_C_Cum, simulation$C)
  mod_sim_D_Cum <- cbind(mod_sim_D_Cum, simulation$D)
  obs_sim_dC <- rpois(length(timepoints) - 1, lambda = diff(simulation$C))
  obs_sim_dD <- rpois(length(timepoints) - 1, lambda = diff(simulation$D))
  obs_sim_C_Cum <- cbind(obs_sim_C_Cum, cumsum(c(0, obs_sim_dC)))
  obs_sim_D_Cum <- cbind(obs_sim_D_Cum, cumsum(c(0, obs_sim_dD)))
}

# Calculate the point-wise quantiles to construct an approximate 95% CI and a 95%
prediction interval (cases).
mod_sim <- mod_sim_C_Cum
obs_sim <- obs_sim_C_Cum
x_grid <- timepoints
mod_q <- apply(mod_sim, MAR = 1, FUN = quantile, probs = c(0.05, 0.95))
obs_q <- apply(obs_sim, MAR = 1, FUN = quantile, probs = c(0.05, 0.95))
simulation <- as.data.frame(ode(init,x_grid,SEIR,parms=trans(coef(fit))))
plot(x_grid, mod_q[2,], ylim = c(0,4000), ty="l", lty=2, lwd = 1, col = "red",
xlab=NA, ylab="Cumulative number of cases",frame=FALSE,axes=FALSE)
axis(1, weeks - begin, weeks)
axis(2)
polygon(x = c(x_grid, rev(x_grid)), y = c(obs_q[1,], rev(obs_q[2,])), col = rgb(1, 0, 0,
alpha=0.2), border = NA)
lines(x_grid, mod_q[1,], lty = 2, lwd = 1, col = "red")
lines(x_grid, simulation$C, lwd = 1, col = "red")
points(data$times[1:728],(data$cases)[1:728],col="red")

```

```

mod_sim <- mod_sim_D_Cum
obs_sim <- obs_sim_D_Cum
x_grid <- timepoints
mod_q <- apply(mod_sim, MAR = 1, FUN = quantile, probs = c(0.05, 0.95))
obs_q <- apply(obs_sim, MAR = 1, FUN = quantile, probs = c(0.05, 0.95))
plot(x_grid, mod_q[2,], ylim = c(0,2500), ty="l", lty=2, lwd = 1, xlab=NA,
ylab="Cumulative number of deaths",frame=FALSE,axes=FALSE)
axis(1, weeks - begin, weeks)
axis(2)
polygon(x = c(x_grid, rev(x_grid)), y = c(obs_q[1,], rev(obs_q[2,])), col = grey(0.7,
alpha=0.5), border = NA)
lines(x_grid, mod_q[1,], lty = 2, lwd = 1)
lines(x_grid, simulation$D, lwd = 1)
points(data$times[1:728],(data$deaths)[1:728],pch=0)

```

```

# Calculate the effective reproduction number vs time (including approximate pointwise CI)
beta <- function(t, pars) Exponential(t, pars[["beta0"]],pars[["k"]],pars[["tau1"]])

```

```

pars <- trans(coef(fit))
Re <- beta(timepoints, pars) / pars[["gamma"]]
Re_sim <- numeric()
for(i in 1:n_sim) {
  pars_i <- trans(c(unlist(sim_coef[i,]), fixed))
  Re_i <- beta(timepoints, pars_i) / pars_i[["gamma"]]
  Re_sim <- cbind(Re_sim, Re_i)
}
Re_q <- apply(Re_sim, MAR = 1, FUN = quantile, probs = c(0.05, 0.95))

```

```

# Plot the effective reproduction number

```

```

par(mfrow=c(1,1))
control <- min(which(Re<1)) - 1.5
control_l <- min(which(Re_q[1,]<1)) - 1.5
control_u <- min(which(Re_q[2,]<1)) - 1.5
plot(timepoints,Re,type="n",col="blue",ylim=c(0,4),xlab=NA,ylab=bquote("Effective
reproduction number " ~ italic("R"["0"])),axes=FALSE,frame=FALSE)
polygon(x = c(timepoints, rev(timepoints)), y = c(Re_q[1,], rev(Re_q[2,])), col =
rgb(0, 0, 1, alpha=0.2), border = NA)
lines(timepoints, Re, col = "blue")
lines(timepoints, Re_q[1,], col = 'blue', lty = 2)
lines(timepoints, Re_q[2,], col = 'blue', lty = 2)
axis(1, weeks - begin, weeks)
axis(2, 0:16)
lines(c(0,control),c(1,1))
lines(c(control,control),c(0,1))
points(control,1,pch=19)

```

