A simulation model of an Ebola epidemic to investigate the effectiveness of intervention strategies

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Declaration

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Abstract

A significant increase in the number of lives lost and material damages were seen in the past decade caused by natural and man-made disasters. The complex and dynamic environment of a disaster response effort demands agility and adaptability which could only be achieved with adequate preparation and strategic planning. In this project, simulation modelling is applied to the Ebola epidemic disaster of late 2014 in Sierra Leone to study the effectiveness of intervention strategies. Given financial and logistical constraints the most effective intervention strategy or combination of strategies should be implemented to minimise the number of infected individuals at a minimum cost. The impact of four intervention strategies used during the epidemic namely, contact tracing, quarantine, safe burials, and vaccination, are evaluated. A metapopulation modelling approach is followed whereby a group of spatially separated populations interact through migrating individuals. A compartmental model consisting of a set of difference equations is used to model the spread of Ebola within each local population. A proportion of individuals in each local population move to other local populations. This spatial representation is used to gain better insight on how spatial interaction of individuals in neighbouring regions in a country affect the efficiency of intervention strategies. With the ability to test various intervention strategies, an effective combination of intervention strategies may be found that has the greatest impact on the spread of the disease. The results may impact the design and implementation of future intervention strategies.

Uittreksel

'n Beduidende toename in die aantal lewens wat verlore gegaan, asook en materiële skade as gevolg van beide natuur- en mensgemaakte rampe is gedurende die afgelope dekade waargeneem. Die implementering van 'n intervensiestrategie in die ingewikkelde en dinamiese omgewing van 'n ramp vereis 'n hoë aanpasbaarheidsvermoë wat slegs bereik kan word met voldoende voorbereiding en strategiese beplanning. In hierdie projek word 'n simulasiemodel geformuleer om die doeltreffendheid van intervensiestrategieë op die Ebola epidemie van laat 2014 in Sierra Leone te bestudeer. Gegewe finansiële en logistieke beperkings moet die effektiefste intervensiestrategie of kombinasie van strategieë geïmplementeer word om die aantal besmette individue te minimeer teen die laagste moontlike koste. Die impak van vier intervensiestrategieë wat tydens die epidemie gebruik was, naamlik kontakopsporing, kwarantyn, veilige begrafnismetodes en inenting, word ondersoek. 'n Metapopulasie modelleringsbenadering word gevolg waarin 'n groep aparte populasies met mekaar in wisselwerking is. 'n Kompartementele model wat beskryf word deur 'n stel verskilvergelykings word gebruik om die verspreiding van Ebola binne elke plaaslike populasie te modelleer. 'n Deel van die individue in elke plaaslike bevolking migreer na ander plaaslike bevolkingsgroepe. Hierdie ruimtelike voorstelling word gebruik om 'n beter insig te kry oor hoe ruimtelike interaksie van individue in naburige streke in 'n land die effektiwiteit van intervensiestrategieë beïnvloed. Met die vermoë om verskillende intervensiestrategieë te toets, kan 'n effektiewe kombinasie van intervensiestrategieë gevind word wat die grootste invloed op die verspreiding van die siekte het. Die resultate kan die ontwerp en implementering van toekomstige intervensiestrategieë beïnvloed.

Contents

List of Reserved Symbols

Symbol	Description
$S_{i,t}$	Size of the susceptible subpopulation of spatial region i at time t
$E_{i,t}$	Size of the exposed subpopulation of spatial region i at time t
$I_{i,t}$	Size of the infected subpopulation of spatial region i at time t
$Q_{i,t}$	Size of the quarantined subpopulation of spatial region i at time t
$R_{i,t}$	Size of the recovered subpopulation of spatial region i at time t
$D_{i,t}$	Size of the death subpopulation of spatial region i at time t
$B_{i,t}$	Size of the buried subpopulation of spatial region i at time t
$N_{i,t}$	Size of the total subpopulation of spatial region i at time t
β_1	Exposure rate within communities
β_2	Exposure rate due to unsafe funeral practises
δ	Symbol used to denote the infection rate
γ_I	Recovery rate of infected individuals
μ_I	Death rate of infected individuals
f_1	Proportion of exposed individuals quarantine
f_2	Proportion of infected individuals quarantine
f_3	Proportion of infected individuals resulting in death
f_4	Proportion of quarantined individuals resulting in death
q_E	Quarantine rate of exposed individuals
q_I	Quarantine rate of infected individuals
γ_Q	Recovery rate of quarantined individuals
μ_Q	Death rate of quarantined individuals
v	Vaccination rate
r_{ij}	Proportion of individuals moving from county i to county j

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CHAPTER 1

Introduction

Contents

Classified as one of the world's most contagious viruses to date, Ebola has claimed thousands of lives in a series of outbreaks in Africa [101]. Sierra Leone had the highest number of cases during the West African outbreak in 2014. The World Health Organisation (WHO) reported 14 124 confirmed, probable and susceptible cases and 3 956 deaths from March 2014 [101]. The weak state of Sierra Leone's health system prevented the government to mount a robust response. International and humanitarian aid were slow to respond to the alert of Médecins Sans Frontiéres (MSF), who realised the severity of the threat early on. The initial response was characterised by confusion, chaos and denial. Due to the a lack of knowledge and understanding of the disaster's dynamics and planning intervention efforts accordingly, the Ebola virus disease led to a public health emergency of international concern.

1.1 Humanitarian crisis

A humanitarian crisis is defined as an occurrence of a single event or series of events causing damages to the health, safety and well-being of a community or a large population [79]. Humanitarian crises are classified as either natural disasters, man-made disasters or complex emergencies, that prevent a population from satisfying their fundamental need for food, clean water and shelter [38]. Military conflicts, epidemics, famine, floods, earthquakes and hurricanes

are examples of disasters that led to humanitarian crises. As a result of these life threatening events large populations are displaced, leading to refugee crises, economical and political downfalls and other secondary setbacks.

Generally spanning over a large land area, a humanitarian crisis could be a result of internal or external causes. Local, national and international responses are necessary, due to the scale of disorder caused by these events. Several national and international agencies are required to collaborate in response to the havoc caused. For each humanitarian crisis, a unique response is required depending on the various factors that cause the crisis. Both short-term and long-term damages have to be considered. The Ebola outbreak of late 2014 threatened the health, safety and well-being of the West-African population, resulting in a humanitarian crisis demanding a timely emergency response from national and international parties.

1.2 Humanitarian logistics

A significant increase in the number of lives lost and material damages were seen in the past decade caused by natural and man-made disasters. Since 1997 the number of natural disasters has doubled to an average of 329 events per year within the last 20 years [28]. In 2017 alone, 335 disasters Killed 9,697 and affected over 95.6 million people, with a total cost of US $335 billion [27]. These numbers are expected to increase fivefold in the next 50 years [7]. The exponential growth in disaster trends and the great demand for global relief efforts has brought valuable attention to the evaluation of disaster response operations.

The primary aim of disaster response efforts is to provide relief to large-scale emergency areas to minimise the number of human suffering and death [17]. Achieving an effective and efficient response is dependant on the design and operation of the relief chain. Each response should be uniquely tailored to the characteristics of the disaster at hand. Management of the logistics of a potential response is the first step in preparing for an effective relief response.

The use of the term ‘logistics’ varies according to the organisation and people to which it applies. Military operations logistics refers to the sustaining of military operation and bridging the gap between strategic logistics and tactical logistics [5]. The business sector relies on logistics as a planning framework to manage material, services, information and capital flow, and it is the cornerstone of the increasingly complex information and communication systems of the everyday business environment [86]. Disaster logistics is defined by humanitarian organisations such as Medicines Sans Frontiers (MSF) and the World Food Program (WFP) as the combination of planning, implementing and controlling efficient and cost effective flow of information and material goods from point of origin to point of consumption with the primary focus of meeting the demand of the beneficiaries [7]. Humanitarian agencies face a large number of operational challenges as they respond to disasters and may be argued to be one of the most dynamic and complex systems in the world [7]. Coordinating processes, technologies, and communication capabilities are ways in which logistical preparation is done before a disaster strikes, improving the efficiency and effectivity of the supply chain and in effect improving the response.

Various challenges arise in the complex and dynamic environment of a disaster response effort, demanding agility and adaptability which can only be achieved with adequate preparations or prepositioning of infrastructure for the appropriate capacity and resources. Reviewing previous response efforts provides valuable information to overcome future challenges. One of the most valuable lessons learnt from previous disaster response efforts is the vital impact of collaboration between various stakeholders, both internal and external to the system - military and civilian, private sector and non-profit organizations - to determine the successful execution of a well-

planned response strategy. Without such collaboration human relief operations would be derailed by the multiple set of agents and governments [7].

1.3 Ebola virus disease

Over the course of 40 years, Ebola, also referred to as Ebola haemorrhagic fever, has claimed more than 12 000 lives globally [24]. Ebola was first discovered in 1976 with a simultaneous outbreak in both Nzara, South Sudan and Yambuku, Democratic Republic of Congo (DRC) [98]. The virus was named after a small river in the north west of the DRC where the first outbreak was documented. Various African countries such as Guinea, Liberia, Gabon, Mali, Nigeria and Senegal, have experienced the disease periodically emerging [24]. The DRC has experienced ten outbreaks over the course of 40 years with a recent death toll of 1 866 reported by the MSF on the 6th of August 2019 [57]. This was the DRC's largest outbreak to date and the second largest Ebola outbreak recorded [57].

The Ebola outbreak of 2014-2016 in West Africa was documented as the largest and most complex outbreak to date, with more cases and deaths compared to all other Ebola outbreaks [98]. The number of recorded cases was found to be 28 616 by October 2015, although the true figure is said to be two to three times more [98]. With the virus killing 25% to 90% of exposed individuals, communities feared greatly the possibility of becoming infected.

The disease is frequently misdiagnosed or goes undetected due to a latent phase where individuals are exposed to the virus without any major symptoms present. The latent phase is argued to be one of the reasons for the exponential growth rate in Ebola cases [30]. A lack in prior knowledge of the disease may also have contributed to the exponential growth in the number of Ebola cases. West African burial purification rituals may have been a heightening factor contributing to the transmission of the disease, as family members would cleanse the deceased bodies from all food and organs with their bare hands. The disease is transferred through bodily fluids, infected blood and contaminated meat, which makes the deceased body a considerable health hazard for susceptible individuals. In an attempt to prevent the unsafe burial ceremonies, WHO mobilized more than 200 burial teams to carry out safe burials [103].

Considerable attention was focussed on preventing the epidemic from spreading to neighbouring countries or international soil. The attempts to contain the spread of the disease are in principle straightforward, such as earnestly tracing any person who made contact with an infected individual and the use of protective equipment for healthcare takers. However, with limited resources and the supplementary added fear of an epidemic, implementing such interventions are far from simple.

1.3.1 Biology

Ebola is part of the Filovirus family. The Ebola virus has five different strains, namely Zaire, Sudan, Cote d'Ivore, Bundibugyo (Uganda) and Reston [34, 98]. Of these five species the Zaire virus is seen as the most dangerous with a fatality rate of 60%-90%, the primary cause of most of the recorded outbreaks, and also the cause of the high fatality rate in the West African outbreak of 2014 [34, 98].

The first case of Ebola was a 18 month old boy infected by a fruit bat that was of the Pteropodidale family and is thought of as the natural host of the Ebola virus [101]. The WHO has identified cases of animal to human transmission through the handling of contaminated bush

meat. Gorillas, monkeys, chimpanzees, porcupines, fruit bats and forest antelopes are all confirmed as carriers of the disease while also being food sources for many in the West African region [101]. Transmission amongst humans occur through direct contact of broken skin or secretion, organs, blood and other bodily fluids of an infected individual. Contaminated clothing, bedding and other surfaces can also led to exposure of the disease [101]. Healthcare workers have a higher risk of becoming infected due to their close contact treatment methods for infected Ebola patients. With traditional burial ceremonies, family members have direct contact with the deceased body which significantly adds to the transmission factors of the disease. The virus is also found in the semen of human males [1]. Only after two negative tests three months after onset of the disease should the male continue with normal sexual practice without fear of virus transmission [101].

Ebola has four different states in which individuals could be classified, namely susceptible, exposed, infected and with the fourth state divided into recovered or deceased.states. The exposed state is referred to as the incubation period, where individuals have been exposed to the virus but have not yet shown any symptoms. Susceptible individuals are not at risk of becoming infected by individuals in the exposed state, since the individuals in this state are not yet infectious. Only after developing symptoms do individuals become infectious and move into the infected phase of the disease. The incubation time, also known as the latent time, is between 2 to 21 days where the symptoms are not yet visible [9]. Individuals are removed from the disease progression either due to death or recovery of the disease. In Figure 1.1, the various phases of the disease are illustrated.

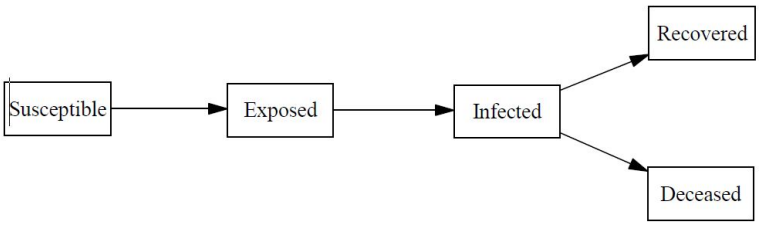

FIGURE 1.1: Representation of the phases of Ebola.

The first symptoms are muscle pain, fatigue, fever, sore throat and headache. Thereafter, diarrhoea, vomiting, symptoms of impaired kidneys and liver function, skin rash and in some cases both internal and external bleeding may follow [62]. Ebola, Typhoid fever, Meningitis and Malaria share these same symptoms, making it difficult to distinguish between them at first, but confirmation is provided when a sample is subjected to an antibody-capture enzyme-linked immunosorbent assay (ELISA), antigen-capture detection tests and serum neutralization tests [94]. Extreme biological containment precautions are taken during these tests as these samples are highly contagious.

Currently no proven treatment for Ebola is available [22, 30]. Control strategies are therefore mainly focused on stopping the transmission instead of the treatment of the disease [30]. Basic treatments, if used early, could significantly improve chances of recovery. Symptoms are treated as they appear with oral or intravenous re-hydration, oxygen therapy and medication to control blood pressure, vomiting, diarrhea and other infections [22]. Patients who do recover have an immunity of at least 10 years [22]. Joint and vision problems may be long term complications occurring within survivors of Ebola [22].

Two potential vaccinations were on trial during the Guinea outbreak in 2015, namely the recombinant adenovirus type-5 Ebola vaccine and the rVSV-ZEBOV (the ring vaccine). The ring vaccine is not yet licensed but has been approved for compassionate use since there is no other alternative. It has been proven to be sufficiently safe and effective [100]. The ring vaccination was shown to be highly effective in the prevention of Ebola in a trial in Guinea, and was said to be a new and essential tool in the control of Ebola epidemic by the WHO Assistant Director-General, Dr Michael Ryan [100]. Since May 2018, the vaccine has been distributed amongst family members, friends who came into contact with an infected Ebola patient, Ebola healthcare workers and frontline responders in the DRC [100]. Further research on the safety of the vaccines on populations such as children and people with HIV are in progress.

1.3.2 Intervention strategies

Critical management and public policy challenges arise with infectious disease outbreaks such as Ebola. Through the years, intervention strategies were trailed to the state of successful implementation. A combination of strategies has been proven to be most successful in preventing an epidemic, though the implementation of the best possible intervention strategies could be hindered by the economic, social and cultural status of a community [101]. Without an immediate treatment for Ebola, response teams are required to rely on various other methods to control the outbreak. These methods include contact tracing, quarantine, vaccinations, specific symptom treatment, safe burials and educational and awareness campaigns.

Quarantine, also known as isolation, is the removal of a potentially or already infected individual from his or her environment to prevent further infections to the persons with which they come in contact. Quarantine is one of the most well-known and frequently implemented non-pharmaceutical strategies used to control an epidemic. The WHO's Infection Prevention and Control (IPC) guidance summary states that a person should be assigned to a single room with minimum contact with other individuals [94]. Challenges that arise with this control strategy include limited available space to set up for each patient to have an isolated room or area, as well as the violation of human rights by placing someone in quarantine [48]. Quarantine has been implemented worldwide as an intervention strategy to control the outbreak of viruses such as smallpox, influenza and severe acute respiratory syndrome corona-virus [37]. According to Lisa Sattenspiel, a researcher at University of Missouri, quarantine had a significant effect on the containment of the 1918-19 flu epidemic in Canada [71]. Simulations showed that limited mobility between communities altered the disease patterns and appreciably delayed the growth of the epidemic. Sattenspiel also emphasises the importance of introducing quarantine measures at the appropriate time [71]. For the Ebola outbreak in West Africa, hospitalisation was used as a quarantine measure, where infected patients could be monitored closely with limited human interaction.

Surveillance teams who are mobilised in the attempt to trace all people with whom an infected individual has come in contact with is referred to as contact tracing. By tracing all contacts an infected person has made, the number of infected individuals roaming in public domains may be limited. Contact tracing proved in many epidemics to significantly decrease the rate at which an epidemic is growing [37]. In some countries, the logistical challenge of finding all contacts are increased if no national identification system is in place, contacts have no address or are referred to by nicknames. Partial solutions to these difficulties included engaging community leaders for help in finding individuals [98]. A combination of contact tracing and quarantine was simulated by Christopher Fraser from the Imperial College in the United Kingdom, to assess the effect

of this strategy combination on diseases with high R_0 values[1] [37]. He found the combination to effectively control the smallpox pandemic with a realistic assumption made towards size of the proportion of transmission that occurs before the onset of symptoms [37]. An attempt was launched by the WHO in the West Africa Ebola outbreak to find those people that each new case individual was in contact with by means of a questionnaire and help of local volunteers. If any individual showed signs of infection, they would immediately be safely transported to an isolation area to prevent further exposure.

With 20% of new Ebola infections caused by cultural rituals during burial ceremonies more than 200 burial teams were appointed to safely bury deceased individuals during the 2014 West African outbreak [102]. Infections occur during these cultural ceremonies as family members touch, wash and distribute the deceased amongst family members while the corpse still contains high levels of Ebola and is extremely contagious [102]. The greatest challenge the burial teams faced was to prove to the families that the situation would be handled with sensitivity and care, allowing family members to safely take part in the process.

Dr Pierre Formenty, one of WHO's top Ebola experts, said: *"By building trust and respect between burial teams, bereaved families and religious groups, we are building trust and safety in the response itself. Introducing components such as inviting the family to be involved in digging the grave and offering options for dry ablution and shrouding will make a significant difference in curbing Ebola transmission."* [95].

Vaccination as a control strategy focuses on preventing infection. Two main vaccination distribution strategies are used, namely mass vaccination or ring vaccination. On the 21st of May 2018 more than 7 500 doses of the trial ring vaccine was deployed to the DRC. The vaccine is still under investigation for full FDA approval and is administered on a voluntary basis. The vaccine is distributed through a ring strategy in which only contacts of an Ebola case is provided with the vaccine. This strategy is therefore greatly dependant on the tracing of individuals who came into contact with an Ebola case. In underdeveloped regions such as the DRC many communities have limited knowledge of vaccines and their use. Introducing a vaccine to such a community should be done with caution and in such a way that their decision will be informed and made with ease [58]. In a simulation study by Rachah *et al.* [65] of the Ebola outbreak in Liberia during 2014 and 2015, vaccination was indicated to reduce the spread of the disease within a short period of time while increasing the number of recovered individuals. An optimal control approach was used to find the period in which the infected curve reached zero. Without vaccination the infection curve reached zero after 90 days, whereas with vaccination the curve reaches zero within 45 days [65]. Vaccination intervention strategies present various logistical challenges. Remote communities are difficult to reach, adding to the complexity of transporting vaccines in controlled temperature units [58].

Another intervention approach is to educate and bring awareness to the public of the risks of the virus. By educating members of the community on how to prevent the contamination of others the infection rate decreases [60]. Fear is the driving force of this strategy since fear causes a society to change its ways [74]. However, this same fear causes people to retract from cooperation with authorities which impedes the success of this approach. Sylvie Diane, a PhD student from Stellenbosch University, found that educational and media campaigns reduce the prevalence of Ebola, but would need to be implemented in combination with other intervention strategies such as quarantine, contact tracing and case identifying to fully control the disease [30]. A shortcoming of Diane's model is the underlying assumption that individuals in different communities would all respond to a media campaign and would therefore led to a decrease

[1] R_0 is known as the reproductive value of a disease. It is described as the rate at which a disease reproduces among individuals.

in contaminations. This is not necessarily a true reflection of reality. By adding a function that represents the behaviour of the individuals after exposure to the media campaign a more accurate representation of reality may be obtained [30]. Educational and awareness campaigns have proven to decrease the number of infected and exposed individuals in the Ebola outbreak of West Africa, as well as showing evidence of behaviour change in the susceptible population, such as cooking animal meat more thoroughly, performing safer funeral ceremonies and training and equipping healthcare workers better [60].

These are the primary intervention strategies implemented during an Ebola outbreak in addition to providing household protection kits. It was found that a combination of these strategies proved to be most effective, though still dependant on the social, economic and cultural status of the community [30, 37].

1.3.3 WHO interventions

Numerous attempts at intervention strategies have been made to successfully contain Ebola in West Africa, including vaccine development, quarantine, contact tracing and awareness campaigns. According to the WHO, a package or combination of intervention strategies may prove to be more successful than single intervention strategies. For example, safe burials, surveillance and contact tracing, case management, good laboratory service and community mobilization may all be used together as an integrated intervention strategy [98]. Deciding on an integrated intervention strategy for any given community strongly depends on its economic, social and cultural status. It may be noted that for countries with limited resources, including most West African countries, the best possible intervention scenario may be inadequate for efficient outbreak control. The WHO views strategies for prevention and control of epidemics such as Ebola to comprise of the following four phases:

1. Pre-epidemic preparedness

Surveillance systems to identify Ebola cases are setup and collaboration with wildlife mortality surveillance are set in place to receive early warning triggers as animal Ebola virus outbreaks usually precede human outbreaks. Standard infection control precautions are reinforced. Avoiding direct contact with blood and/or body fluids is deemed as the minimum level of infection prevention precautions in the treatment and care of all patients. In this phase the public should also be prepared for risk of infections by educational campaigns on preventing infection measures such as hand washing [94].

2. Alert phase

In the case of a suspected outbreak through surveillance systems reports, a team with the necessary protective equipment is immediately sent to investigate the situation. An epidemiological evaluation is launched to calculate the risk, gather samples and send it to the national laboratory. While waiting upon the results, initial control measures are implemented [94].

3. Outbreak response and containment operations

After an Ebola outbreak has been confirmed, various teams will implement a multi-sectoral action which involves coordinating prevention and containment attempts and distribution of resources. Surveillance systems are set up in pursuit of active cases. Encouragement of social and behavioural interventions aimed to alert the public of transmission of the virus, whereas clinical conduct consists of isolation area establishment, safe transport of patients, performance of safe burials and psychosocial support for health workers, patients and families. This phase is also adapted or strengthened where needed [94].

4. Post-epidemic phase

After 42 days without a new Ebola case reported, health authorities announce an epidemic free state. Pre-epidemic interventions are resumed in an attempt to prevent relapse, with the added task of keeping survivors under surveillance for any complications or degeneration [94].

1.4 Ebola virus disease in Sierra Leone

Sierra Leone experienced a slow and silent start to the Ebola epidemic, with initial cases identified in March 2014, but without further investigation. A sudden burst of cases were identified late May and early June, whereafter an exponential increase was experienced leading up to a peak of 6 987 cases in September [23]. Being one of the poorest countries in the world and emerging from a civil war, Sierra Leone was left with a weak healthcare system and severely damaged infrastructures unfit to contend with the severity of an Ebola epidemic, having one to two doctors per nearly 10 000 people [96]. Weak transportation systems, communication services and a lack in healthcare personnel led to the national emergency.

The first identified case was identified as woman returning from an infected host family in Gueckedou, Guinea. Short after her return she passed away, but her death was never investigated nor reported. An increase in vigilance was experienced as members of the same infected family from Guinea arrived for the funeral. A retrospective report classifies this as the first Ebola case of Sierra Leone [96]. The number of cases increased gradually leading to a sudden spike in late May. The source of the spike was traced to a funeral of a traditional healer who treated Ebola infected individuals in Sokoma, in the Kailahun district close to the Guinea border. Her death started a chain reaction of more infections, more deaths, more funerals. Epidemiologists identified this single funeral as the cause of 365 confirmed Ebola cases as well as cases identified in Liberia [96].

Kailahun was announced to be in a state of emergency on 12 June 2014, and various public areas such as schools, cinemas and places of night gathering were closed. Vehicle checkpoints were established along the borders of Liberia and Guinea. Kailahun and Kenema were the initial epicentre of the outbreak and was the focal point of WHO and other partner's response strategies. A laboratory and isolation ward initially used for management of Lassa fever was transformed into the treatment centre for Ebola cases identified in Kenema. The number of new patients greatly surpassed the capacity of the ward and services collapsed due to mismanagement [96]. Kenema's government hospital used two of their patient wards as designated Ebola treatment centres. Eight nurses were infected within these wards, causing fear among healthcare workers refusing to work under life-threatening conditions. The number of infected healthcare workers from the district hospital grew to more than 40.

MSF opened the Kailahun Ebola treatment centre on 24 June 2014 with a capacity of 50 beds. Realising the severity of the situation with so many people dying from Ebola, teams were burying more than 50 bodies within 12-day periods [96]. Within the first four weeks of the centre being open more than 90 patients were treated for. WHO established a mobile laboratory to aid in the confirmation of new cases but by mid-July the number of new cases outweighed both the capacity of the treatment centre and the mobile laboratory. Kailahun and Kenema's greatest demand was for more treatment beds and faster laboratory results. In collaboration with the United Nations Population Fund (UNPF), the WHO implemented contact tracing as a response strategy through the mobilisation of hundreds of local volunteers to search for possible cases. Low quality of contact tracing was provided due to the shortage of experienced staff able to supervise. This caused exposures to be missed, under reporting and transmission chains to

continue to multiply.

After the death of Dr Sheik Humarr Khan, Sierra Leon's only expert on haemorrhagic fevers and leader of the Ebola response in Kenema, WHO requested the governments of all three countries, Sierra Leone, Guinea and Liberia, and the international community to provide safety and motivation for healthcare workers through incentive, protection and treatment, ensuring uninterrupted healthcare services [96]. After an epidemiologist working in Kailahun and three staff members of the hotel where foreign medical teams resided became infected in late August, foreign medical staff suspended all healthcare services in Kailahun [96]. An investigation was launched by WHO logisticians and infection prevention experts to identify the reason for medical staff becoming infected. After confirming conditions were safe and confidence was resorted amongst healthcare workers, operations resumed in September.

Crowded household environments caused a rapid increase in the number of cases throughout the Kenema region. Infected residents were left with no other choice but to stay with their susceptible family members due to weak response capacity. Only after a test had confirmed an individual as infected were they moved to a treatment centre. These confirmation tests could take up to four days, resulting in many more infections within the household. The spread of the disease within a household was rapid as five or six children would commonly share a mattress [96]. After observing the high risk of becoming infected while placed in confined spaces and isolation wards with at least one infected individual, village leaders requested a safe environment where uninfected family members, waiting on confirmation test results, could reside as a measure of self-isolation. These tents were administered by WHO, the international Federation of Red Cross and Red Crescent Societies as a means to create spaces where a safe distance could be kept from infected individuals. This community initiated innovation had a small yet significant impact on the overall outbreak. No new cases were observed from household contact where confirmed cases chose to self-isolate [96]. Authorities and response teams learnt a valuable lesson, to listen to the community as they know their needs and would be more willing to receive and implement response strategies if they are included in the planning thereof [96].

On 23 June 2014 the first case in the capital of Sierra Leone, Freetown, was reported to the WHO. With a slow onset of cases, infected individuals from both Freetown and Port Loko districts were transported to Kenema for treatment. Kenema and Kailahun remained the districts with the most number of cases throughout July and August due to the high transmission rate [96]. A national state of emergency was declared on the 8 August, with military enforced quarantine. By August, anyone who was found hiding an infected individual or dead body could receive a jail sentence of up to two years. A cumulative total of 1 026 cases were reported in Sierra Leone by the end of August, with 648 in Guinea and 1 378 in Liberia. As the virus exponentially spread through Freetown's population of 1 055 964, it became the epicentre of the outbreak in early September, with more than 30 bodies per day [96]. Due to a overwhelmed treatment centre in Kenema, South Africa deployed a mobile laboratory and soon thereafter began construction on a treatment centre in Freetown. Kenema and Kailahun were able to stabilise the situation, though the epidemic spread further to Freetown's neighbouring districts, Port Loko, Bombali and Tonkolili. An estimate of 530 additional treatment beds were required with the sharp and alarming spike in cases [96]. The greatest challenge faced in the densely populated capital was the lack in treatment bed capacity and diagnostic facilities, causing difficulties in contact tracing. Households were occupied by more than three families, creating high risk environments that further increased the risk of infection.

At the peak of the epidemic in August 2014, the spread of Ebola was declared as a public health emergency of international concern by the director of the WHO [101]. In Sierra Leone, coordination of the Ebola outbreak control measures was initialised on a national scale on the 8

August 2014 when armed forces established checkpoints to restrict movement of infected areas [69]. International assistance was deployed on the 20th of September 2014, leading to 356 Ebola treatment unit (ETU) beds by the 26th of November 2014 [90]. During June to October, a total of 2 200 patients were admitted to ETU's in Sierra Leone, where 600 patients were confirmed dead due to Ebola [22]. A total of 21 ETU's with over 1 500 beds were planned, though only 19 were built of which two were never functional and many were underutilised by mid-2015 [97]. All outbreak response activities were directed by the incident management system (IMS), contact tracing, surveillance of patients, case identification, laboratory confirmation testing, safe transportation of suspected Ebola patients, quarantine, prevention of infection within the healthcare system, community awareness, and safe burial [61]. Emergency care facilities are complex and required a substantial number of staff and time to set up correctly. By December 2014 the number of ETU beds greatly surpassed the number of new cases per week due to a delay in implementation, resulting in falling behind the epidemic curve [47].

As October approached, no treatment beds were available in Port Loko, and nurses were left without personal protective equipment, food or rehydration fluids to treat patients. The WHO's attempts to provide transportation of patients to treatment facilities, provide food, medicine and protective equipment were futile due to the tremendous demand on an already overwhelmed capacity. By mid-October districts nationwide reported at least one case, with more than 400 new cases per week in Freetown. The state of control of disease transmission in Kenema and Kailahun was temporary as the number of cases began to rise again. In all regions, inadequate bed capacity remained the greatest problem for patients and families. Contact tracing was limited without facilities to receive and safely treat infected individuals, leaving responders without further actions [96]. Response coordinators quickly realised the different control strategies were powerless if not used in conjunction with one another; failure of one threatened the success of the other. Patients desperately requiring some form of treatment led to the establishment of safe isolation units called community care centres. These units were not hospitals but treatment facilities quickly set up in town halls, churches and schools. Sierra Leone was the pioneer of establishing these centres and making them work [96]. A lower level of treatment was provided at these centres compared to that of the Ebola treatment centres, however, patients received essential treatment far greater than the treatment exercised by family members in homes. These community centres met logistical constraints, including poor road systems and patient transportation to distant treatment facilities. Centres allowed patients to remain in the community, providing the opportunity for loved ones to visit patients and interact with them over low fences while keeping a safe distance. The development of the centres made an immediate large-scale difference in the country's care capacity [96].

By early December 2014, Sierra Leone's cumulative number of cases surpassed those of Liberia. More than 400 new cases were reported per week, three times more than Guinea and Liberia combined. The disastrous impact of the disease spreading to the capital cities were seen in all three countries, with Freetown accounting for a third of the country's cases [96]. Port Loko, Western Area Rural (WAR) and Kono districts experienced the highest transmission rate with all of them either having a capital city or neighbouring one. Denial, fear and traditional burials remained the catalyst to the intense transmission experienced throughout Sierra Leone. Contact tracing suffered tremendously with communities reluctant to receive any support or guidance. At the end of December 2014 more than 9000 cases were counted within Sierra Leone's population of 6.2 million. The epidemic endured for two years, as WHO declared Sierra Leone Ebola free on 17 March 2016, with a cumulative of 14 122 cases and 3 955 deaths [96].

1.5 Informal problem description

For a humanitarian relief response to be effective and efficient, the design and operation of the relief chain should be tailored to the unique characteristics of the disaster. Such knowledge may be gained through investigating the implementation and impact of various strategies and policies on a disaster. It is difficult, however, to investigate the effectiveness of single intervention strategies through field experiments within a real world setting where lives are at stake, let alone an effective combination of intervention strategies. Mathematical and simulation modelling may be helpful to investigate changes made to an existing system without altering the system itself. Mathematical and simulation models that take into account the complex and non-linear dynamics of infectious diseases may be helpful in understanding the propagation of the epidemic and the impact of proposed intervention strategies [67]. This would allow for exploration of possible intervention strategies and combinations thereof to be implemented within a disaster's system without putting any lives and/or resources at stake. Gaining insight and a better understanding of an epidemic is the first step towards developing a control strategy.

In this project, simulation modelling is applied to the Ebola epidemic disaster of late 2014 in Sierra Leone to study the development of the epidemic and the effectiveness of intervention strategies in such a setting. Quantifiable guidance and support could be given to policy makers, healthcare workers and the public health community using such models. Four intervention strategies, namely contact tracing, quarantine, ring vaccination and safe burials are considered. Given financial and logistical constraints, the most effective strategies should be implemented that minimises the number of infected individuals. The results may benefit future attempts to control an outbreak of Ebola.

1.6 Scope and objectives

Only the 2014 Ebola outbreak in Sierra Leone and the 14 counties affected are considered in this project. Five species of Ebola have been identified, only the Zaire species responsible for the 2014 West African outbreak will be considered. In addition, only the spread of Ebola among humans will be investigated. Data gathered by the United Nations Office for the Coordination of Humanitarian Affairs (OCHA) from Sierra Leone in the time frame of August 2014 to March 2015 is used.

Various intervention strategies have been implemented in an attempt to control the 2014 West African epidemic. This study will only include four interventions known as quarantine, contact tracing, safe burials and vaccinations.

A population-based approach is followed where the behaviour and movement of specific individuals is not explicitly considered. The spatial dynamics of this problem is limited to modelling the proportion of the population moving between neighbouring counties.

The following objectives are pursued in this thesis:

Objective I: Conduct a literature review on Ebola, various intervention strategies against the virus, their effectiveness towards controlling the outbreak and the spatial interacting dynamics of the affected population.

Objective II: Perform a literature survey of

(i) the various mathematical models previously used to investigate the dynamics of Ebola within a population.

(ii) simulation modelling techniques with the focus on techniques to study the interacting dynamics of a disease outbreak under the influence of intervention strategies.

Objective III: Develop a simulation model that describes the spread of Ebola through a population by

(i) Constructing suitable equations;

(ii) Determining suitable parameter values to sufficiently describe the spread of Ebola in a specific country through model calibration.

This model should be informed by the research done in Objectives I and II.

Objective IV: Validate the simulation model in Objective III by standard model validation principles and guidelines.

Objective V: Perform a sensitivity analysis to gain insight into the contribution of different parameters on the dynamics of a Ebola outbreak.

Objective VI: Apply the model in Objective III to a real-world scenario in order to illustrate how the model may be utilised to provide guidance in the design of a human relief response effort. Ebola outbreak in Sierra Leone of 2014-2015 will be used as the case study epidemic for this project.

Objective VII: Provide possible improvements or additions to the model as well as future studies that may stem from the work reported in this thesis.

1.7 Thesis structure

The introductory chapter is the first of six chapters contained in this thesis. The chapter describes the necessary background information on Ebola to supply the various assumptions established in the subsequent chapters. The various intervention strategies previously used in an attempt to control Ebola epidemics are discussed with the addition of a brief review of Ebola spread in Sierra Leone during 2014-2015.

In Chapter 2, various mathematical models used to evaluate different epidemics are discussed. This chapter provides the reader with the mathematical background to understand the epidemic modelling in this thesis, their spread and various control attempts, together with shortcomings of the current models describing the population dynamics of Ebola. This chapter provides a basis for the development of the model in following chapters.

The different aspects and considerations of simulation modelling are reviewed in Chapter 3, providing the reader with information on the different simulation types, modelling concepts, advantages and disadvantages, and the steps followed to validate such a simulation model. This chapter concludes with a review of the application of simulation modelling in an epidemiological context and supplies various examples of such modelling approaches.

Chapter 4 comprises of a detailed description of the construction of the meta-population model used to mathematically describe the population dynamics of the spread of Ebola in a country. The various assumptions made within the development of the model is provided, as well as a discussion of the data collection process and analysis thereof. The validation and verification process is explained in this chapter with an elaborate description of the implementation of the simulation model in *PYTHON 3.7*.

In Chapter 5, the model is applied to a real-world epidemic scenario to illustrate the valuable insight simulation modelling can provide into the design and implementation of a human relief

response effort. The Sierra Leone outbreak of 2014-2015 is chosen as case study for this simulation application. Calibration of the parameter values are done with the root mean square error approach to best describe the spread of Ebola. Various scenarios of intervention strategy implementation are investigated to evaluate the effectiveness thereof. The results provided in this chapter may prove to be beneficial to future attempts of controlling an outbreak of Ebola.

Finally, Chapter 6 contains a brief summary of the work presented in this study, as well as an overview of the main contributions of the study with respect to the simulation modelling of human relief response strategies. The chapter concludes with suggestions for possible future work to further this research.

CHAPTER 2

Mathematical epidemiology

Contents

A brief introduction to the interdisciplinary scientific research field, namely mathematical epidemiology is given in this chapter. A short overview of the origin of epidemiological models is provided in §2.1 followed by examples of such models applied to the Ebola epidemic in §2.2. The chapter closes with a brief discussion of epidemiological models incorporating spatial movement in §2.3.

2.1 Epidemiological modelling

Epidemiology first evolved from supernatural explanations for occurrences of disease, to a point of view based on scientific foundations. Since Hippocrates (460-337 BC) first attempted to understand disease occurrences from a rational viewpoint, epidemiology has rapidly progressed with contributions from researchers such as John Snow, Ignaz Semmelweis, Louis Pasteur, Robert Knoch, Florence Nightingale and many others [55]. Arguably the first epidemic to be modelled with a mathematical approach was the Great Plague in London in 1665-166 [20]. Thereafter, countless mathematical modelling attempts were executed, aiming to understand the underlying mechanics of the spread of the disease, which in effect identified control strategies. These mathematical models identified behaviour patterns not easily found within experimental data, as data could not be replicated with limited data points and errors found in the measurement thereof [20].

Epidemiological modelling is used as a tool to understand an explain, from an observational point of view, illness, injury and death. The information obtained is used for the purpose of preventing and controlling health related phenomenons. A trade-off between high level insight on the behaviour patterns within an epidemic and more specific predictive results is found in the complexity of the model and how much detail is considered.

Compartmental models are used as a base to model the complex dynamics of epidemiological systems. These compartments are used to divide a population into sub-groups according to the state of the biological progression of the disease. Homogeneity is assumed for each compartment, presuming all individuals in the same compartment has the same characteristics. Simplified assumptions are made about the interacting dynamics of each state with one another, as well as the rate at which an individual would move from one state to another. Numerous variations of the compartmental models are found in literature, ranging from the simplest Susceptible-Infected-Recovered (SIR) models, describing an individual moving from susceptible phase to the infected phase to be removed from the disease system by recovering from the disease, to more complex Immunity-Susceptible-Exposed-Infected-Recovered-Dead-Susceptible (MSEIRDS) models taking into account passive immunities, susceptible population, a latent phase of disease development within an individual, infection state, both recovery and death removal from the disease system and re-entering of the susceptible state in cases of no immunity obtained after recovery. Differential equations are used to mathematically describe the rates of transition between compartments and the size of each compartment, with time as the independant variable [20]. The set of differential equations governing a the simplest form of the SIR model is given by

$$\frac{dS}{dt} = -\beta SI/N, \tag{2.1}$$

$$\frac{dI}{dt} = \beta SI/N - \gamma I, \tag{2.2}$$

$$\frac{dR}{dt} = \gamma I. \tag{2.3}$$

where the rate of infection is denoted by β, which is defined as $\beta = c \times \rho$, where c denotes the contact rate and ρ that probability of becoming infected. The rate at which an individual is removed from the disease system is denoted by γ. The total number of individuals in the population at time t is denoted by $N(t)$, where $N(t) = S(t) + I(t) + R(t)$. Variations of the simplified SIR model are tailored to the unique characteristics of a specified disease or to the research question. Both a deterministic or stochastic approach could be used, though the latter is more realistic but significantly more complex to analyse. These models are used to investigate the behaviour between various compartments and their representing individuals. This allows for prediction of various properties of the disease spread, such as the prevalence or the duration of the epidemic, as well as outcomes related to various scenarios within the epidemic. The basic reproduction number, R_0, denoting the number of secondary infections caused by a single infected individual, is used as an indication whether a disease would spread through a population or whether it would die out. If $R_0 > 1$ the disease is classified as an epidemic and would spread through the population. The opposite is true where if $R_0 < 1$ the disease is not classified as an epidemic. The R_0 is given by $\frac{\beta}{\gamma}$, where β denotes the infection rate and γ the duration of infection. The higher the R_0 value the more difficult the epidemic is to control.

Numerous approaches have been used to investigate the dynamics of infectious diseases. Partial differential equations (PDE) models relating to compartmental models are typically used to investigate more than one independant variable at a time. Feng *et al.* [35] used a PDE model to investigate age dependant immunity determining the susceptible population for pertussis disease. The advantage of PDE models is the ability to add complexity to the model, allowing the study of a greater set of factors influencing the disease system. Agent based models are used in an epidemiological context to understand the influence of the behaviour of an individual on the overall disease system. Rao *et al.* [66] used a simulation model approach with stochastic interactions between waterfowl, poultry, and humans to identify the epicentres and temporal

spread of an avian influenza outbreak. These models have the ability to capture detailed interacting relationships influencing the dynamics of an infectious disease, however it is challenging to validate these models due to the low level of abstraction. The model chosen by the user is highly dependant on the research question, the unique characteristics of disease being modelled and the specific aspect of the disease dynamics under investigation.

2.2 Mathematical and simulation modelling of the Ebola epidemic

Different aspects of Ebola have been studied through various model types. Chowell *et al.* [25] fitted their dynamic Susceptible-Exposed-Infectious-Recovered (SEIR) model of Ebola transmission to historical data from Congo 1995 and Uganda 2000 in an attempt to determine the R_0. The impact of interventions, contact tracing followed by quarantine and educational awareness was investigated, and a delay of 2 weeks in implementation of public health measure was found to result in an approximation of double the outbreak size [25]. A SEIR model was presented by Althaus [3] which was fitted to reported data of infected cases and deaths as a result of Ebola in Guinea, Sierra Leone and Liberia. The model was not able to take into account fluctuations in new cases with an exponential decay of transmission rates due to the smooth nature of the differential model. With more data accumulated these simplified assumptions can be reviewed to estimate a more accurate reproductive number.

Legrand *et al.* [52] considered a spatial rationality study of different settings for transmission of Ebola such as in the hospital, communities or during the traditional burial ceremonies and estimated the R_0 thereof. The population is divided into six compartments. The susceptible, exposed and infectious compartments represented the natural progression of the disease. Thereafter a fraction of the infected individuals were removed to be hospitalised. Individuals in the death compartment could either be removed from the disease system since they have recovered form the disease or progress to the funeral compartment where they would further infect susceptible individuals. The model is calibrated through the use of a maximum likelihood method and the rapidness of intervention implementation was found to be a key parameter in the dynamics observed. The most important parameters related to the epidemic size were identified to be the time of intervention implementation, the rate of hospitalizing infected individuals and the mean time between onset and hospitalization. This led to the conclusion that the epidemic size could be reduced through the strengthening of intervention strategies such as contact tracing that would allow for more rapid hospitalization.

River *et al.* [67] used a deterministic version of Legrand *et al.*'s model and the least-square optimisation to fit the case data of the 2015 outbreak in Liberia and Sierra Leone. This model indicated the epidemic peak would only be reached by 31 December 2015 with implemented intervention strategies as opposed to the actual peak reached in September 2014 [67]. Using the same model Legrand *et al.* provided, Gomes *et al.* approximated the transmission coefficients through the use of a structured meta-population scheme, of a global epidemic and mobility model, integrating stochastic modelling of the disease dynamics, high resolution census and human mobility patterns at the global scale [40]. The cumulative number of deaths during the period 6 July - 9 August 2014 from Liberia, Siera Leone and Guinea was used to calibrate the model for parameters estimations. Gomes *et al.* investigated the possibility of Ebola spreading to other countries and found the risk to be very low [40].

Using similar methods to Gomes *et al.*, Merler *et al.* [54] accounted for individuals taking care of non-hospitalised infected individuals, the movements of non-infected healthcare workers and

those who attended funerals. A drastic decrease in new cases was observed due to an increase in safe burial ceremonies, Ebola treatment centres and provided household protection kits.