```

# Plot outbreak probability as a function of R0
x_grid <- seq(1, 16, 0.01)
plot(x_grid, 1 - 1/x_grid, type = 'n', ylim = c(0, 1), xlab=bquote("Basic reproduction
number " ~ italic("R")["0"]),ylab="Probability of outbreak from a single
case",frame=FALSE,axes=FALSE)
axis(1,seq(1,16,3),seq(1,16,3))
axis(2)
countrie <- c("North Kivu & Ituri Ebola outbreak")
R0 <- c(Re[1])
polygon(x = c(1,Re_q[1, 1],Re_q[1, 1],Re_q[2, 1],Re_q[2, 1],1), y = c(1 - 1/Re_q[1,
1],1 - 1/Re_q[1, 1],0,0,1 - 1/Re_q[2, 1],1 - 1/Re_q[2, 1]), col = grey(0.7, alpha=0.5),
border = NA)
lines(x_grid, 1 - 1/x_grid)
lines(c(Re[1],Re[1]),c(0,0.79))
lines(c(1,Re[1]),c(1-1/Re[1],1-1/Re[1]))
lines(c(Re_q[1, 1],Re_q[1, 1]),c(0,1-1/Re_q[1, 1]), lty = 2)
lines(c(Re_q[2, 1],Re_q[2, 1]),c(0,1-1/Re_q[2, 1]), lty = 2)
lines(c(1,Re_q[1, 1]),c(1-1/Re_q[1, 1],1-1/Re_q[1, 1]), lty = 2)
lines(c(1,Re_q[2, 1]),c(1-1/Re_q[2, 1],1-1/Re_q[2, 1]), lty = 2)
points(R0,1-1/R0,pch=19,col="red")
text(R0,1-1/R0,countrie,pos=c(4,2,4,1),cex=0.7)

```

##SEIRD graph

```

# Definition of the SEIR model
SEIR <- function(t, x, parms){
  with(as.list(c(parms,x)),{
    dS <- - beta*S*I/N
    dE <- beta*S*I/N - sigma*E
    dI <- sigma*E - gamma*I
    dR <- (1-f)*gamma*I
    dD <- f*gamma*I
    return(list(c(dS, dE, dI, dR, dD)))
  })
}

# Set parameters

# Proportion in each compartment:
init <- init <- c(S = 11999999, E = 0, I = 1, R = 0, D = 0)

# Parameters
parameters <- c(beta = 0.162072291, gamma = 0.10204, f = 0.66, sigma=0.142857)

# Time frame
times <- seq(0, 1000, by = 1)

# Solve using ode (General Solver for Ordinary Differential Equations)
out <- ode(y = init, times = times, func = SEIR, parms = parameters)

```

```

# Change to data frame
  out <- as.data.frame(out)

# Delete time variable
  out$time <- NULL

# Show data
  head(out, 10)

# Plot
  matplot(x = times, y = out, type = "l",
    xlab = "Time", ylab = "Number of people", main = "SEIRD Model",
    lwd = 2, lty = 1, bty = "l", col = 1:5)
  legend("topright", col=1:5, legend=c("S","E","I","R","D"), lwd=2)

## Daily incidence of EVD cases and deaths
  library('incidence')

# Read the data file
  Data_Base_Ebola_NK_2018_2020$Date<-
  chron(as.character(Data_Base_Ebola_NK_2018_2020$Date),format=c(dates = "y-m-
  d"))

  data <- (Data_Base_Ebola_NK_2018_2020[c("Cases","Deaths")])
  names(data) <- c("New Cases","New Deaths")

  Data_Base_Ebola_NK_2018_2020$Date <- c("18-04-30", "18-06-15", "18-09-
  15", "18-12-15", "19-03-15", "19-06-15", "19-09-15", "19-12-15", "20-03-15", "20-06-
  15", "20-06-25")
  as.Date(Data_Base_Ebola_NK_2018_2020$Date, "%y/%m/%d")

# replace NA with 0
  data[is.na(data)] <- 0

# convert pre-computed incidence in data.frame into incidence object
  incidence <- as.incidence(x = data, dates =
  as.Date(Data_Base_Ebola_NK_2018_2020$Date))

# plot incidence
  plot(incidence) + my_theme + theme(legend.position = c(0.9, 0.7))

```