A compartmental model of Ebola by Camacho *et al.* [21] divided the exposed state was into two categories, and found evidence of transmission decreasing considerably before the closure of a community hospital, due to possible behaviour change in hosts. Diane *et al.* [30] investigated the potential role media coverage of Ebola has on the transmission of the disease by constructing an optimal control model.

Sharareh *et al.* [75] investigated the impact of public attention and awareness on an Ebola epidemic using system dynamics (SD). These SD models were developed in an attempt to simulate the social and behavioral factors contributing to the disease dynamics and was validated through comparing the number of deaths and incidences of Ebola to historical time series data received from the WHO. A basic SIR model evolved through trial and error to a final model consisting of seven population stocks including Susceptible, Infected that are Asymptomatic and Symptomatic, Quarantined and Hospitalized, Recovered and Dead. Since higher situational awareness increases the willingness to be quarantined/hospitalized, the rate at which the population was hospitalized was modelled as a dynamic parameter changing over time. Calibration of parameters in the simulation model were done by referring to literature on Ebola outbreaks. The final model captured the social and behavioral factors that had a significant influence on leading to the outbreak, including the change of social awareness during the epidemic, the process of quarantining and asymptomatic period, where infected individuals do not show any symptoms, which are essential when modelling Ebola. Sharareh *et al.* found the system dynamics approach an extremely useful tool to grasp the greater picture of the epidemic and to provide key actors with a better understanding of their impact within the chaotic behaviour of an epidemic. In further research Sharareh *et al.* developed a simulation model to evaluate the influence public fear has on the disease dynamics [74]. Sharareh *et al.* concluded by stating that constant monitoring and adaptability to various changes throughout the epidemic are the key factors any response to a infectious disease such as Ebola requires [75].

Both Astacio *et al.* [9] and Ouyang *et.al* [62] formulated models consisting of a system of differential equations, which was first introduced by Kermack and MacKendrik in 1927. Astacio *et al.* [9] modelled two outbreaks of the Zaire species of the Ebola virus, Kikwit in 1995 and Yambuku in 1976. For the first they introduced a SIR model, describing the system in two stages: moving from susceptible to infected and from infected to dead. The proposed model is given by

$$\frac{dS}{dt} = -\beta SI/N, \tag{2.4}$$

$$\frac{dI}{dt} = \beta SI/N - \gamma I, \tag{2.5}$$

$$\frac{dR}{dt} = \gamma I. \tag{2.6}$$

The total number of individuals in the population is denoted by $N(t)$ at time t, where $N(t) = S(t) + I(t) + R(t)$. The probability of infection of a susceptible individual is denoted by β and γ denotes the rate of an individual in the susceptible population dying. The second model they introduced was based on a SEIR model adding an exposed state to the system for number of individuals in a latent state of the virus cycle. The model is represented by the set of differential equations

$$\frac{dS}{dt} = -\beta S(I + qE)/N, \tag{2.7}$$
$$\frac{dE}{dt} = \beta S(I + qE)/N - \delta E, \tag{2.8}$$
$$\frac{dI}{dt} = \delta E - \gamma I, \tag{2.9}$$
$$\frac{dR}{dt} = \gamma I. \tag{2.10}$$

Since susceptible individuals are more likely to become infected from an individual in the infected state than from an exposed individual, an added weight factor q $(0 \leq q \leq 1)$ is used to take the higher chance into account [9]. Latent individuals become infectious over time as they progress to show symptoms of the disease and move to the infectious stage with the rate denoted by δE.

Astacio *et al.* estimated the R_0 of the disease, which indicates the rate at which the disease spreads. This number is found at a steady state with mathematical methods such as the Jacobian matrix of the system of equations. The study showed that the R_0 of the 1995 outbreak was lower than the R_0 of the 1976 outbreak and stated that it is due to the population misunderstanding and misdiagnoses of the disease in the first outbreak. They also found that the R_0 number was significantly lower than expected compared to other diseases such as the measles outbreak in England and Whales (1950-68) or the HIV in Uganda (1985-7) [9]. This may have been due to the people's fear of becoming exposed to Ebola, which made them more cautious, as well as the method by which Ebola is transmitted.

Astacio *et al.* proposed the number of deaths due to Ebola could be minimized by altering the environment, therefore lowering β. This could be accomplished by implementing quarantine. This proposal was implemented by Ouyang *et al.* [62] in their study of the spread of Ebola. The model was based on a SEIR model such as Astacio *et al.* with an added variable Q denoting the number of infectious population being hospitalised This was done at a rate of $\alpha \cdot I$. The model is given by

$$\frac{dS}{dt} = -\frac{\beta}{\gamma} S(1-\alpha)I, \tag{2.11}$$
$$\frac{dE}{dt} = \frac{\beta}{\gamma} S(1-\alpha)I - \frac{\delta}{\gamma} E, \tag{2.12}$$
$$\frac{dI}{dt} = \frac{\delta}{\gamma} E - I, \tag{2.13}$$
$$\frac{dR}{dt} = I, \tag{2.14}$$
$$\frac{dQ}{dt} = \alpha I. \tag{2.15}$$

Ouyang *et.al* [62] suggested that, though there is no cure to Ebola yet, an effective way to prevent the spread is the use of quarantine methods. They assumed hospitalized individuals share the same death probability as normal infectious individuals, but do not infect any exposed or susceptible individuals. It was realized that a necessary amount of individuals should be kept in quarantine to control the spread of the disease. Although it would be impossible to hold as many quarantine spots as the infectious population, the relation where the growth of infectious population is not greater than the removed people, *i.e.* $\frac{dI}{dt} \leq \frac{dR}{dt}$, is deemed sufficient to control

the spread of the disease. The following relationship denotes the point at which the spread of the virus would be under control

$$E \leq \frac{2\gamma}{\delta} I. \tag{2.16}$$

Hereafter, a graph theory model was used to estimate the number of infectious individuals and rate at which infectious individuals should be removed from the total population such that all individuals of the population would be isolated and control the spread of the disease. A realistic estimate of the removal rate was $\alpha = 0.2$, 20% of the population at a given time t. Introducing contact tracing as a possible intervention strategy could achieve such a removal rate though was not investigated in this research. Ouyang *et.al* concluded their work by introducing another variable to their model, a class of individuals who have been vaccinated for Ebola.

2.3 Models considering spatial movement

Mobility of individuals within a population has a significant impact on the propagation spread of a disease and the effectiveness of the intervention strategies implemented [83]. The movement of individuals is a key factor in accurately describing the behaviour of a epidemiological system and has been lacking in the research done on the Ebola virus disease. Research has been focused on describing the epidemic over large regions such as countries, assuming homogeneous status to each population. These simplifications to the system help to mathematically representing the spread of the disease but fail to accurately model all factors influencing the behaviour of the disease. Various approaches may be followed to incorporate spatial dynamics, such as partial differential equations and agent based simulation, which requires more complex data and analysis. A spatial system dynamics approach can also be utilised by modelling small epidemics on regional scale and connecting them through migration to represent an epidemic on a large scale.

Valdez *et al.* [83] followed a spatial systems dynamics approach to model the spread of Ebola within Liberia through the movement of individuals between counties. A set of differential equations was used as a quasi-deterministic representation of a stochastic model to understand the affect the mobility of populations on the spread of the disease. Understanding the movement patterns within a epidemic system was claimed to be essential when planning and implementing intervention strategies, and the lack of information led to the partial success achieved with the control strategies used during the 2014 outbreak. The model was developed with 10 compartments, classifying individuals as susceptible (S), exposed (E), infected (I), hospitalised (H), recovered (R) and dead (F) following unsafe burial ceremonies leading to further transmission. Infected individuals were further sub divided based on their fate. Individuals infected and hospitalised would either die (I_{DH}) or recover (I_{RH}), whereas non-hospitalised individuals would also be classified by either dead (I_{DNH}) or recovered (I_{RNH}) from the disease. Hospitalised individuals would either die (H_D) or recover (H_R) from the disease. Mobility data was collected from literature done by Wesolowski *et al.* [88] who used cellphone network data to investigate the movement patterns of individuals within West African countries. A gravity model was applied to telephone network data to estimate spatial interaction patterns of various countries. Though mobile data was historical it was accepted as a good approximation of the mobility patterns of individuals in West Africa. Each state of the disease progression in each county c is represented by the following set of differential equations,

$$\frac{dS^c}{dt} = -\frac{1}{N_c}(\beta_I S^c I^c + \beta_H S^c H^c + \beta_F S^c F^c) + \sigma_c(\overline{S}) \tag{2.17}$$

$$\frac{dE^c}{dt} = \frac{1}{N_c}(\beta_I S^c I^c + \beta_H S^c H^c + \beta_F S^c F^c) - \alpha E^c + +\sigma_c(\overline{E}) \tag{2.18}$$

$$\frac{dI^c_{DH}}{dt} = \alpha\delta\theta E^c - \gamma_H I^c_{DH} \tag{2.19}$$

$$\frac{dI^c_{DH}}{dt} = \alpha(1-\delta)\theta E^c - \gamma_H I^c_{RNH} \tag{2.20}$$

$$\frac{dI^c_{RH}}{dt} = \alpha(1-\delta)(1-\theta) E^c - \gamma_I I^c_{RNH} \tag{2.21}$$

$$\frac{dH^c_D}{dt} = \gamma_H I^c_{DH} - \gamma_{HD} H^c_D \tag{2.22}$$

$$\frac{dH^c_R}{dt} = \gamma_H I^c_{RH} - \gamma_{HI} H^c_R \tag{2.23}$$

$$\frac{dF^c}{dt} = \gamma_D I^c_{DNH} + \gamma_{HD} H^c_D - \gamma_f F^c \tag{2.24}$$

$$\frac{dR^c}{dt} = \gamma_I I^c_{RNH} + \gamma_{HI} H^c_R + \gamma_f F^c \tag{2.25}$$

where σ_c represents the total rate of mobility for county c is given by

$$\sigma_c(\overline{x}) = \sum_{c \neq j} \frac{x^j}{N_j} r_{jc} - \frac{x^c}{N_c} \sum_j r_{cj}, \tag{2.26}$$

where $x^j(x^c)$ is the number of susceptible or exposed individuals in county $j(c)$. The total population of county $j(c)$ is represented by $N_j(N_c)$. The mobility rate from county $j \to c$ and $c \to j$ is given by r_{jc} and r_{cj} respectively. The average time for the incubation period $\frac{1}{\alpha}$, the average time from the onset of the disease to the hospitalisation $\frac{1}{\gamma_H}$, the average time from onset of the disease to death $\frac{1}{\gamma_D}$, the average time from onset of the disease to recovery $\frac{1}{\gamma_I}$, the average time from death to traditional burial ceremonies $\frac{1}{\gamma_f}$, fraction of cases hospitalised θ, fraction of cases resulting in death δ and the average time from hospitalisation to dead due to the disease $\frac{1}{\gamma_{HD}}$ was defined to be 7 days, 5 days, 9.6 days, 10 days, 2 days, 50%, 50%, 5 days and 4.6 days respectively, as reported in literature. The various infection rates for the various environments, in the community β_I, in hospitals β_H, at funerals β_F, were calibrated through least square optimisation, by comparing the simulated data to the number of cases for Liberia in March-April 2014 as reported by the WHO. The various beta values were approximated at $\beta_I = 0.14, \beta_H = 0.29$ and $\beta_F = 0.40$. Since the evolution of Ebola is much slower than the population growth, the assumption was made that all N_c were constant. Each county could be viewed as a node within a meta-population network in which proportional weights are given to each link. If the flow mobility was disregarded and the number of counties c was lowered, the behaviour of the disease within the counties are no longer under investigation but rather the disease spread of the entire country.

Modelling the mobility of the 15 counties in Liberia, Valdez *et al.* could estimate the arrival time of the disease in each county with Lofa county being the first case reported on 17 March 2014 as initial condition. These results were compared to arrival times reported by the WHO for each county and found all counties fell in a confidence interval of 95%, except for Margibi and Grand Gedeh [83]. The mobility rates were decreased by 80%, representing an intervention

strategy aiming to control the spread of the disease but found that the arrival of the disease was merely delayed by a few weeks. Valdez *et al.* proposed that mobility restrictions would not stop the disease but slow it down to develop alternative strategies, such as increase in hospitalisation capacity and safe burial, which would have a more aggressive intervention affect on the disease spread [83]. Implementation of a decrease in mobility by 80%, exponentially increasing hospitalisation response to $\theta = 1$ and decreasing all infectious rates to 10^{-3}, a upper bound for the end of the epidemic was found and resulted in a decrease of the R_0 value of 2.11 to $R_0 = 0.69$. This upper limit was implemented in two scenarios, (i) implementing intervention strategies on August 15 (as reported by WHO for Ebola outbreak in West Africa) and (ii) implementing intervention strategies July 15, aiming to investigate the effect of delayed intervention strategy implementation on the spread of the disease. The results indicated an approximate decrease of 80% in the number of cases and an extinction of the epidemic three months earlier, if intervention strategies were implemented by July 15 [83]. Valdez et al. [83] that concluded early and rapid interventions increasing hospitalisation capacity and the rate of safe burials would be the most effective response to any possible re-emerging Ebola epidemic. However, the study did not take into account all intervention strategies implemented during the West African outbreak of 2014. Both contact tracing and vaccination had a significant impact on the disease propagation and should be considered when evaluating the most effective control strategy. Further expansion of this model could incorporate all three countries, Liberia, Sierra Leone and Guinea, to study the possible effects migration had on the inter-spatial dynamics of the spread of the disease.

2.4 Chapter summary

In this chapter the multidisciplinary scientific research field, epidemiological modelling is discussed, mentioning a brief overlook of the origin of epidemiology in §2.1. In §2.2 examples are given of models previously used to better understand the dynamics of an Ebola system with additional models incorporating the spatial movements of individuals discussed in §2.3.

CHAPTER 3

Simulation modelling

Contents

This chapter serves as an introduction to simulation, with a broad description of simulation modelling in §3.1. The most important concepts and elements are mentioned which are found in the various simulation modelling types described in §3.2. Furthermore, simulation modellings advantages and disadvantages is described in §3.3. The steps in simulation modelling are discussed in §3.4, following with the various methods a simulation model could be of verified and validated in §3.5. The chapter closes with examples of simulation models used in the epidemiological context and the contribution thereof.

3.1 Simulation modelling concept

Banks [14] defines simulation to be the design of a model mirroring a real-world system in order to study the behaviour of the system, and the data manufactured by this model is used in the analyses of the system's behaviour as if it was collected from the real world system itself. These analysis investigate the performance of the systems processes and provide insight for the design

and management of the real world systems being studied [14]. Simulation is a powerful real-world problem solving tool in that it can both model conceptual and existing systems, allowing the analyses of "what if" questions.

Simulation enables complex problems which are challenging to model analytically to be solved numerically through the aid of computers [14, 49]. Through simulation modelling, improved understanding of the system may be gained, allowing for exploration of different policies appropriate to the system under specified constraints [73].

Various aspects and concerns should be considered when designing a simulation model. A good understanding of the problem given and the desired outcomes is the first step to developing a model. Aspects such as the information available concerning the system being modelled, and what measures should be used to obtain the required information to substantiate the model, are to be considered prior to model development [85]. Distinguishing between fundamental system characteristics and minor, perhaps negotiable characteristics could decrease model complexity with the use of assumptions and mathematical relationships [85]. Most importantly, the validity and integrity of the simulation model needs to be taken into consideration to establish whether it is possible to acceptably represent the real-world system while obtaining accurate and viable results [32].

Law [49] describes the selection criteria of an appropriate level of model detail to be an art in itself. The level of abstraction determines the accuracy of the simulation model's replication of the real-world systems behaviour [32]. Three abstraction levels are defined, namely a strategic level, an operational level and a physical level [106].

A strategic level abstraction aims to recognise and examine organisational issues attaining to high level aggregation of the entities being modelled [32]. Strategic level abstraction typically require less detail than the operational level and physical level abstraction [85]. Market place and competition models are examples of a strategic level approach, as well as population dynamics on large scale and ecosystems development [19].

The operational level abstraction requires more accurate data and detail, due to tactical decisions made about the real-world system being imitated. Modelling at a more detailed level would demand a greater precision of data to be reliable. Examples of models where operational level detail is required include modelling of supply chains, examining the scheduling of staff or inventory within a company, as well as the analysis of specified performance measures [106].

The last level of abstraction is the physical level with models requiring the most detail. Such models observe and investigate the individual's behaviour within the system [106]. For such a simulation reliable and accurate information is needed for the movement, actions and timing of entities to be validated [85]. This is typical when studying the interaction of agents in biological or ecological systems resulting in the emergence of structures and functions, passenger flow analyses and transportation networks. Through investigation of the microscopic behaviour of the system the resulting macroscopic dynamics could be observed [106].

3.1.1 Components of a simulation model

Simulation modelling has various modelling paradigms consisting of basic structures. Common modelling concepts such as *system, attributes, model, activities, events, entities, system state variables* and *resources* are used within a simulation model.

A *system* is defined to be principles or processes consisting of interconnecting *entities* as an organised scheme to achieve a common goal [39, 73, 105]. A *system* is represented by a *model*

with a set of assumptions to predict the performance of the *system* if implemented in reality [14, 49, 73]. *Events* are known as the occurrences that change the *system state variables* which in effect change the state of the system [14, 49].

A system is made up of objects referred to as *entities*, representing a person or machine, which is either static, remains fixed within the system (*e.g.* a cashier), or dynamic, where it would move within the system (*e.g.* a customer) [14, 73]. The unique characteristics describing the behaviour of entities are known as *attributes*. The change in systems are due to the entities interacting with *activities*, resulting in an *event* [14, 43, 73]. Processes within the system are seen as *activities*, of which queues, delays and logic are the most common activities [43]. *Resources* are modelled as restricted entities with limited capacity, used to serve dynamic entities within the system. Examples of resources are traffic intersection, machines or bank tellers which could take on various states such as active, blocked, failed, busy or idle.

The status of a given system at an instant in time is described to be the *state* of the system, through the use of variables [14, 49, 105]. These variables are referred to as the *system state variables* and are unique to the type of system being modelled. The total number of customers in the bank, the number of busy tellers compared to the idle bank tellers and the rate at which the customers arrive at the bank would be state variables of a bank system simulation.

3.1.2 Various classes of simulation modelling

There are various classifications of different simulation modelling techniques. A system simulated at an instant in time, independant of time, is seen as *static*, and a system changing over time would be seen as *dynamic* [14, 39]. Static models are commonly referred to as *Monte Carlo* simulations, where a model simulating the outcome of a rolling dice would be an example of such a model [105]. *Dynamic* models are models which are dependant of time and would evolve as time changes [14, 39, 43, 53, 72]. The time elapsed from the moment the simulation is initiated, is simulated by a simulation clock. A typical dynamic simulation model example would be the dynamics of a population-based epidemic.

Stochastic models are defined by a randomness factor within the model [53, 73]. Probability distributions are defined for inputs and variables, allowing for variation in outcomes [72]. Examples of such models are customers within a bank or arrival, service and departure of patients at a medical centre. *Deterministic* models contain no random variables and therefore give the same outcome for all model runs with the same defined variables [39, 53].

Events occurring within a dynamic model, which evolve over time, can either be *discrete* or *continuous*. A *discrete* event only occurs at a certain time within the simulation and causes a change in the system only at that time [39, 53, 105]. *Continuous* events are continuously taking place and have an effect on the system for the duration of the event occurrence [105]. The change in temperature is an example of a continuous event changing a system over time.

3.1.3 Types of simulation modelling techniques

Different simulation modelling approaches are available to replicate real-world systems. The choice of modelling approach should be critically considered such that the engaged system is modelled as realistically and as accurately as possible. The selection processes are governed by factors such as the level of abstraction and the details of the underlying problem. There are four simulation modelling approaches, namely *agent-based modelling, discrete-event modelling, systems dynamics modelling* and *dynamical systems modelling* [106].

Although each modelling approach offers specific details and level of abstraction, an integrated approach where elements and principals of different techniques are utilised in combination to reach a desired outcome, is not unheard of [19].

Agent-based modelling is defined as a model consisting of agents or self-governing entities, with unique defining characteristics and behaviour [18]. These agents are free to make their own decisions within a scope of predefined rules which result in composite behaviour observed in the system. The macro-phenomena emerges from the microscopic behaviour of heterogeneous agents interacting with one another [44]. Agent-based modelling is seen as a decentralised, individualistic-centred method [106] where individual agents behaviour are defined rather than the global system as a whole, and is described as a bottom-up model design [19]. Animals, vehicles, people, insects, companies or departments are all examples of agents within a agent-based simulation [106].

Discrete-event modelling is an approach where the states of the system are predefined, and the progression of the model is dependant on a series of activities moving the system from one state to another. These events occur at a defined time and therefore the state of the system only changes at the instant the event occurs. The aim of this kind of simulation approach is to see how the entities interact within these events. As the simulation advances through time the state of the model remains the same but the dynamic working in the system changes with these events occurring [13].

SD modelling is used to understand the system as a whole by viewing the interaction between organisational structures and other influencing factors. By means of causal feedback loops and stock-and-flow diagrams, the real-world system is replicated. Individuals are represented by their quantities, due to the assumption of high level abstraction and aggregation in SD models, and therefore lose the individual's characteristics and dynamics. SD is usually employed for long term strategic models [106]. Epidemiological models frequently employ SD to model the propagation of a disease within a population. SD models provide insight into non-linear behaviours within an epidemiological system to aid in informed decision making by stakeholders and policymakers [59]. SD models have the capability to incorporate temporal spatial dynamics influencing the interacting dynamics of the system under study. The exchange of data amongst the SD and spatial systems is either modelled in an asynchronous manner, where the spatial model and SD model independantly generate data, or a synchronous manner where direct inter-system communication is allowed during model execution [59].

Dynamic systems modelling, in contrast with SD, rely on state variables and differential equations pertaining to these state variables to model a system [19]. Physical attribute such as location, acceleration or velocity are assigned to these integrated variables, without any aggregation, and all begin in a continuous state [6, 19]. Tools have been developed with embedded dynamic systems modelling for technical engineering purposes and through the use of graphical modelling computer languages, visual representation of these models may be provided [6].

3.2 Advantages and disadvantages of simulation modelling

Due to the exponential increase in competition within the information technology sector, computer hardware became more powerful and easier to use. The simulation software industry benefit from these advancements as simulation software took advantage of the computer performance improvements to execute more accurate results within a shorter time, allowing for expansion of the simulation application capabilities. Many companies have turned to simulation as a modelling approach after realising the benefits when studying a complex system [13, 50].

Various authors that have mentioned simulation modelling having both advantages and disadvantages are for example, Banks [13], Banks *et.al* [16], Law [50] and Robinson [68].

3.2.1 Advantages

The most intrinsic advantage of simulation modelling is the use of investigating the mechanics of a system prior to the execution of a not yet existing system. It allows for the removal of factors that may cause difficulties and deficiencies in the system's real-world implementation.

Existing systems requiring modifications, upgrades or addition of new components can often incur considerable cost. Validated simulation models provide the opportunity to test various designs and strategies without utilising any resources for the real-world system itself. This allows for modifications and additions to be made and analysed without the required cost and disruptions of implementation to the real-world system.

Simulation modelling allows for the tempo of time to be increased or decreased to a desired rate. Processes spanning over days, months, years could be analysed within minutes, allowing observers to see the impact over a long period of time. Conversely, simulation time could be slowed down to observe the effects of interacting entities in processes taking place momentarily in real-world time. This level of control of the simulation model gives a valuable insight of the practical operations of the system as well as the greater understanding into the causes of certain occurring phenomena.

Investigating the interdependencies of various entities with other entities or their environment is made possible with simulation modelling. This can be helpful in understanding the reason for events that occur in the system and to identify the responsible entities for these events. This form of problem diagnosis may be adapted to a bottleneck analysis and possibly provide alternatives to a current system.

A visual representation of the real-world system is a particularly important trait which simulation offers and is used in better communicating and describing the system to a client. Various simulation modelling software allow for animation of the simulated system, which is vital when explaining a complex system to the a client who is not necessarily technically qualified, as visualization is inherently intuitive [85].

Simulation modelling, finally, could aid in decision making, allowing various parties to build confidence in the proposed policies or systems from a simulation model that has been validated, verified and vigorously tested. By visually presenting a solution, decision support is given to concerned parties, by minimising the risk of relying of speculation, personal experience or opinions.

Simulation modelling is beneficial to epidemiological systems as it allows for the investigation of of a system without putting lives or resources at stake. Utilizing this in this thesis provides the means to investigate the effect of various intervention strategies without limitations to time and resources. Countless 'what if' scenarios could be investigated, with simulation modelling allowing constant changes to be made to the system. With the ability to increase the rate of the simulation model over time, the model could be used as a means of forecasting the expected behaviour of the epidemiological system or decrease the rate to investigate the interacting dynamics of various components in the system at a given time point. With a greater understanding of the underlying interacting dynamics due to the models output analysis, the decisions and policy making process is aided.

3.2.2 Disadvantages

Though simulation modelling has numerous advantages, it is not without fault. Some of the disadvantages of utilising a simulation modelling approach, as discussed in literature, is described in this section.

Simulation modelling demands an adequate amount of expertise to develop an accurate model representing the real-world system [16, 39, 73]. These skills are learnt over time and are gained through experience and specific training. However, recent development of more advanced software packages has somewhat offset this drawback. Introduction of newly developed software packages allow users with less experience to simply complete a partial model or input the desired variables to test a system.

Since simulation modelling is frequently developed with random factors, it is sometimes hard to distinguish whether the output is due to the system interaction or stochastic input factors. It is therefore recommended to have an input dataset of the real-world system, as well as an expected outcome if possible, to ensure the model is operating as expected and for further calibration purposes [16, 56, 85]. To aid in analysing the results, many simulation software packages provide output analysis tools.

Though simulation modelling is inexpensive compared to testing the modified or potential system in real-world, constructing a realistic and accurate simulation model is a slow and tedious process requiring particular simulation modelling software capable of sophisticated and professional modelling, which is relatively expensive [16, 85]. As technology advances, a wider variety of simulation software are released, from basic packages to more advanced professional versions, decreasing the capital expense of a complete professional version and providing alternative simpler versions of a simulation software package.

Finally, simulation may be used in ways not suited for a particular problem, for example providing a simulation model to a problem sufficiently, even preferably, answered with an analytical solution [85]. This results in substandard, inaccurate models which provide favourable solutions instead of a true representation of the system being investigated.

3.3 Steps followed in typical simulation study

There are a number of steps to follow during a simulation study, which are applied in various chapters of this thesis, to produce an accurate and successful simulation. These steps are presented in this section as a flow chart in Figure 3.1.

1. *Problem formulation.* The development of a simulation model starts with a problem statement. This statement contains the objective of the study. The statement gives an indication of the required level of detail to model.

2. *Project planning.* An outline of the intended scope and objectives should be given, indicating which scenarios will be investigated. The statement must include the performance measures that will be used to measure the efficiency of each configuration of the different systems simulated. The project plan will be an indication of the time required to complete the task, as well the hard- and software required to complete the investigation. Mentioning each stage and its expected outcomes is required within a project plan.

3. *Conceptualisation.* Through the use of abstraction the system being investigated is developed into a simplified conceptual model through a set of mathematical and logical relationships representing the elements and structures of the system. Modelling the problem requires abstraction

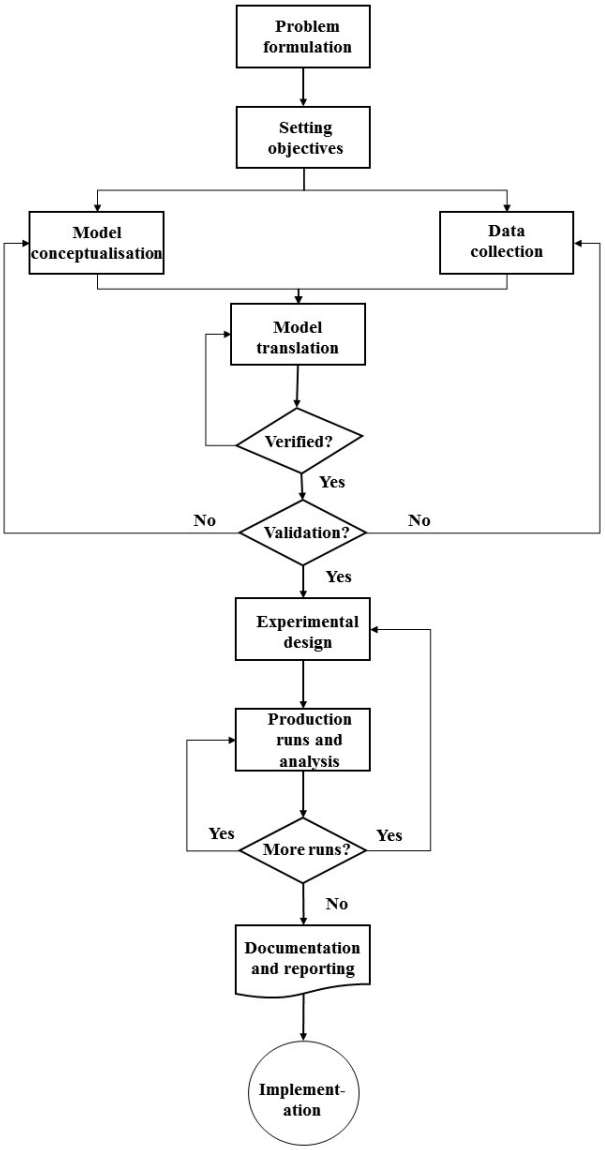

FIGURE 3.1: *Steps in a simulation study [13].*

of the essential characteristics defining the system, and then designing a model to accurately represent the real world system [15]. Considerations to take into account when abstracting model detail are the project objectives, performance measures, the availability of data and the performance capability of the computer system used for the simulation implementation [50].

4. *Data collection.* At the construction stage of the model, model construction and data collection should take place simultaneously. As complexity of the model increase the demand for data or alternative data should be considered as the model is iteratively built. Data is also required for simulation validation in order to compare the simulated output data to the data of the physical system.

5. *Model translation.* Through the use of a suitable programming language or simulation modelling software package, the conceptual model is converted into an operational simulation. The advantage of using a more well known programming language is that it gives the user greater control of the simulation, whereas with a simulation software package the programming time

could be reduced significantly [50].

6. *Model verification.* The verification process relates to assessment of whether or not the conceptual model implemented in a computer model is behaving as expected [15]. Advised by Banks [15], the verification process should be continuous throughout the modelling stage, using interactive run controllers and debuggers to support in the verification process.

7. *Model validation.* Validation is done to conclude whether or not the conceptual model is an adequate delineation of the physical system. The validation process is done through comparing of the simulated model to the physical system being replicated. The use of discrepancies and input of subject experts may also in enhance the accuracy of the model. Replications of the model is produced and only when the desired level of accuracy is achieved is the validation process terminated [15].

8. *Experimental design.* Once the model is acceptable, the different experimental designs or scenarios are decided upon. For each case the simulation run length, the number of simulation runs and the initial conditions are chosen.

9. *Scenario runs and analysis.* Variations in model runs and their relevant analysis are used to provide a performance measure for each scenario, which enables the user to compare alternative system configurations and their simulated results.

10. *Further production runs.* If previous production runs are not sufficient, based on initial outputs, more production runs are formulated and executed.

11. *Reporting.* Two forms of documentation are provided, namely program documentation and progress documentation. In the case of program documentation, the information relating to the program development is important if the simulation model is to be used by other researchers. Sufficient documentation is important for further development or modification to the program. The results are documented to provide the respective parties of the simulation with an answer to the initial problem. The progress documentation also contains the information on the prototype demonstrations, model specifications, progress reports and model animations, which are all necessary to provide a presentation to the relevant parties [15]. In an academic context, documentation in the form of a thesis or article focus on presenting the problem formulation, conceptualisation, experimental design and output analysis.

12. *Implementation.* The implementation of the proposed system or decision based on model results is dependant on how successfully the above eleven steps were completed, as well as how convincing the final report and simulation outputs are to the decision maker.

3.4 Simulation model verification and validation

Verifying and validating a simulation model is essential to ensure the outputs of the model is accurate and correct [73]. Both verification and validation, as shown in Figure 3.2, are focused on building a sufficiently accurate model. The verification process ensures that the model is built correctly, compared to the validation process which confirms that the correct model is built [12, 73].

3.4.1 Verifying a simulation model

The verification process of a simulation model ensures the model behaviour is as expected [73], *i.e.* confirming whether the output is in agreement with the programming logic. Otherwise

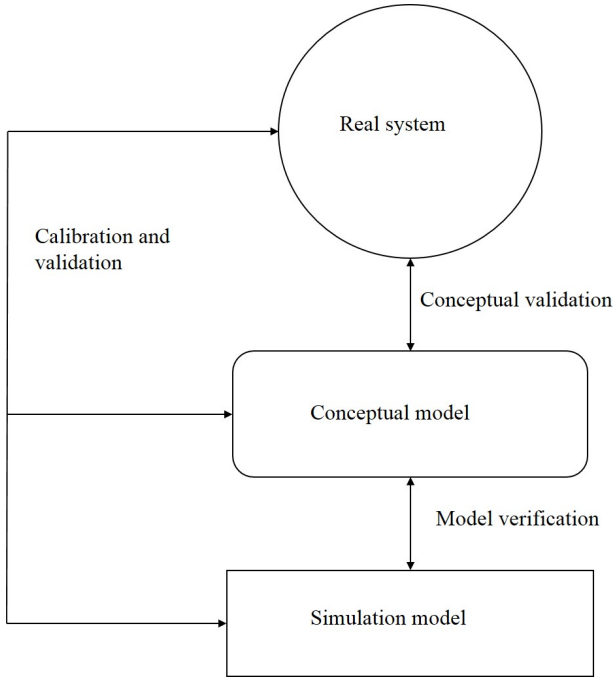

FIGURE 3.2: *Verification and validation in simulation the modelling process*

stated, it is ensuring that the model has no logical errors. Various techniques are available to verify a simulation model.

The simplest form of these techniques is to vary the input variables over their ranges and investigate whether the output is as expected in accordance with the model logic [4, 53]. Through the use of interactive debuggers or run controllers, potential errors can be found effectively and be resolved. Debuggers or run controllers allow for surveillance of variable changes as the simulation runs, indicating when and under which conditions the variables might change, aiding in the discovery of logical errors [4, 53]. Animation may be a helpful tool in locating logical errors occurring within a simulation model, as the behaviour of entities could be observed as the variables change over time [4, 53]. A third technique of verification, called a "sanity check", analyses the results of the simulation model to determine whether or not they make sense and are as expected [4].

An *extreme conditions test* is another verification technique, where unlikely "extreme" values are chosen as input values and the output is evaluated for reasonableness [70]. An example of this would be to set an infection rate of an epidemic to zero and then to expect the number of infected individuals to be zero, therefore causing no further spread of the epidemic.

3.4.2 Validating a simulation model

The process of validation is important in the development of a simulation model to ensure the conceptual model is accurately representing the real-world system [14, 51]. Shannon [73] states three important questions that validation should answer namely, is the actual system being represented sufficiently in the simulation model, are the generated results in accordance with real-world data, and are the users confident with the generated results of the simulation model? As with verification, there are various techniques used to validate a simulation model.

One of the most effective validation test is the *results validation test*, where the simulated output

is compared to the output of the physical system being investigated [51, 53]. This requires data from the physical system and can only be performed if both the simulation and real-world system are investigated under the same conditions. The output data is compared with the real-world data through the use of various statistical tests, indicating the significance of the differences between the sets.

Validation of the model may be achieved by having informed individuals thoroughly inspect the results for consistency and reasonability [51]. Major factors influencing the performance of the model may be identified through sensitivity analysis. Comparative tests may aid in validating a simulation model, where a relevant field expert is asked to identify the simulated systems output in comparison to the real-world system [51, 70].

In certain conditions, a simulation model may be validated by comparing historical data of variables in independant simulation runs. Comparing these data sets may indicate any discrepancies between runs and experts observe and provide feedback through the use of graphical representation.

3.5 Simulation modelling in the context of epidemiological systems

Auping *et al.* [11] presented a SD model with endogenous responses related to the 2014 Ebola outbreak in Liberia. They emphasised the importance of explicitly accounting for dynamic development of intervention capabilities and associated delays in the system [11]. Their SD model was used to predict the spread of the Ebola disease within Liberia due to deep uncertainties of proactive and reactive policies. Comparing the model output to both pre- and post- epidemic data, confidence was established in the accuracy of the SD model's ability to simulate the endogenous responses. The effect of the endogenous responses on the spread of the epidemic was measured through estimating the effective reproduction value. The results revealed that delayed and timely but ineffective responses significantly increased the effective reproduction value and consequently accelerates the rate of new cases observed [11]. The model however assumed a homogenous population with no temporal spatial movement which caused various characteristics and uncertainties of a heterogeneous population and heterogeneous regions to be overlooked. The capacities of the endogenous responses presented by Auping *et al.* could be viewed as the minimum required capacities and revised accordingly to a specified region during real world planning and implementation.

Agent based modelling provides a means to take into account the characteristics and uncertainties observed in a heterogeneous population within heterogeneous regions. Siettos *et al.* [76] developed an agent based model to investigate the epidemic dynamics of the Ebola outbreak in Liberia and Sierra Leone. The model presented used an equation free approach to replicate the spread of the disease within a heterogeneous population represented by a small-world network. Individuals within the population would move through the states of the disease by means of a discrete time, discrete state non-Markov random process [76]. The agents within the model is represented over a network where each node represents an individual within the population and vertices represents the interaction of these individuals. The model was fit to data collected from the WHO's reported cumulative number of infected cases and deaths from May to December 2014, estimating the major epidemiological parameters. The approximation of the reproductive number was found to be close to those reported by WHO response teams. Siettos *et al.* used the simulation model to predict the number of cases and deaths 10 weeks after December 2014. It was estimated the disease would be under control by March 2015 in Liberia but further height-

ened to more than 18 000 cumulative cases and 5 000 cumulative deaths in Sierra Leone [76]. Although the model presented by Siettos *et al.* accounted for a heterogeneous population, it did not explicitly take into account the influence of temporal spatial movements of individuals within the population. The biological characteristic of the virus and the epidemiological features associated with the transmission of the disease replicated in the model provides a platform to develop an effective strategy of control measures to prevent further spread of the disease.

The use of discrete-event simulation modelling is beneficial in strategically planning the implementation of various intervention strategies. The success of resource allocation, facility location and supply chain management within a disaster system is dependant on the successful implementation thereof. Discrete-event simulation is a methodology used by the Center for Emergency Response Analytics (CERA) to investigate points of dispensing in the case of responding to an Anthrax attack. Client transportation, supply chain operations, staff levels and physical limitations of the points of dispensing (POD) site are unique factors contributing to the extreme complexity of the POD operations. These complicate analysis by means of static tools and techniques, such as spreadsheets and mathematical models [89]. Complete response plans are executed based on developed simulations [7]. Assumptions are made such as geographically only restricting the attack to an island as well as limiting the attack to only one. Evaluation of dispensing is measured by the performance of the cycle time for a family, formulation of queues in the process, waiting time in traffic, client population in the POD, length of car-back-up and utilization of staff. The models conclude with the results of the importance of assumptions compared alternatives, whether communities achieved their goals and evaluating the significance of how the plan would work despite incorrect assumptions.

3.6 Chapter summary

Within this chapter various simulation models and approaches were described. The chapter opened with the explanations of frequently used concepts and aspects of simulation modelling in §3.1. The four types of simulation modelling namely, Agent-based modelling, Discrete-event modelling, system dynamics modelling and dynamical systems modelling, were discussed in §3.2. This was followed by a comparison of the advantages and disadvantages of simulation modelling in §3.3. §3.4 set out the typical twelve steps followed when developing a simulation model. Verifying and validating a simulation model was discussed in §3.5 and the role of simulation in epidemiological systems were finally discussed in §3.6.

CHAPTER 4

Mathematical model

Contents

The key to effective modelling is to maximise simplicity, while taking into account as much of the reality as possible such that the findings still stand relevant to the context of interest. In this chapter, the development of a mathematical model for describing the spread of Ebola through a susceptible population is presented. The conceptual model is presented first, followed by a discussion of the explicit and implicit assumptions made within the model. Thereafter, the model formulation is given in §4.3. The parameterisation of the model is discussed and the pseudocode of the software implementation is presented. The chapter concludes with the verification process of the model.

4.1 Conceptual model

The conceptual model is based on Kermack and McKendrik's compartmental model of describing an epidemic over time [10]. Four intervention strategies are considered, namely contact tracing, quarantine, safe burials and vaccinations. The inter-spatial dynamics of the disease spread is modelled through a metapopulation approach in which a large geographical area is divided into spatially separated smaller areas with mobility between the smaller geographical areas.

Consider a metapopulation in its various stages of Ebola infection, which in the context of this study is assumed to be a group of distinct populations contained within a set of geographically separated regions. These regions (each containing a uniformly spread population) are linked

through the spatial movement of individuals between regions. Each area containing a population may be viewed as a node in a network where the weight of each link is proportional to the flow of individuals between the populations. The various stages of Ebola include susceptible, exposed, infected, recovered and dead. In this study, a quarantine stage is also considered, and deaths are separated into safely buried and unsafely buried to include the transmission from deceased individuals to susceptible individuals. A schematic representation of the conceptual model is presented in Figure 4.1 as a network of spatially separated populations linked through spatial movements. For each node in the network, the red boxes represent the various stages of the disease and the connecting arrows the progression rates between states.

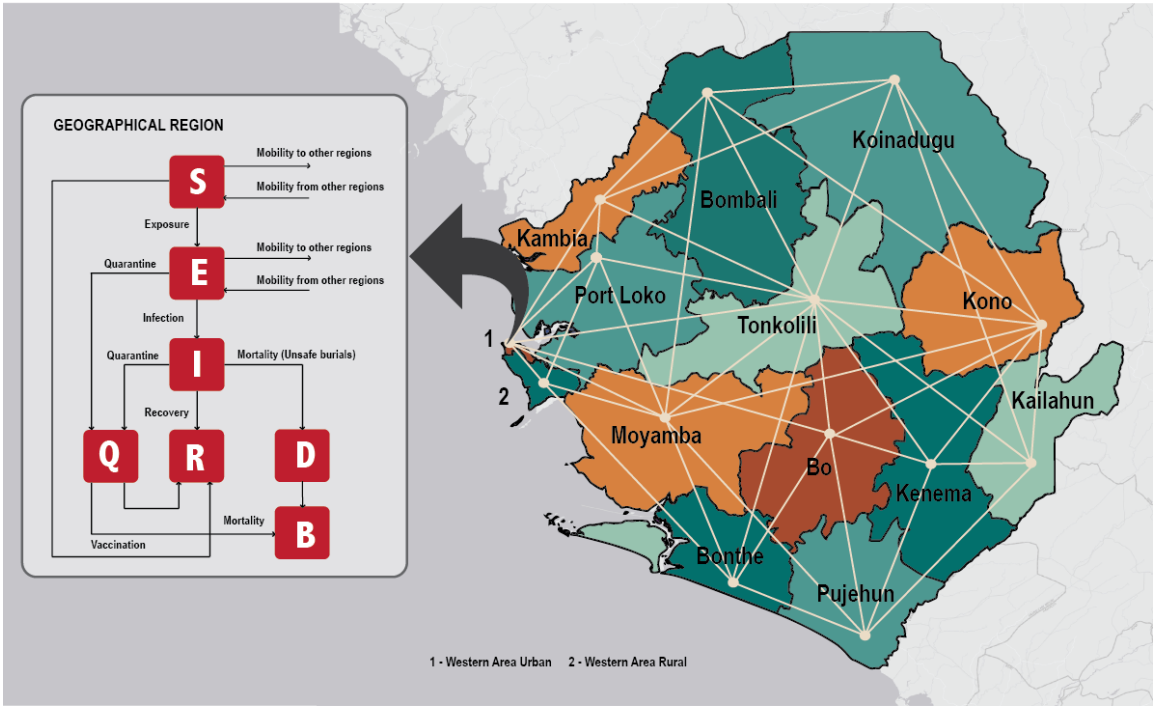

FIGURE 4.1: *A schematic representation of the conceptual Ebola progression model with it's various states applied to a real world geographical area.*

Individuals are removed from the susceptible state either by becoming exposed to the disease or vaccinated in which case they would move to a recovered state that is classified as immune to the disease. A fraction of susceptible individuals are vaccinated proportional to the number of individuals quarantined, mimicking a ring vaccination approach. Susceptible individuals become exposed through contact with either infected individuals, or through contact with dead individuals during unsafe burial. A proportion of exposed individuals are quarantined through contact tracing. The natural progression of the disease would be for exposed individuals to become infected and infectious once symptoms show. Infected individuals would either leave the infected state through dying or recovering from the disease. Infected individuals could also be removed from the infected state to be quarantined. The individuals in the quarantine state

would either result in death or recovery from the disease. A proportion of deceased individuals are buried by trained burial teams, and are therefore removed from the death state from further infecting susceptible individuals during safe burial ceremonies. All other deaths are assumed to be buried in an unsafe manner.

4.2 Assumptions

In this model, the spatial interactions amongst individuals within a smaller geographical area (presented by a node) is assumed to be equally likely. The smaller the geographical area, the more realistic the assumption becomes, though it does not fully represent the spatial complexity of the real world scenario. It is noted however, that even though individual spatial movement and consequently contact between individuals are not explicitly modelled, a smaller average contact rate between infected and susceptible in the larger population, can indirectly account for the slower spread of Ebola as might be observed in a spatially explicit model. Movement in and out of each population is not assumed zero and therefore represent migration between different sub-population in the metapopulation. Flow of individuals is assumed between all populations. The intra-spatial dynamics within a population is not considered in this model, and all individuals within a population is assumed fully mixed.

Only susceptible and exposed individuals are assumed to be mobile. Due to the severity of the disease, the impact on the health of an individual is severely affected when recovered. Travelling recovered individuals are therefore disregarded in the model, and assumed negligible. Recovering from Ebola allows for immunity against becoming infected again and therefore recovered individuals are not returned to the susceptible subpopulation.

Resource limitations are not explicitly taken into account, although it is noted that choosing an integrated intervention strategy for a given community strongly depends on the economic, social and cultural status of a community. The aim of the simulation exercise is to investigate how different intervention strategies impact the Ebola system. Practical implementation thereof may be considered once more knowledge is obtained of the best combination of intervention strategies that would yield desired results. A trial based ring vaccination approach was followed during the 2015 outbreak in Sierra Leone since vaccination were not fully FDA approved, limiting administration thereof [33]. Vaccination is therefore assumed only to be administrated to the close contacts of quarantined individuals, modelling a combined strategy of quarantine, contact tracing and vaccination.

For the model development discrete time is assumed, based on the data used to calibrate the model. The data is presented as the number of Ebola cases and deaths for each county of Sierra Leone per day. Each report of the number of deaths is given as collectively reported per day. Therefore there is no need to know the number of deaths observed in half or quarter of a day, allowing a discrete time assumption to be suitable. The use of discrete time would ease the process of implementing various time dependant intervention strategies during the experimental design.

4.3 Mathematical formulation

Let $S_{i,t}, E_{i,t}, I_{i,t}, Q_{i,t}, R_{i,t}$ and $D_{i,t}$ denote the size of the susceptible, exposed, infected, quarantined, recovered and dead subpopulations of the spatial region i at time t, respectively, and $B_{i,t}$ denote the individuals who have been buried by trained burial teams who do not follow

traditional burial ceremonies, causing no further transmission. This is contrary to the $D_{i,t}$ subpopulation, representing individuals who are not safely buried and may cause further infection, though this is only for a period of time until they have been buried. Furthermore let $N_{i,t} = S_{i,t} + E_{i,t} + I_{i,t} + Q_{i,t} + R_{i,t} + D_{i,t} + B_{i,t}$ denote the total population, of the spatial region i at time t. The system of difference equations governing the spread of the disease in the SEIQRDB-model is given by

$$\begin{aligned} S_{i,t+1} &= S_{i,t} - \frac{\beta_1 S_{i,t} I_{i,t} + \beta_2 S_{i,t} D_{i,t}}{N_{i,t}} - \frac{\upsilon S_{i,t} Q_{i,t}}{N_{i,t}} \\ &\quad + \sum_{j=1}^{A} \frac{S_{j,t}^2}{N_j} r_{ji} - \sum_{j=1}^{A} \frac{S_{i,t}^2}{N_i} r_{ij}, \end{aligned} \tag{4.1}$$

$$\begin{aligned} E_{i,t+1} &= E_{i,t} + \frac{\beta_1 S_{i,t} I + \beta_2 S_{i,t} D_{i,t}}{N_{i,t}} - [(1-f_1)\delta + f_1 q_E] E_{i,t} \\ &\quad + \sum_{j=1}^{A} \frac{E_{j,t}^2}{N_{j,t}} r_{ji} - \sum_{j=1}^{A} \frac{E_{i,t}^2}{N_{i,t}} r_{ij}, \end{aligned} \tag{4.2}$$

$$I_{i,t+1} = I_{i,t} + (1-f_1)\delta E_{i,t} - I_{i,t}(1-f_2)[(1-f_3)\gamma_I + f_3\mu_I] - q_I I_{i,t} f_2, \tag{4.3}$$

$$Q_{i,t+1} = Q_{i,t} + q_I I_{i,t} f_2 + f_1 q_E E_{i,t} - (1-f_4)\gamma_Q Q_{i,t} - f_4 \mu_Q Q_{i,t}, \tag{4.4}$$

$$R_{i,t+1} = R_{i,t} + [(1-f_3)\gamma_I I_{i,t}](1-f_2) + (1-f_4)\gamma_Q Q_{i,t} + \frac{\upsilon S_{i,t} Q_{i,t}}{N_{i,t}}, \tag{4.5}$$

$$D_{i,t+1} = D_{i,t} + f_3 \mu_I I_{i,t}(1-f_2) - f_5 D_{i,t}, \tag{4.6}$$

$$B_{i,t+1} = B_{i,t} + f_4 \mu_Q Q_{i,t} + f_5 D_{i,t}, \tag{4.7}$$

where β_1 denotes the rate at which an individual is exposed to Ebola in any other environment than unsafe burial ceremonies, and δ denotes the rate at which an individual becomes infected with Ebola. Furthermore, γ_I an μ_I denotes the rate at which an infected individual would leave the infected state through either recovering or dying from the disease, respectively. Note that $\frac{1}{\delta}$, $\frac{1}{\gamma_I}$ and $\frac{1}{\mu_I}$ are the average durations of the incubation and infectiousness. A factor f_1 denotes the proportion of individuals quarantined from the exposed state through contact tracing and the proportion of individuals removed from the infected state for quarantine is denoted by f_2. The proportion of reported cases resulting in deaths is denoted by f_3 and the proportion of quarantine cases resulting in deaths are denoted by f_4. The rate at which individuals leave the exposed state to the quarantine state is denoted by q_E. The rate at which individuals would recover or die from the quarantine state is denoted by γ_Q and μ_Q, respectively. The rate at which infected individuals are quarantined is denoted by q_I and assumed to be at the same rate as the rate at which exposed individuals are quarantined, q_E. A fraction of susceptible individuals are vaccinated proportional to the number of individuals quarantined, mimicking a ring vaccination approach with a vaccination coefficient υ. The rate at which individuals are exposed to the Ebola at an unsafe burial ceremony is denoted by β_2. A proportion of f_5 individuals are buried by trained burial teams, therefore removed from the death state to not further infect susceptible individuals during unsafe burial ceremonies. All other deceased individuals are assumed to be buried in an unsafe manner. The total number of deaths is the sum of the proportion of individuals safely buried and the proportion of individuals remaining in the death state, representing the number of individuals not safely buried or still to be buried, and is denoted by $TD_{i,t} = B_{i,t} + D_{i,t}$.

To determine the geographical spread of the disease it is assumed that there is a flow of only the susceptible and exposed individuals (capable of travelling) between geographical areas. The

total inflow of individuals into area i for $i \in [1, A]$, where A represents the total number of geographical areas, is calculated by using the proportion of individuals moving from county $j \to i$ denoted by r_{ji}. The total outflow of individuals out of area i for $i \in [1, A]$, is calculated by using the proportion of individuals moving from county $i \to j$ denoted by r_{ij}. The proportion of individuals moving from region i to region i, r_{ii}, is assumed to be zero, as this migration movement does not change the population size within an time step.

A proportional decrease of the transmission coefficient is experienced in the prior state and an increase of the same proportion is experienced in the succeeding state with every time step. The exposure coefficient β_i for $i \in [1, 2]$ is defined to be, $\beta_i = c \times \rho_1$, where c denotes the contact rate amongst individuals in the population under study and ρ_1 denotes the probability of becoming exposed. Both contact rate and the probability of exposure are not explicitly defined in the model as β_i is the coefficient mostly reported on in literature [10, 30, 67, 74, 87].

The vaccination coefficient, υ, is defined to be $\upsilon = c \times \rho_2$, where c denotes the per capita contact rate and ρ_2 the probability of vaccination. Similar to the exposure coefficient, both the per capita contact rate and probability of vaccination is not explicitly defined in the model since υ is the coefficient mostly reported on in literature [8, 26, 81].

4.3.1 Boundary conditions

The meta-population is modelled as a closed system which assumes a constant population in the greater geographical area. No movement is modelled on the borders of the spatial network and therefore only the inter-spatial movements of the smaller geographical areas are taken into account. This assumption is justified for countries facing an epidemic restricting or closing movement across country borders as a means of quarantine. By increasing border control, the epidemic could be contained within a country, preventing the spread of a disease to neighbouring countries.

4.3.2 Initial conditions

The Ebola system is modelled as a closed system, not taking into account births or deaths due to other factors, and a fixed total population size, N in the network. To introduce Ebola within the closed population at least one individual should be infected and another exposed such that the virus can be transmitted to the susceptible population causing the spread of the disease. Two sets of initial conditions are used, a set of conditions for populations in which the disease is introduced at $t = 0$ presented in Table 4.1 and a set of conditions for the populations in which the disease is not introduced at time $t = 0$ presented in Table 4.2. The populations chosen to have the disease initialised within them are those who have a initial number of deaths due to the disease, indicating the disease is present in the population at point $t = 0$. The initial number of deaths is assumed to be the number of deaths of the first available historical data entry. Since the epidemic is modelled as a closed system with $N = S + E + I + Q + R + D + B$, the initial susceptible population is the total population without the initial exposed and infected individuals as well as the initial number of individuals reported dead.

4.4 Parameterisation

To effectively investigate the interacting dynamics of the spread of a disease within a spatial area, a set of parameters are defined. The defined parameters could be categorised as those

Parameter	Initial condition
Susceptible (S_0)	N-$E_0 - I_0 - D_0$
Exposed (E_0)	1
Infected (I_0)	1
Quarantined (Q_0)	0
Recovered (R_0)	0
Dead (D_0)	Number of deaths of first date
Buried (B_0)	0

TABLE 4.1: Initial conditions for populations in which disease is introduced at $t = 0$ for the SEIQRDB-model.

Parameter	Initial condition
Susceptible (S_0)	N
Exposed (E_0)	0
Infected (I_0)	0
Quarantined (Q_0)	0
Recovered (R_0)	0
Dead (D_0)	0
Buried (B_0)	0

TABLE 4.2: Initial conditions for populations in which disease is not introduced at $t = 0$ for the SEIQRDB-model.

describing the biological characteristics of the specified disease and the parameters representing the various intervention strategies investigated. Values for parameters that describe the biological characteristics of the disease are assumed to be consistent with literature, therefore average values of the literature reviewed ranges are used in this study. These parameters are presented in Table 4.3. The parameters uniquely calibrated for the specific case study in this thesis are given in Table 4.4.

Parameter symbol	Definition of parameter symbol	Value assigned	References
δ	Infection rate	0.09	[10, 67, 74, 84]
υ	Vaccination coefficient	0	
γ_I	Recovery rate	0.10	[10, 74, 84]
μ_I	Death rate	0.095	[10, 67]
f_3	Proportion of cases resulting in deaths	0.3186	[10, 67, 84]
f_4	Proportion of cases resulting in death after quarantine	0.3186	[67, 74, 84]
μ_Q	Death rate within quarantine	0.09	[67, 74, 84]
γ_Q	Recovery rate within quarantine	0.11	[74, 84]

TABLE 4.3: Parameters for which the average values of literature reviewed ranges are assigned.

The parameters $\frac{1}{\delta}, \frac{1}{\gamma_I}, \frac{1}{\mu_I}, \frac{1}{\gamma_Q}$ and $\frac{1}{\mu_Q}$ are regarded as the parameters describing the biological progression of the disease as an average duration of incubation and infectiousness. These values are independant of the region in which they are modelled and are therefore viewed as a universal representation of the disease which allows for the mean of the values found in literature to be assigned. The mean of the incubation period was assigned as the infection rate, δ. The infectiousness period follows after initial symptoms become visible. The average of the duration to death or recovery of an infected individual was assigned as the death and recovery rate, μ_I and γ_I, respectively. Due to medical treatment received within quarantine the recovery rate to increase and the death rate to decrease within a quarantine environment. This observation could be made from the probable ranges found within literature for the duration of quarantine

to recovery or death.

The parameters relating to the various intervention strategies implemented are υ, q_E, q_I, f_1, f_2, f_3, f_4 and f_5. The values assigned to these parameters are typically calibrated or deduced from relevant data as these values are dependant on the region in which the disease spread is modelled.

Parameter symbol	Definition of parameter symbol
β_1	Exposure rate of community
β_2	Exposure rate of traditional funerals
q_E	Quarantine rate
q_I	Quarantine rate from infected sate
f_1	Proportion exposed individuals quarantined
f_2	Proportion infected individuals quarantined
f_5	Proportion dead individuals safely buried

TABLE 4.4: Parameters for which the values are calibrated using historical epidemic data.

Though the exposure rate β is seen as a biological characteristic of the specified disease it is dependant on the various underlying factors of the specific region the disease is modelled in and therefore should be calibrated according to the spread of the disease within the region. Furthermore, two exposure rates are uniquely defined to represent two different scenarios of becoming exposed to the disease. The rate of becoming exposed in any other environment other than unsafe burials is denoted by β_1, where as exposure to the disease experienced at unsafe burials is denoted by β_2. Due to the absence of accurate data the probable range used to calibrate f_1, f_2 and f_5 is set to be between 0 and 1, taking all possibilities into account. Both β_1 and β_2 are calibrated in the range of 0 and 2 since ranges in literature was found to be greater than 1 but smaller than 2. The average duration of quarantining exposed or infected individuals is denoted by $\frac{1}{q_E}$ and $\frac{1}{q_I}$, respectively. The probable ranges in which these values are calibrated could be found within literature and translated into the average rate of quarantining exposed or infected individuals, q_E and q_I, respectively.

4.5 Software implementation

The model was developed in *PYTHON* 3.7. The pseudocode of the implementation is given in Algorithm 4.1. The model outputs were plotted with the built-in functions of the Matplotlib package in *PYTHON* 3.7.

4.6 Model verification

A fundamental step in the building process of a simulation model is determining whether the simulation accurately represents the real-world system being studied. Law defines *verification* as the stepwise process of determining whether the simulation model performs as intended [49]. Verification compares the conceptual model to the computer representation of the model. The verification process asks the questions: *Is the conceptual model implemented correctly in the computer? Is the representation of the parameters and the logical structures correct in the*

Algorithm 4.1: SEIQRD model

Input: β_1, β_2, δ, f_1, f_2, f_3, f_4, f_5, υ, q_E, q_I, γ_I, μ_I, μ_Q, γ_Q, migration proportion matrix, Initial state values of SEIQRDB, number of days to simulate, number of regions;
Output: The cumulative number of individuals in each state of the SEIQRD model for the number of simulated days, for each county;
for $i \leftarrow c+1$; `// Number of regions and an additional region representing the sum of all regions`
do
  for $j \leftarrow n$; `// Number of states in SEIQRDB model`
  do
    Generate a list for each state in the epidemic for each region;
  end
end
for $i \leftarrow t$; `// Number of simulated days`
do
  for $j \leftarrow c$; `// Number of regions`
  do
    Provide input parameters to set of difference equations 4.1 - 4.7;
    Add the day's number of individuals of each state to the corresponding regions list;
    Add the summation of the each region's number of individuals in each state to the additional regional list
  end
end
return The set of lists containing the cumulative number of individuals in each region and sum of all regions for various states of the disease.

computer implementation? This is the step described by Law as the debugging of the model from any logical errors [49].

Throughout the development of the model, an iterative approach was followed by compiling and executing the simulation continuously to ensure errors are resolved with each new addition to the model. Various verification methods mentioned by Law were applied in this study [49].

4.6.1 Theoretical structure test

An initial verification of the model equations were done through a theoretical structure verification test in which each equation is compared to knowledge available in literature. The initial equations were verified by the use of both Kermack and McKendrik's and Attenborough's models to derive the equations used in the simple SEIRD model [1, 9, 10]. In a previous model developed by Van Heerden [84], contact tracing and quarantine were added as intervention strategies, forming the SEIQRD model. The establishment of the final model with spatial temporal movement as well as safe burials intervention were done through the use of Valdez *et al.*'s model [83].

Extreme-conditions test

Direct extreme-conditions testing, introduced by Peterson and Elberlein [31] is the second approach followed to verify the output logic of the model. This gives an indication of whether the

model behaves as expected under prescribed simplified conditions. If successfully implemented, it enhances the client's confidence in the model. Once such tests are developed and implemented they can be executed at any time. Parameter values found in literature were assigned during implementation of the extreme-conditions test, as given in Table 4.5. The vaccination coefficient was chosen to be 0, since no accurate values are available within literature. The vaccination campaign was implemented as an experimental investigation which took place outside the scope of this project's data time frame. The initial conditions for each state of the model during execution of the extreme-conditions test are given in Tables 4.1, 4.2, 4.3 and 4.5.

Parameter symbol	Definition of parameter symbol	Value assigned	Reference
β_1	Exposure rate	0.57	[1, 10, 63, 67, 74, 84]
β_2	Exposure rate due to unsafe burials	0.30	[42, 63]
q_E	Quarantine rate from exposed state	0.25	[67, 74, 84]
q_I	Quarantine rate from infected state	0.24	[67, 74, 84]
f_1	Proportion quarantined through contact tracing	0.15	[67, 74, 104]
f_2	Proportion of infected individuals removed for quarantine	0.20	[67, 74, 104]
f_5	Proportion of deaths safely buried	0.37	[42, 63, 80]

TABLE 4.5: Initial parameters values used in the simple SEIQRD-model for model verification purposes.

Sixteen automated verification tests were executed, verifying each phase of the epidemic as implemented in the model.

1. With no susceptible people (S=0), there will be no stock of vulnerable individuals to infect and therefore the number of infected people added to the infected population is expected to be zero.
2. With a zero exposure rate none of the susceptible individuals would be expected to become exposed and the exposed subpopulation would remain zero.
3. As β strives to ∞, it is expected that all susceptible individuals would become exposed.
4. With a zero infection rate, none of the susceptible individuals would become infected and there should be no increase in the infected subpopulation.
5. As the infection rate strives to ∞ all susceptible and exposed individuals will become infected, and the time to steady state will decrease.
6. With a quarantine rate of zero it is expected that all individuals would follow the biological path of the illness resulting in either the death or recovery state and a quarantine subpopulation of zero.
7. If the recovery rate is set at zero it is expected that all infected individuals will become deceased.
8. With a recovery rate striving to ∞, the time to steady state of the recovered subpopulation should decrease, and the death subpopulation's steady state remain the half of the infected subpopulation.
9. If the death rate is set to zero, it is expected that all infected individuals would recover from the disease.

10. With a death rate striving to ∞, the time to steady state of the death stock should decrease, and the recovered subpopulation is expected to remain half of all infected individuals.
11. If the proportion of individuals removed for quarantine is zero it is expected that all individuals would follow the biological path of the illness resulting in either the death or recovery state.
12. If the proportion of reported cases resulting in death is set at zero it is expected that all infected individuals would recover from the disease and therefore resulting in a zero death subpopulation.
13. If the proportion of reported cases resulting in deaths equal to 1, the number of infected individuals to recover from the disease is expected to be zero.
14. If the proportion of safe buried individuals is set at zero, it is expected that all non quarantined deaths would be unsafe burials, though deaths observed from the quarantine state would still be safely buried.
15. If the proportion of safe buried individuals is set at one, it is expected that all deaths would result in safe burials.
16. Modelling infectious diseases there can be no negative values in the model, therefore if all variables are greater or equal to zero the expected output should be values greater or equal to zero.

Table 4.6 contains the sixteen verification tests with each test's unique conditions, expected outputs and the outputs given by the model. The model successfully achieved all expected outputs.

Test ID	Condition	Expected output
T_1	$S_0 = 0$	R,D,B $= 0$; $S = S_0, E = E_0, I = I_0$
T_2	$\beta = 0$	$E = E_0, I = I_0$ R,D $= 0$
T_3	$\beta = \infty$	$S = 0$; $E = S_0$
T_4	$\delta = 0$	$I = I_0$ R,D $= 0$
T_5	$\delta = \infty$	$S, E = 0$
T_6	$q_E, q_I = 0$	$D = 0.75I; R = 0.25I; Q = 0$
T_7	$\gamma_I, \gamma_Q = 0$	$D = I$; R=0
T_8	$\gamma_I, \gamma_Q = \infty$	$R = 0.25I$; $D = 0.75I$
T_9	$\mu_I, \mu_Q = 0$	$R = I$; D=0
T_{10}	$\mu_I, \mu_Q = \infty$	$D = 0.75I$; $R = 0.25I$
T_{11}	$f_1, f_2 = 0$	Q $= 0$; $R = 0.25I; D = 0.75I$
T_{12}	$f_3, f_4 = 0$	$R = I$; D=0
T_{13}	$f_3, f_4 = 1$	$D = I$; R=0
T_{14}	$f_5 = 0$	$D = (1 - f_2)f_3I; B = f_4Q$
T_{15}	$f_5 = 1$	$D = 0; B = D + f_4Q$
T_{16}	S,E,I,R,D,B ≥ 0	S,E,I,R,D,B ≥ 0

TABLE 4.6: Verification test with conditions and expected outputs for SEIQRDB model.

Structure oriented behaviour test

A final theoretical structural verification test was implemented, through a structure oriented behaviour test, where simulations are run to validate the behaviour of each parameter against either the real system events or theoretical knowledge available in literature [107].

Comparing the model output to available knowledge of epidemic curves within literature, the verification of the simulation model was established. Kermack and McKendrik's SIR model for infectious diseases with its noticeable characteristics was used to verify the simulation model presented [1, 9, 10]. The time series output of both individuals recovered and safely buried should resemble an increasing s-curve shape evolving into a steady state, after equilibrium is reached. The number of infected individuals should rapidly increase over time until the local maximum is reached, at which point the rate of becoming infected is equal to the rate of recovery. Thereafter, a decrease in the number of infected should be seen due to the number of susceptible individuals decreasing to a point where there are no more susceptible individuals to infect. This behaviour produces a hill-like shape in the infected individuals curve. This same hill like shape is expected of the number of quarantined individuals, since an increase in infected individuals would cause in increase in quarantined individuals as this is the natural progression of the model. A decrease in number of quarantined individuals are expected as the infected individuals curve decreases, however the number of quarantined individuals surpasses the number of infected individuals since both exposed and infected individuals could be quarantine. The number of deaths are in direct relationship with the number of infected individuals causing a expectation for it to resemble the same hill-like form, though the peak would be experienced at a later stage compared to the infected individuals due to the natural progression of the disease. These are the unique characteristics of Kermack and Mckendrik's SIR model and as may be seen in Figure 4.2, the simulation model successfully resembles all above mentioned characteristics.

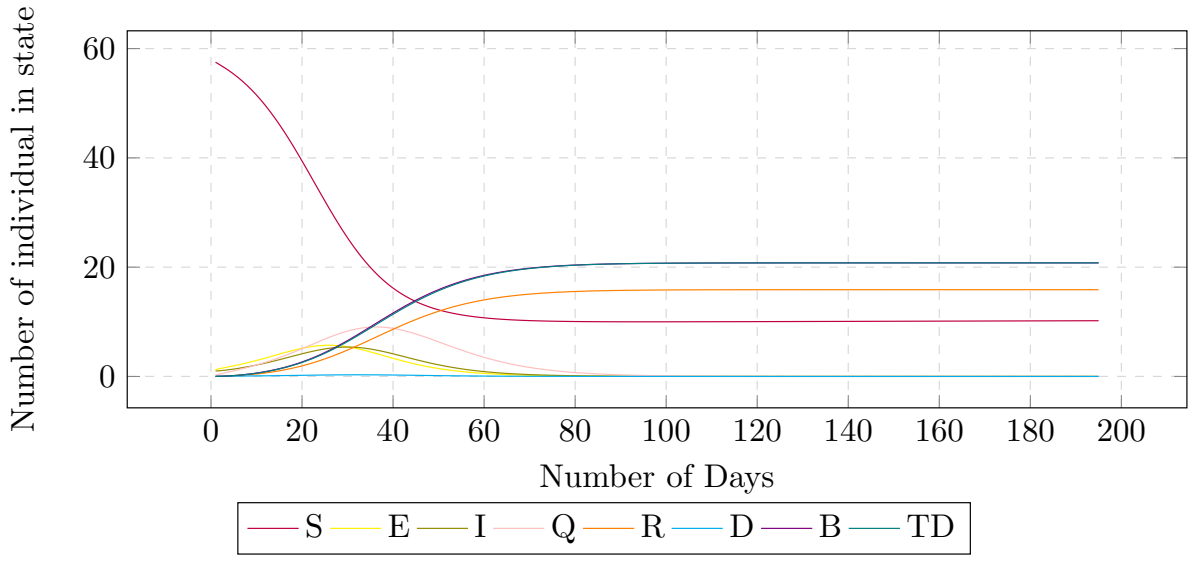

FIGURE 4.2: *Structured oriented behaviour test of SEIQRD model with simulation output.*

4.7 Chapter summary

Within this chapter the conceptual model is presented in §4.1 providing the reader a visual representation of the model.A brief discussion of the conceptual models formulation is given, explaining the challenges in the approach. The explicit and implicit assumptions used during the model conceptualisation are discussed in §4.2. The mathematical formulation of the model is given in §4.3, along with the boundary conditions and the initial conditions used in the model. In §4§.4 the parameterisation process is explained followed by a discussion on the software implementation. Finally the chapter concludes with the verification of the model implemented in Python through various simulation runs. The model was therefore deemed valid to be used to accurately replicate the interacting dynamics of the Ebola virus disease.

CHAPTER 5

Case study: Sierra Leone

Contents

In this chapter, a case study of the model application is presented. The chapter opens with a brief discussion of the Ebola outbreak in Sierra Leone of 2014-2015 in §5.1, followed by a geographical representation of the 14 counties within Sierra Leone and their population distribution of 2015 in §5.1.1. The data used in the model calibration is presented in §5.1.2 with a discussion of each county's number of reported cases and deaths. The chapter includes the validation process of the model in §5.2. Finally the chapter concludes with various simulation experiments evaluating the effectiveness of intervention strategies in the Sierra Leone outbreak of 2014-2015 in §5.3-§5.4.

5.1 The Ebola epidemic in Sierra Leone

Sierra Leone experienced a slow and silent start to the Ebola epidemic, gradually building to an exponential increase in the number of cases during May and June of 2014. By November 2014, more than 7 000 Ebola cases were reported resulting in 2 192 deaths [23]. With a suboptimal health system and poor infrastructure, the severity of the outbreak increased and led to a national emergency. The sudden increase in the number of Ebola cases was traced back to a funeral in

Kailahun of a traditional healer. Epidemiologists identified this single funeral as the cause of 365 confirmed Ebola cases as well as cases identified in Liberia [96]. Kailahun and Kenema were the initial epicentre of the outbreak and was the focal point of WHO and other partners response strategies. An international state of emergency was declared on the 8th of August, deploying military aid to the 13 counties already infected. Freetown, the capital of Sierra Leone, became the epicentre in late September. With a densely populated capital the biggest challenges were the limited treatment facilities and the difficulty to execute effective contact tracing. More than 30 bodies were buried per day in Freetown [96].

5.1.1 Geography

Sierra Leone is made up of four provinces, namely the Western Area, Northern, Southern and Eastern province. Each province is further subdivided into distinct counties. The Western Area province, which contains the capital of Sierra Leone, is divided into two counties, Western Area Rural county and Western Area Urban county. The Northern province is made up of five counties namely, Bombali county, Kambia county, Koinadugu county, Port Loko county and Tonkolili county. The Southern province is subdivided as the Bo county, the Bonthe county, the Moyamba county and the Pujehun county. The Kailahun county, Kenema county and the Kono county are the three counties of the Eastern province of Sierra Leone. The distribution of Sierra Leone's population over the 14 counties for 2015 may be seen in Figure 5.1.

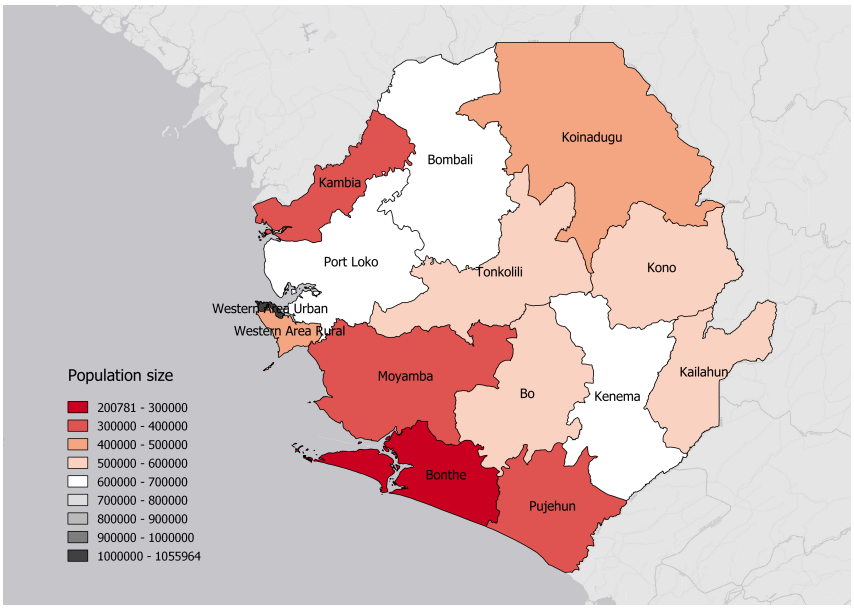

FIGURE 5.1: *The population distribution of the 14 counties of Sierra Leone in 2015.*

Bonthe county in the Southern province has the smallest population distribution compared to Freetown, the capital of Sierra Leone, located in the Western Area Urban county with the highest population distribution. Port Loko and Tonkolili counties has the highest population distribution of the Northern province. In the Eastern province Kenema county had the highest population distribution. Bo county is the county with the highest population distribution in the Southern province of Sierra Leone.

5.1.2 Data

Two data sets, namely population based data and migration data, were used for the validation and calibration of the proposed model.

Population based data

Data gathered from the United Nations Office for the Coordination of Humanitarian Affairs (UNOCHA) database stating the number of recorded cases as well as recorded deaths for August 2014 until March 2015 are used in this project [36]. Sub national data for Sierra Leone was selected for analysis, due to it being the most consistent and complete data available. Daily national reports of the number of reported Ebola cases and deaths is given in Figure 5.2.

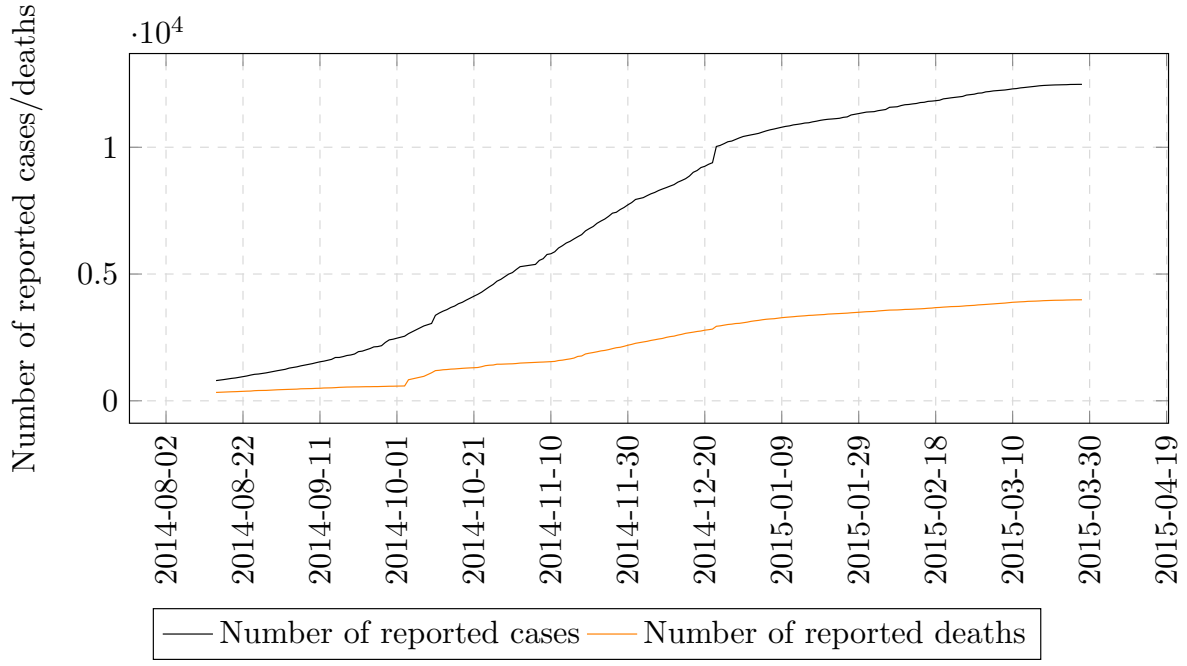

FIGURE 5.2: *The number of reported Ebola cases and deaths for Sierra Leone from 18 August 2014 to 28 March 2015.*

The initial population for Sierra Leone was 6 435 000 as reported by the WHO [99]. Cumulatively, 3 787 deaths were reported by March 2015 for Sierra Leone. These observations may be deemed as an underestimation of the true figure, with the WHO stating that the unrecorded number of deaths due to Ebola, may be two to three times more [98]. By end of March 2016 the number of cases for Sierra Leone was 11 881. The given data provide only the number of clinical reported cases and therefore may be an underestimation of the true figure. The data does not include patient-level information, but rather consist of laboratory confirmed, suspected or probable cases of the Ebola, and is thought to present the best available estimate of the epidemic. Noted from the data is the significant difference between the number of deaths and number of reported cases for each country. Reported cases could either result in recovery or death due to Ebola. By August 15, 2014 a total of 830 Ebola cases and 344 deaths were reported. Observed from the data in the month of September 2014 there was a doubling in the number of reported cases and deaths, which is corresponding to the WHO reports describing this as the peak of the epidemic with more than 500 new cases per week [23]. The daily number of reported Ebola

cases and deaths for all 14 counties in Sierra Leone from August 15, 2014 until March 28, 2015, are plotted in Figures 5.3 to 5.16.

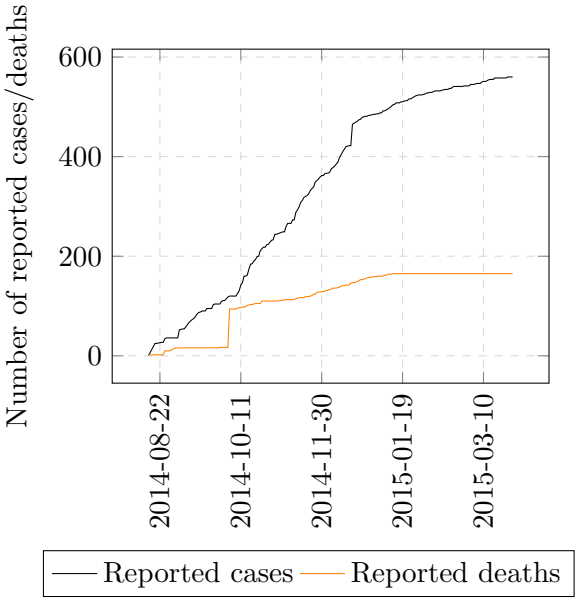

FIGURE 5.3: *Number of reported Ebola cases and deaths for Bo county from 18 August 2014 to 28 March 2015.*

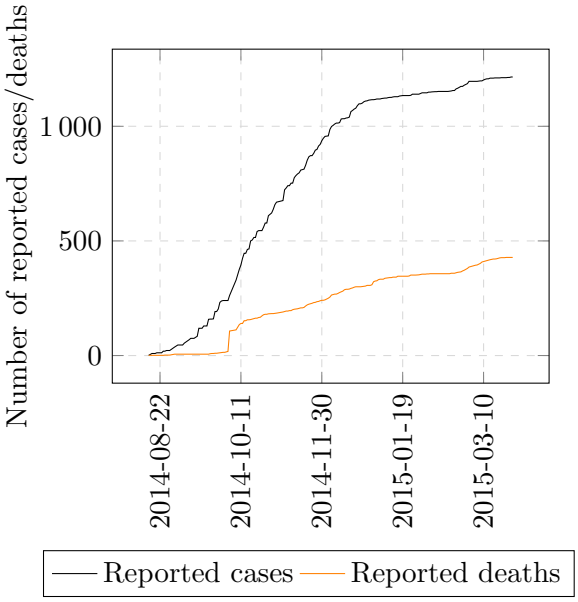

FIGURE 5.4: *Number of reported Ebola cases and deaths for Bombali county from 18 August 2014 to 28 March 2015.*

The Bo county is classified as a rural district, by the population and housing census of 2015, with 66% of the residents living in a rural community [29]. The first case of Ebola in the Bo county was reported on 15 August 2014. By 28 March 2015, a total of 560 cases were reported with 165 deaths (see Figure 5.3). On the 4th of October 2014 a significant spike in the number of deaths was observed, this could be due to delays experienced in reporting of deaths.

The Bombali county reported 1 215 cases by 28 March 2015 and 428 deaths due to Ebola (see Figure 5.4). Approximately 75% of individuals in this county live within a rural community [29]. Bombali shares a border with Kindia, Guinea, allowing for migration across the border to further impact the progression of the epidemic within the county. The same delay in the number of deaths reported was experienced in the Bombali county on the 4th of October 2014.

The coastal county, Bonthe, reported merely 23 cases by 28 March 2015 and 7 deaths due to Ebola (see Figure 5.5). The first case was reported 31 August 2014. Though there was an increase in cases after December 2014, the number of deaths reached a plateau. This could be due to under reporting or patients transported to other counties to be treated and counted as part of the chosen county's death toll. The Bonthe county is the smallest county in population size with limited resource and infrastructure.

For the first stage of the Ebola epidemic, Kailahun county was described as the epicentre with a cumulative count of 625 Ebola cases and 133 deaths by 28 March 2015 (see Figure 5.6). The first case was reported early May 2014 and by 15 August 2014, a total of 428 cases were reported as well as 206 deaths. A significant increase in the number of reported cases and deaths may be observed from the data, which correlates to the reports from the WHO describing this as the peak of the epidemic [23]. By late October 2014 the emergency situation in Kailahun was stabilised which decreased the number of reported cases and deaths, bringing it to a plateau.

Kambia county shares a border with Forecariah county in Guinea, which had a high count of

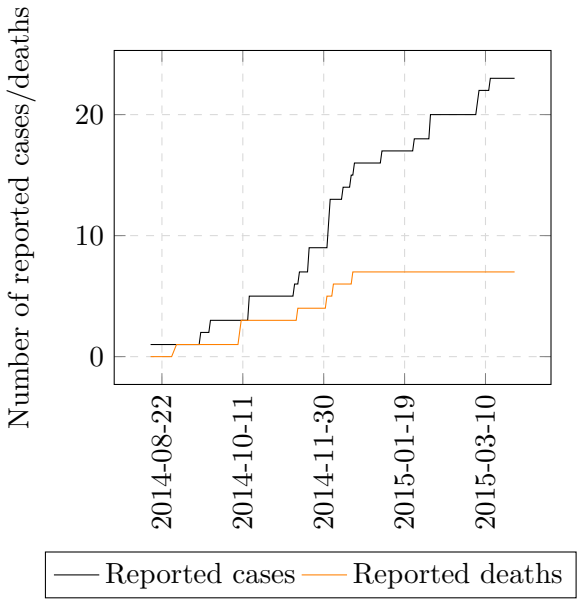

FIGURE 5.5: *Number of reported Ebola cases and deaths for Bonthe county from 18 August 2014 to 28 March 2015.*

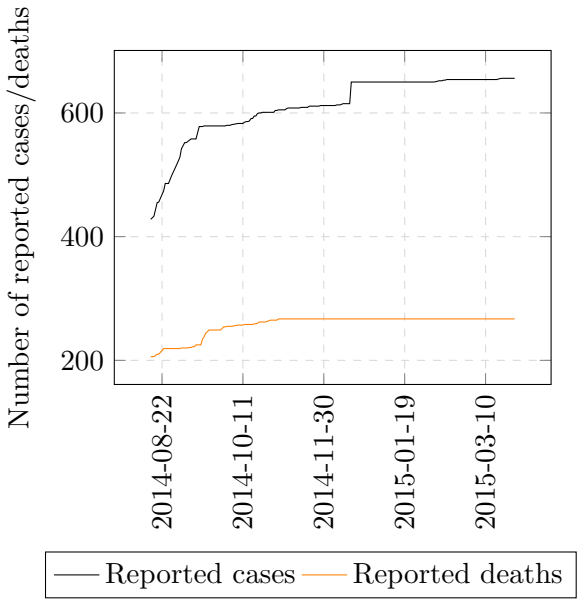

FIGURE 5.6: *Number of reported Ebola cases and deaths for Kailahun county from 18 August 2014 to 28 March 2015.*

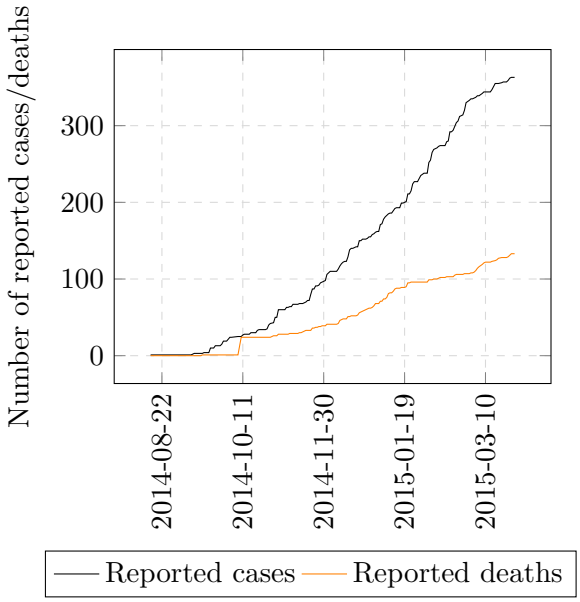

FIGURE 5.7: *Number of reported Ebola cases and deaths for Kambia county from 18 August 2014 to 28 March 2015.*

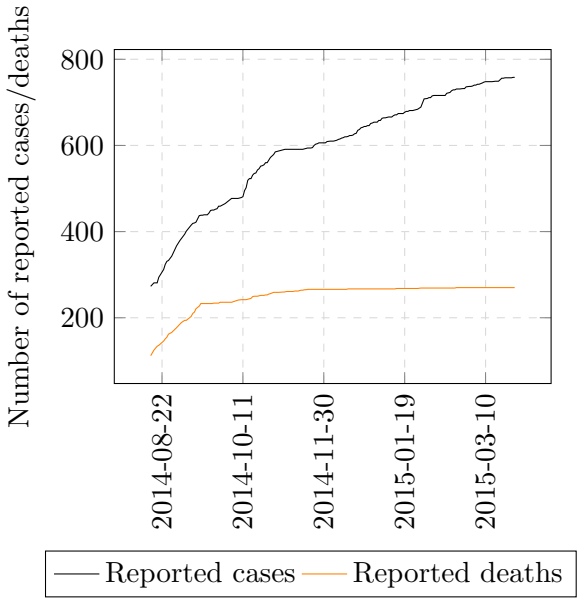

FIGURE 5.8: *Number of reported Ebola cases and deaths for Kenema county from 18 August 2014 to 28 March 2015.*

reported Ebola cases and may have contributed to the number of reported deaths in Kambia county. On 15 August 2014, the first case was reported with the first death only reported by the 16 September 2014. A total of 363 cases were reported by 28 March 2015 with 133 deaths (see Figure 5.7). Kambia county has a population distribution of 4.9% of the total population of Sierra Leone [29]. A spike in the number of deaths may be observed in the data on the 9th of October, possibly due to a delay in case reporting.

As with Kialahun county, Kenema county was regarded as the epicentre of the epidemic for the

first stage of disease spread. A total of 758 cases were reported by 28 March 2015 with 270 deaths. By 15 August 2014, 273 cases has already been reported with 112 deaths. The first case was reported in June 2014. A rapid increase in both cases and deaths may be observed in the data for the months of September and October, whereafter the emergency situation stabilised and reached a plateau. The Kenema county was the focal point of the WHO and other partners' response strategies for the first stage of the epidemic, whereafter a greater demand evolved in the capital city, Freetown [96].

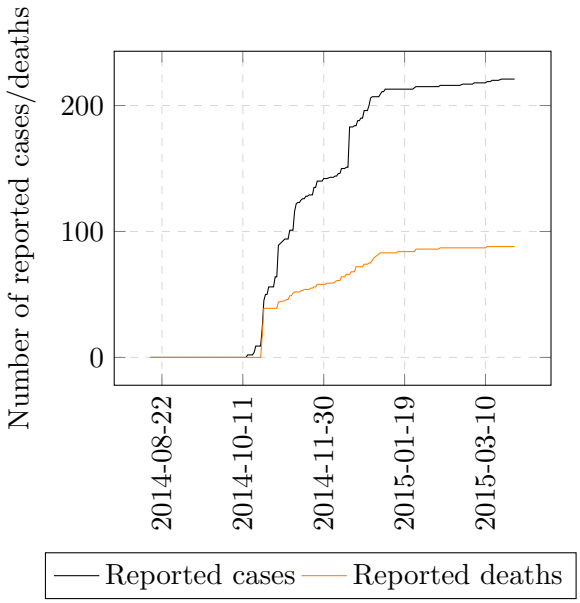

FIGURE 5.9: *Number of reported Ebola cases and deaths for Koinadugu county from 18 August 2014 to 28 March 2015.*

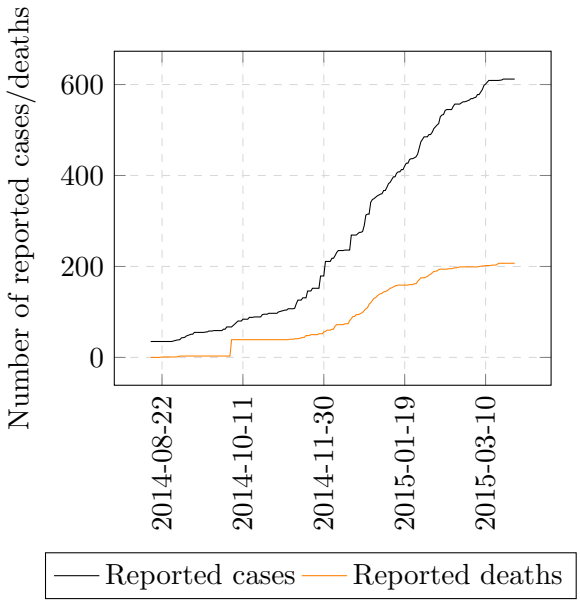

FIGURE 5.10: *Number of reported Ebola cases and deaths for Kono county from 18 August 2014 to 28 March 2015.*

Koinadugu county, situated in the northern province, bordering Guinea, reported 221 cases and 88 deaths by 28 March 2015 (see Figure 5.9). Weak data collection or delay in case reporting could explain the spike in cases observed on 24 October 2014. The Koinadugu county has a population distribution of 5.8% of the total population of Sierra Leone, and is also classified as rural with 58% of the residents living in a rural community [29].

A total of 612 cases and 207 deaths were reported by 28 March 2015 in Kono county (see Figure 5.10), ranking it as one of the counties with the highest number of cases. The first case was reported in June 2014 and by 15 August 2014, 35 cases were reported. Due to overwhelmed treatment centres, hospitals and community centres, delayed reports were received causing a spike in the number of cases reported in October of more than 30 new cases. The Kono county is located in the southern region of Sierra Leone, bordering Guinea, which may have increased the number of reported cases in Kono due to Ebola infected individuals seeking medical treatment.

The coastal county, Moyamba, reported 343 cases and 107 deaths by 28 March 2015 (see Figure 5.11), with an initial case and death count of 6 and 3, respectively, on 15 August 2014. Moyamba has a population size of 4.5% of the total population of Sierra Leone and is classified as a rural county with 51% of individuals in Moyamba living in a rural community [29].

Port Loko reported 1 923 cases and 624 deaths by 28 March 2015 (see Figure 5.12), making it the county with the second highest number of reported cases and deaths. The first case was identified in June 2014, leading to 27 cases and 3 deaths reported by 15 August 2014. Though a slow onset of the disease spread was experienced in the Port Loko county, the high population

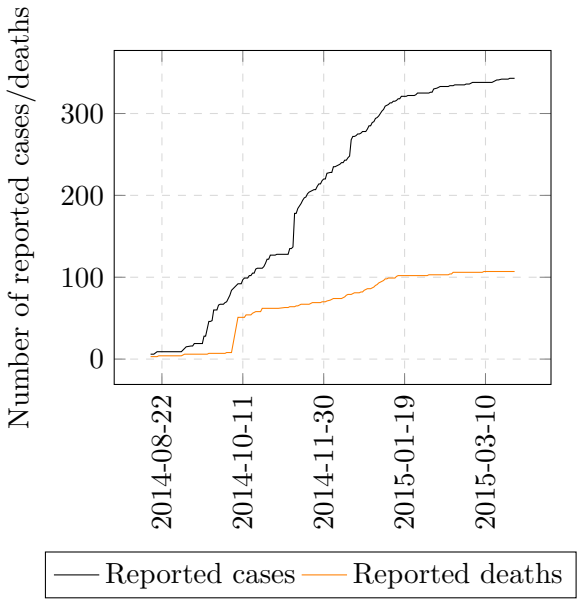

FIGURE 5.11: *Number of reported Ebola cases and deaths for Moyamba county from 18 August 2014 to 28 March 2015.*

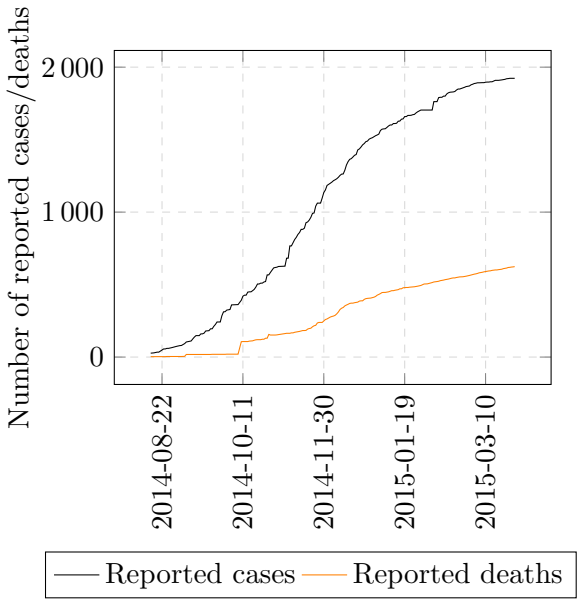

FIGURE 5.12: *Number of reported Ebola cases and deaths for Port Loko county from 18 August 2014 to 28 March 2015.*

distribution and highly affected neighbouring counties led to an exponential growth in number of reported cases and deaths.

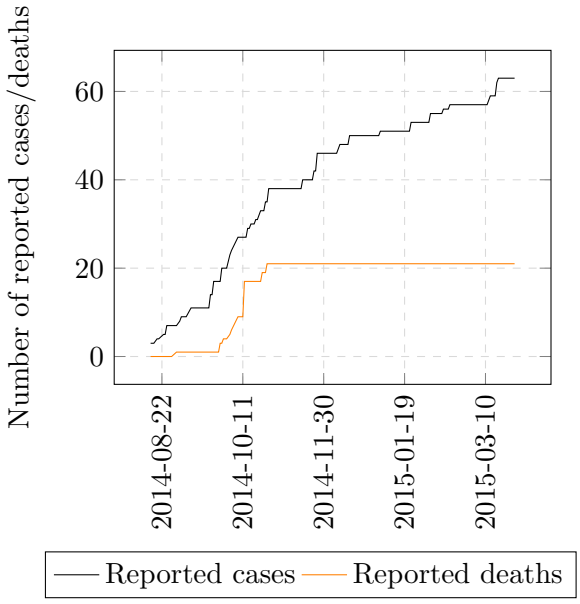

FIGURE 5.13: *Number of reported Ebola cases and deaths for Pujehun county from 18 August 2014 to 28 March 2015.*

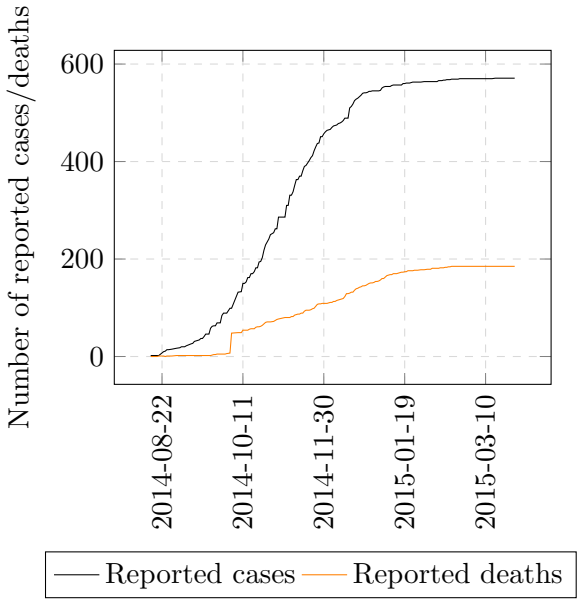

FIGURE 5.14: *Number of reported Ebola cases and deaths for Tonkolili county from 18 August 2014 to 28 March 2015.*

The coastal county, Pujehun, situated in the southern region of Sierra Leone reported 63 cases and 21 deaths by 28 March 2015. The closest treatment centre to Pujehun was in Kenema, the neighbouring county, causing tremendous delay with both reporting and treating of new cases. This could be a possible explanation of the stepwise appearance in the data (see Figure 5.13). The Pujehun county is classified as rural with more than 55% of the residents living in rural

communities.

In the heart of Sierra Leone lies Tonokolili county. By 28 March 2015, a total of 571 cases were reported with 185 deaths (see Figure 5.14). Tonokolili has a population size of 7.5% of the total population of Sierra Leone, and the county is classified as rural with 73% of individuals living in rural communities.

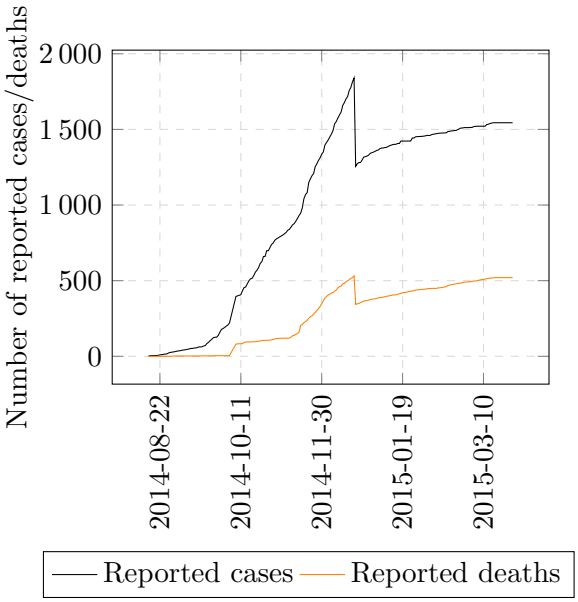

FIGURE 5.15: *Number of reported Ebola cases and deaths for Western Area Rural county from 18 August 2014 to 28 March 2015.*

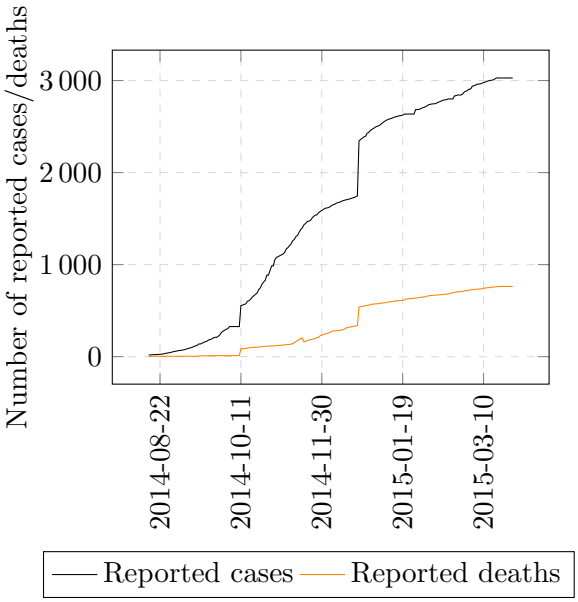

FIGURE 5.16: *Number of reported Ebola cases and deaths for Western Area Urban county from 18 August 2014 to 28 March 2015.*

Both Western Area Rural and Western Area Urban are regarded as the smallest counties in surface area, though Western Urban Area county includes the capital city, Freetown, has the highest population size of all other counties. A large part of the rural community of Sierra Leone daily commute or migrate to the Western Urban/Rural Areas seeking work. Western Urban Area reported 3 028 cases by 28 March 2015 with 763 deaths whereas Western Rural Area reported 1 544 cases and 520 deaths (see Figure 5.15 and 5.16). A slow start to the disease spread was seen in the Western Urban Area county until early June, where the first case was identified. These counties are classified as urban counties due to the large population sizes. The Western Urban Area and the Western Rural Area has a population size of 14.9% and 6.9% of the total population of Sierra Leone, respectfully.

A decrease in the cumulative graph is observed for both the cases and deaths in the Western Rural Area county, which is not possible, and may be explained as corrections to the data due to over reporting The date at which the correction was implemented is on the 21 December 2014 and it may clearly be observed that a total of 200 deaths were removed to compensate for over-reporting. Replacing the 200 deaths and allowing the cumulative curve to follow its initial trend, the cumulative number of deaths on 28 March 2015 corresponds to the cumulative number of deaths reported by the WHO on 28 March 2015. The adjusted cumulative number of cases and deaths for the Western Area Rural may be seen in Figure 5.17.

A decrease of a 100 deaths in Western Area Urban is observed between the dates of 19 November 2014 and 22 December 2014. This may be due to delayed reporting or unreliable data exchange or some of the cases reported in Western Area Rural were wrongly identified and later replaced back into the Western Area Urban's number of reported cases. This decrease is not observed

in the cumulative number of cases, indicating that this is a data error. By replacing the 100 deaths and allowing the adjusted cumulative number of cases and deaths for the Western Area Rural as seen in Figure 5.18, to correspond to the cumulative number of deaths reported by the WHO on 28 March 2015.

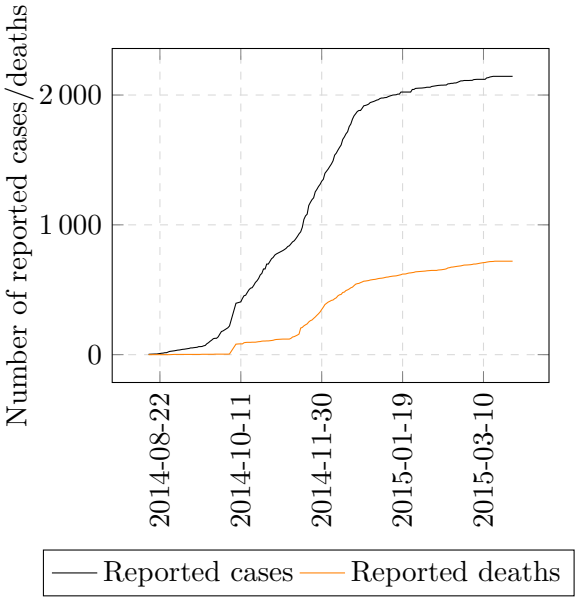

FIGURE 5.17: *Number of reported Ebola cases and deaths for Western Area Rural county from 18 August 2014 to 28 March 2015.*

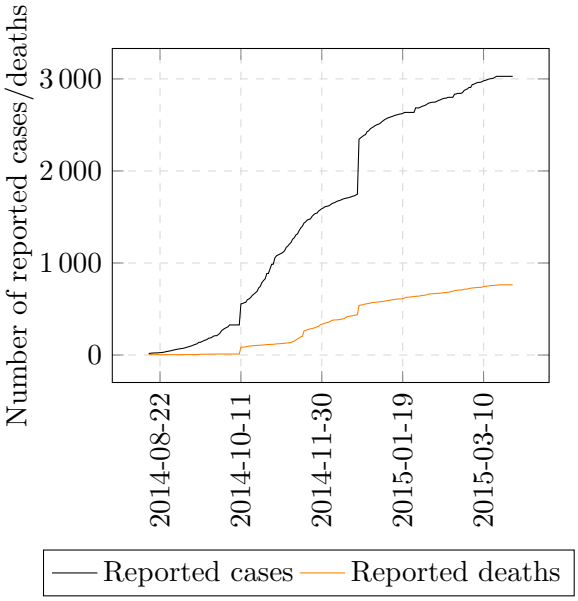

FIGURE 5.18: *Number of reported Ebola cases and deaths for Western Area Urban county from 18 August 2014 to 28 March 2015.*

Mobility data

In literature various data types have been used to model the mobility of individuals within a disaster system, including air and sea travel datasets, census migration data, travel history and displacement surveys, GPS tracking data and volunteered geographical information as well as satellite night time light data. All these data sources are potentially useful for modelling individual movements, however mobile phone call detail records (CDRs) are the most accurate short term human movement estimator. Access to CDRs are restricted due to commercial and privacy concerns, causing difficulties in sharing such datasets. Wesolowski *et al.* and Rutanonchai *et al.* demonstrated that open source census derived internal migration data served as a reliable estimator to the internal connectivity of individuals within a country over various temporal scales [88].

For this project, temporal human internal migration data was collected from the model developed by Sorichetta *et al.* [78], where they applied a gravity model to internal census-based migration microdata available from the online IPUMS-international database to estimate 5-year (2005-2010) internal human migration flows for various malaria infected countries, including Sierra Leone. Since it has been demonstrated that both 1- and 5-year census-based internal migration data closely corresponded to short term population movements and mostly 5-year temporal time interval data was available from the IPUMSI database, Sorichetta *et al.* used this dataset as a representation of the individual movements within the various countries . Although this dataset may be deemed as historical and not reflecting the behaviour changes due to the crisis of Ebola, it is still assumed that the mobility patterns obtained by Sorichetta *et al.* is a good approximation of the routine commuting patterns of the population of Sierra Leone prior to the outbreak.

This project therefore focusses on the movement of individuals prior to the outbreak, describing the movement patterns which caused the vigorous disease spread instead of the post-outbreak movements of individuals avoiding infection.

Data preparation was done through the use of a spreadsheet, translating the raw data to a migration proportion matrix where the sum of each row entry represents the migration proportion received by county i and the sum of each column entry represents the migration proportion moving from county i (see Table 5.1)). The data provided by the model developed by Sorichetta *et al.* is used for both calibration and parameter analysis in this project. The results of Sorichetta *et al.*'s gravity model provided an estimated average number of people migrating from county i to county j per day, for $i, j \in [1, 14]$. Each element within the migration matrix is the proportion of individuals in county i migrating to county j, which is estimated by the number of individuals migrating from county i to county j over the total population of county i. Only the inter-spatial dynamics between counties are modelled and therefore the diagonal elements of the proportion matrix is zero. This is in conjunction with the assumption that all individuals within a county are fully mixed. The migration matrix for the 14 counties of Sierra Leone is given in Table 5.1.

	Bo	Bombali	Bonthe	Kailahun	Kambia	Kenema	Koinadugu	Kono	Moyamba	Port Loko	Pujehun	Tonokolili	WAR	WAU
Bo	0.00000	0.00217	0.00589	0.00265	0.00267	0.00833	0.00251	0.00308	0.00796	0.00194	0.00476	0.00626	0.01195	0.00686
Bombali	0.00211	0.00000	0.00170	0.00170	0.00751	0.00200	0.00522	0.00235	0.00258	0.00395	0.00108	0.00565	0.01061	0.00623
Bonthe	0.00394	0.00117	0.00000	0.00124	0.00152	0.00151	0.00111	0.00145	0.00565	0.00113	0.00254	0.00139	0.00759	0.00418
Kailahun	0.00233	0.00153	0.00164	0.00000	0.00140	0.00668	0.00203	0.00662	0.00218	0.00116	0.00137	0.00187	0.00593	0.00304
Kambia	0.00176	0.00507	0.00149	0.00104	0.00000	0.00146	0.00191	0.00175	0.00229	0.00505	0.00083	0.00198	0.01258	0.00807
Kenema	0.00867	0.00214	0.00235	0.00789	0.00230	0.00000	0.00259	0.00663	0.00306	0.00184	0.00451	0.00426	0.01068	0.00560
Koinadugu	0.00172	0.00366	0.00114	0.00158	0.00199	0.00170	0.00000	0.00423	0.00193	0.00134	0.00085	0.00318	0.00686	0.00385
Kono	0.00243	0.00190	0.00171	0.00592	0.00210	0.00502	0.00488	0.00000	0.00242	0.00153	0.00137	0.00397	0.00771	0.00408
Moyamba	0.00506	0.00168	0.00536	0.00157	0.00221	0.00186	0.00179	0.00195	0.00000	0.00389	0.00130	0.00407	0.02543	0.00738
Port Loko	0.00218	0.00456	0.00191	0.00148	0.00862	0.00199	0.00222	0.00218	0.00689	0.00000	0.00127	0.00446	0.03645	0.01410
Pujehun	0.00501	0.00117	0.00400	0.00164	0.00132	0.00456	0.00131	0.00183	0.00216	0.00119	0.00000	0.00159	0.00758	0.00399
Tonokolili	0.00533	0.00493	0.00177	0.00180	0.00256	0.00349	0.00396	0.00429	0.00545	0.00338	0.00128	0.00000	0.00992	0.00569
WAR	0.00306	0.00279	0.00290	0.00172	0.00489	0.00263	0.00257	0.00250	0.01027	0.00834	0.00184	0.00298	0.00000	0.02874
WAU	0.00378	0.00352	0.00344	0.00190	0.00674	0.00296	0.00310	0.00284	0.00640	0.00693	0.00208	0.00368	0.06203	0.00000

TABLE 5.1: Temporal migration data of 14 counties of Sierra Leone based on 2005-2010 census data.

It is expected that neighbouring counties would have higher migration proportions compared to those counties not sharing borders. This is seen in Table 5.1, for example Kailahun county is neighboured by Kenema and Kono county, which have higher migration proportions from Kailahun county to both these counties compared to the migration proportion received by Kambia county from Kailahun county, which is on the opposite north-west border of Sierra Leone.

5.2 Model validation

The *validation* of a simulation model is the confirming of the conceptual model as an accurate representation of the actual system under study. The aim of verification and validation, is to increase the credibility of the simulation to an acceptable level such that decisions can be made pertaining to the real-world system [15]. Law suggests that historically, output analysis of simulations are lacking in the field of simulation due to simulation data rarely being independant, not allowing for classical statistical analysis based on observation to be applicable [49, 85].

The simulation model presented in this thesis is dependant on the input values during model execution. In biological simulation, such as the one presented in this thesis, the input values would ideally be based on data gathered from in-field experiments and measurements. Such fine

data is unfortunately not easily gathered and many times not acquired to the desired level of aggregation through research. The focus then of such a simulation study is the significance of changeable input parameters implemented by the simulation operator and the effect of these parameter changes on the behaviour of the system. The output data could therefore be compared to historical data, which describes the overall behaviour of the real-world system. Noted discrepancies between the simulation output and actual data could give insight that may improve input parameters to more accurately represent the system being studied or inform in-field researchers where a significant lack in understanding of the systems behaviour exists. The process of output analysis and parameter variation mentioned above correlates closely to the validation process described by Banks [15].

An accurate model representation of the spread of Ebola within a population should be achieved in order to analyse and understand the dynamics involved. The complexity of the dynamics is, however, too great to be adequately described in a simple SEIQRDB model. Although all phases of the disease are included in the model, many underlying factors are excluded such as the reaction of the human population due to fear of becoming infected or the impact of media and educational campaigns on interacting dynamics of the population. A simple model can, however, still be useful if it predicts the major behavioural patterns. In order to establish the behavioural validity of the SEIQRDB model a calibration experiment was implemented.

Calibration experiment

A calibration experiment was implemented on the SEIQRDB model to test whether a SEIQRDB model can replicate the major patterns observed in a real Ebola epidemic. The objective function of the calibration experiment is to minimise the difference of the simulated output dataset and the historical dataset as produced by the WHO through minimising the root mean square error (RMSE) of the two datasets compared. All models and parameter calibration experiments were done in *PYTHON* 3.7. The calibration experiment was implemented on the fourteen counties of Sierra Leone and the country as a whole, with fixed migration proportions sampled from the project done by Sorichetta *et al.* [78].

Probable ranges for the parameter values are provided in literature, and were used in the SEIQRDB model calibration. The parameter values for $v, \delta, \gamma_I, \mu_I, f_3, f_4, \mu_Q$ and γ_Q were implemented as the mean value found within literature (see Table 5.2), since these relate to the biological progression of the disease, and are assumed to not be country specific in this thesis. The incubation period, $\frac{1}{\delta}$, reported by the WHO, is between 2 to 21 days, relating to a probable range for the infection rate to be between $0.05 - 0.5$ [101]. The mean of the incubation period was assigned as the infection rate, δ. The infectiousness period follows after initial symptoms become visible with a duration between 6 to 16 days. Recovery from the disease was reported to be between 7 10 14 days, compared to the death following 6 to 16 days after initial symptoms became visible [2]. The average of these ranges were assigned as the death and recovery rate, μ_I and γ_I, respectively. Due to medical treatment received within quarantine the recovery rate is expected to increase and the death rate to decrease. This is observed in the probable ranges found within literature for the duration of quarantine to recovery or death, 7 to 10 and 10 to 16 days, respectively [77]. The proportion of confirmed cases resulting in death was estimated from the data gathered by the WHO to be 31.86% [101]. The proportion of cases resulting in death before quarantine and after quarantine was assumed to be the same as no clear aggregated data is available to uniquely assign values.

The parameter values for $\beta_1, \beta_2, q_E, q_I, f_1, f_2$ and f_5, were calibrated since they are uniquely influenced by community and county specific dynamics. The ranges used to calibrate the uniquely

Parameter symbol	Definition of parameter symbol	Value assigned	Reference
υ	Vaccination coefficient	0	
δ	Infection rate	0.13	[67, 74, 83, 84]
γ_I	Recovery rate	0.10	[10, 74, 84]
μ_I	Death rate	0.095	[10, 67, 83]
f_3	Proportion of cases resulting in deaths	0.3186	[10, 67, 83, 84]
f_4	Proportion of cases resulting in death after quarantine	0.3186	[67, 74, 84]
μ_Q	Death rate within quarantine	0.09	[67, 74, 83, 84]
γ_Q	Recovery rate within quarantine	0.11	[74, 83, 84]

TABLE 5.2: Initial parameters values used in the SEIQRD-model.

defined parameters are provided in Table 5.3. The values assigned to the parameters representing the intervention strategies implemented were calibrated or deduced from relevant data as these values are dependant on the region in which the disease spread is modelled. Due to the absence of accurate data the probable range used to calibrate f_1, f_2 and f_5 was set to be between 0 and 1, taking all possibilities into account. The average duration of quarantining exposed or infected individuals is denoted by $\frac{1}{q_E}$ and $\frac{1}{q_I}$, respectively. The probable ranges in which these values are calibrated was found within literature, ranging from 2 to 4 days [67, 74, 83, 84]. To decrease computation time, the quarantine rate for both exposed and infected individuals were assumed to be the same.

Parameter symbol	Definition of parameter symbol	Probable ranges	References
β_1	Exposure rate of community	[0.1, 0.9]	[1, 9, 21, 26, 67, 74]
β_2	Exposure rate of traditional funerals	[0.462, 0.9]	[21, 52]
q_E	Quarantine rate	[0.25, 0.5]	[5, 67, 74]
q_I	Quarantine rate from infected sate	[0.25, 0.5]	[5, 67, 74]
f_1	Proportion exposed individuals quarantined	[0, 1]	
f_2	Proportion infected individuals quarantined	[0, 1]	
f_5	Proportion dead individuals safely buried	[0, 1]	

TABLE 5.3: Initial parameters ranges used in the SEIQRD-model calibration.

The SEIQRDB model calibration (see Algorithm 5.1) is initialised by generating arrays of various possible parameter values for the chosen parameters to be calibrated. Different possible parameter value combinations are then used to simulate the number of deaths for each county in Sierra Leone and the country as a whole. The output is compared to the historical data using both a unweighted and weighted RMSE approach. For the weighted RMSE approach greater weights are given to the back end of the dataset. More significant discrepancies were observed in the earlier data points and it was therefore allocated a smaller weight. A total of 195 weights were produced using a linear function of which the sum of all weights are equal to one. The unweighted case, where all errors carry the same weight in the RMSE, is represented by the dotted blue line in Figure 5.19, with the midpoint of the data intercepting the y-axis at the origin. The linear Equation 5.1 is represented by the solid red line in Figure 5.19, which is used to assign the lowest weight to the first error, thereafter following the trend of the linear

Algorithm 5.1: Model calibration

Input: Set of calibration parameter combinations, β_1, β_2, δ, f_1, f_2, f_3, f_4, f_5, υ, q_E, q_I, γ_I, μ_I, μ_Q, γ_Q, migration proportion matrix, initial state values of SEIQRDB, number of days to simulate, list of 195 weights;
Output: Minimised RMSE, set of parameter values corresponding to lowest RMSE for each county and Sierra Leone as a whole;
for $j \leftarrow 262144$; `// Number of parameter set combinations`
do
  Run through list of all possible combinations of parameter values and provide these values to the set of difference equations 4.1 - 4.7, to generate simulation data for comparison in RMSE;
end
for $i \leftarrow 14$; `// Number of counties`
do
  for $j \leftarrow 262144$; `// Number of parameter set combinations`
  do
    for $k \leftarrow 195$; `// Number of historical data points`
    do
      error(k) = (county historical data(k) - county simulated data (k))^2;
      sum of errors = $\sum$ (error(k) $\times$ weight(k))
    end
  end
end
for $i \leftarrow 14$; `// Number of counties`
do
  for $j \leftarrow 262144$; `// Number of parameter set combinations`
  do
    mean error = $\frac{\text{sum of errors(j)}}{195}$;
    RMSE = $\sqrt{\text{mean error(j)}}$;
  end
end
return The set of parameter values corresponding to the lowest RMSE for each county

function to assign weights to each error with the greatest weight given to the last error. The y-axis intercept was chosen as $\frac{1}{\text{the number of data points}}$ to ensure the midpoint of the linear function would be the intercepting point. From this the gradient was calculated. The set of parameter values that minimise the RMSE is chosen for each county.

$$y = \frac{1}{18818}x + \frac{1}{195} \tag{5.1}$$

The RMSE for each county is given in Table 5.4, for both the unweighted and weighted cases. As may be observed from the root mean square differences, the calibrated parameter values in most cases provide a good fit to the historical data of the respective county, except for Western Area Rural and Western Area Urban. The calibrated values for each county and the country as a whole is chosen according to the weighted RMSE, since a closer approximation of the major patterns observed in the final values of the data was replicated. More variations of weight distributions for the values in the data could allow for better approximations of the patterns

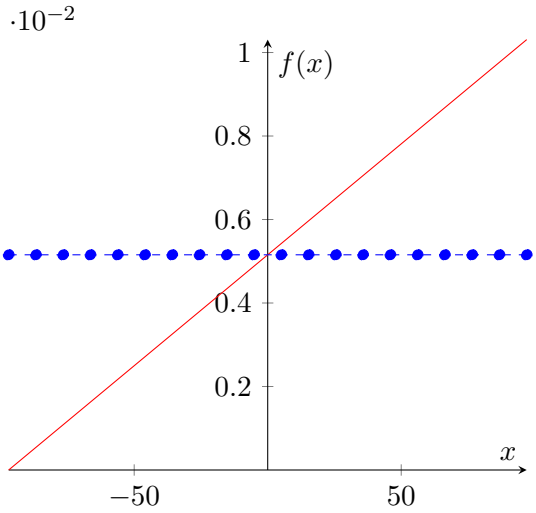

FIGURE 5.19: *Graphical representation of both an evenly and unevenly weighted function.*

observed in the data.

County	Minimised unweighted RMSE	Minimised weighted RMSE
Bo	15.34	0.961
Bombali	41.39	2.453
Bonthe	0.71	0.088
Kailahun	2.21	0.101
Kambia	4.73	0.632
Kenema	9.29	0.291
Koinadugu	6.54	1.169
Kono	9.22	0.848
Moyamba	8.96	0.388
Port Loko	33.28	3.656
Pujehun	1.68	0.511
Tonkolili	9.79	1.073
Western Area Rural	42.99	33.339
Western Area Urban	32.93	13.779
Sierra Leone	219.04	159.351

TABLE 5.4: Minimised RMSE values for each county of Sierra Leone including the country as a whole.

A second calibration experiment was executed in which the weighted RMSE of the deaths of Sierra Leone as a country as a whole was minimised. In Table 5.5, the calibrated parameter values, as uniquely defined for the country, and the average of the calibrated values of the 14 counties for each defined parameter are presented.

In Table 5.6, the calibrated parameter values, as uniquely defined for each county, of the weighted RMSE approach are presented. These values are compared to the average parameter ranges found in literature in Table 5.3. With some exceptions, the calibrated parameter values are close within approximation to average parameter values found in literature. It is expected that some

Country	β_1	β_2	q_E	f_1	f_2	f_5
Sierra Leone	0.71	0.88	0.25	0.40	0.32	0.29
Averages of counties	0.75	0.87	0.31	0.46	0.31	0.24

TABLE 5.5: Calibrated parameter values used within SEIQRDB model Sierra Leone and the average of the calibrated parameter values of all counties in Sierra Leone.

parameter values would be higher compared to values in literature, since the total population size implemented in the model is significantly smaller than literature based investigation. With a smaller initial population, a higher β would be expected to produce the same number of deaths as recorded in the data. Also the probability to come into contact with an infected individual in a smaller population is much greater, given the assumption made that all individuals are equally likely to come into contact with every other individual. Since Ebola is modelled as a closed system, only the individuals who would explicitly take part in the dynamics of the disease, i.e. probably become infected and ultimately recover or die, are taken into account. These individuals are assumed to be the number of reported cases for each specific county. With Ebola spread unique to each county the number of reported cases are unique. For counties with smaller population size, higher rates were expected, since the probability of becoming infected in smaller populations is much greater.

County	β_1	β_2	q_E	q_I	f_1	f_2	f_5
Bo	0.9	0.9	0.5	0.5	0.1	0.1
Bombali	0.82	0.9	0.5	0.4	0.2	0.1
Bonthe	0.76	0.9	0.3	0.6	0.2	0.1
Kailahun	0.6	0.8	0.5	0.6	0.6	0.6
Kambia	0.6	0.87	0.1	0.6	0.6	0.1
Kenema	0.9	0.9	0.5	0.6	0.1	0.4
Koinadungu	0.9	0.9	0.5	0.4	0.5	0.1
Kono	0.61	0.87	0.1	0.6	0.2	0.3
Moyamba	0.62	0.88	0.3	0.6	0.4	0.1
Port Loko	0.61	0.89	0.1	0.5	0.1	0.5
Punjehhun	0.84	0.9	0.3	0.6	0.6	0.1
Tonkolili	0.9	0.9	0.5	0.3	0.6	0.1
WAR	0.9	0.9	0.1	0.1	0.1	0.1
WAU	0.6	0.8	0.1	0.1	0.1	0.6

TABLE 5.6: Calibrated parameter values used within SEIQRDB model for all counties of Sierra Leone.

When comparing the calibrated parameter values for the country and the averages of the calibrated parameter values for the 14 counties it is observed that they are fairly similar, though with some differences due to differences in model calibration. The similarity establishes confidence in the model's ability to accurately replicate the patterns observed in the counties which would ultimately represent the macro patterns observed in the entire country.

The simulation output for each parameter set corresponding to the lowest weighted RMSE for each county is plotted against the historical data as well as the unweighted RMSE, providing a

means of face validation in addition to the RMSE (see Figures 5.21 - 5.27). Although some of the unweighted calibrated parameters replicated the patterns observed in the data better than the weighted parameter calibration experiment, it could not accurately replicate the final values observed in the data set.

Due to delayed reporting the historical data presents a rigid nature in contrast to the smooth output of the simulation data. Therefore, the model cannot precisely replicate the patterns of the real world scenario. In addition, the complexity of the epidemic cannot fully be described by a simple SEIQRDB model, due to many underlying factors influencing the dynamics of the disease. However, the model could successfully replicate the major behaviours observed within the historical data.

The purpose of the calibration experiment was to find the parameter values that best describe the underlying behaviour patterns in the historical data. Much of the counties' calibration experiment output did not reach the final number of deaths reported, however, the overall dynamics of the disease in the specified county was replicated satisfactorily.

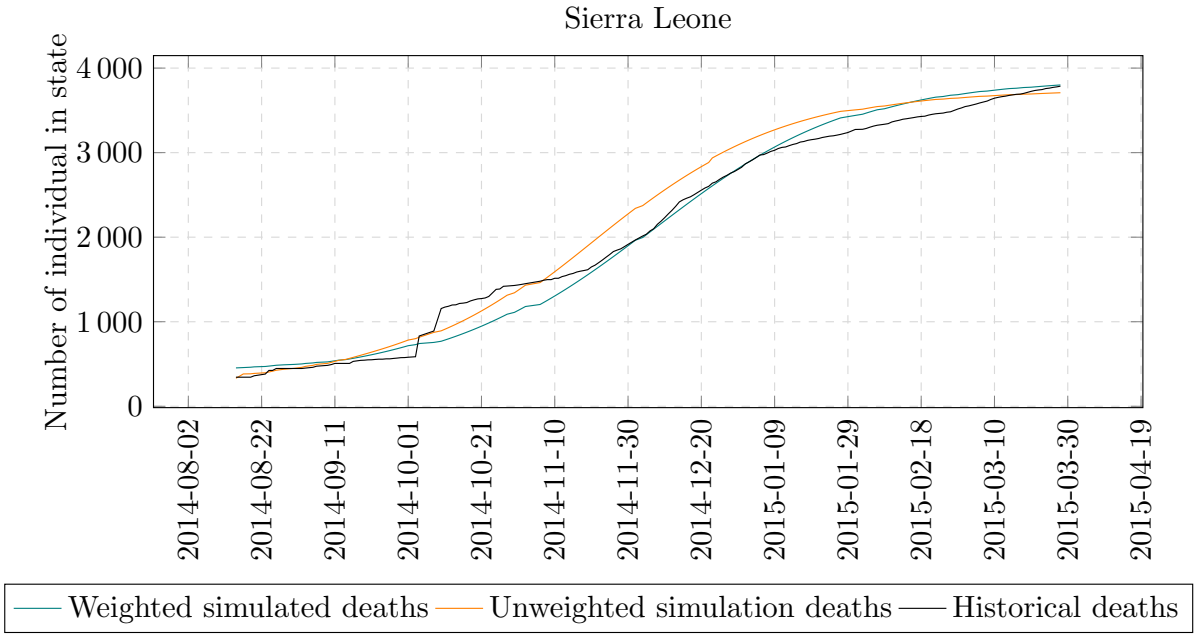

FIGURE 5.20: *Calibrated experiment for SEIQRDB model for Sierra Leone.*

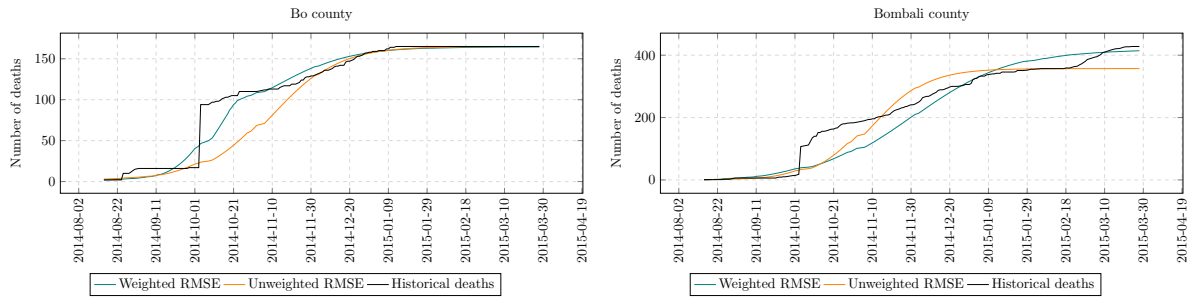

FIGURE 5.21: *Calibrated experiment of the SEIQRDB model for Bo and Bombali county*

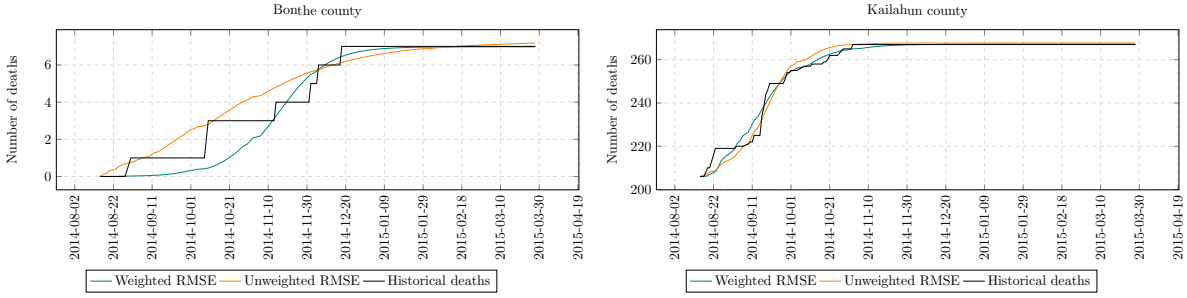

FIGURE 5.22: *Calibrated experiment of the SEIQRDB model for Bonthe and Kailahun county*

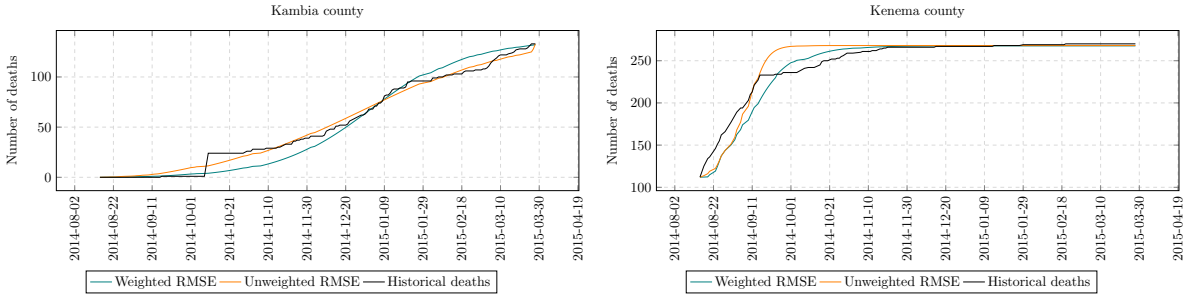

FIGURE 5.23: *Calibrated experiment of the SEIQRDB model for Kambia and Kenema county*

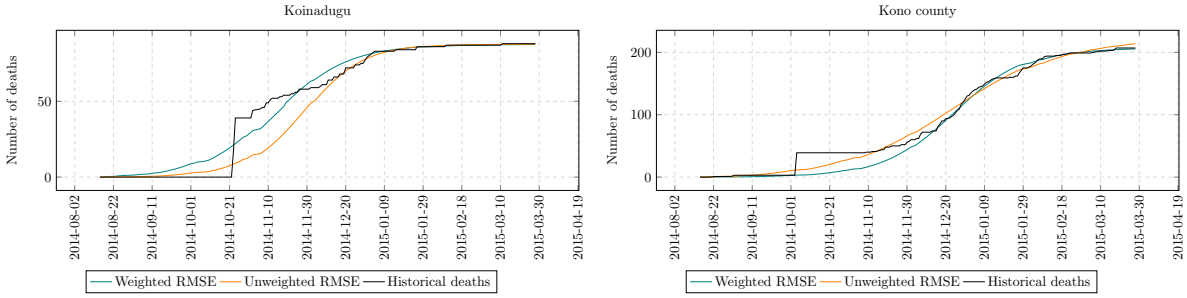

FIGURE 5.24: *Calibrated experiment of the SEIQRDB model for Koinadugu and Kono county*

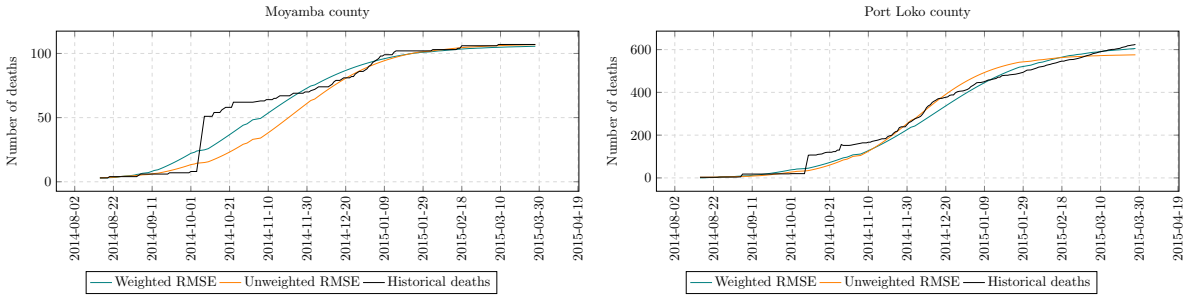

FIGURE 5.25: *Calibrated experiment of the SEIQRDB model for Moyamba and Port Loko county*

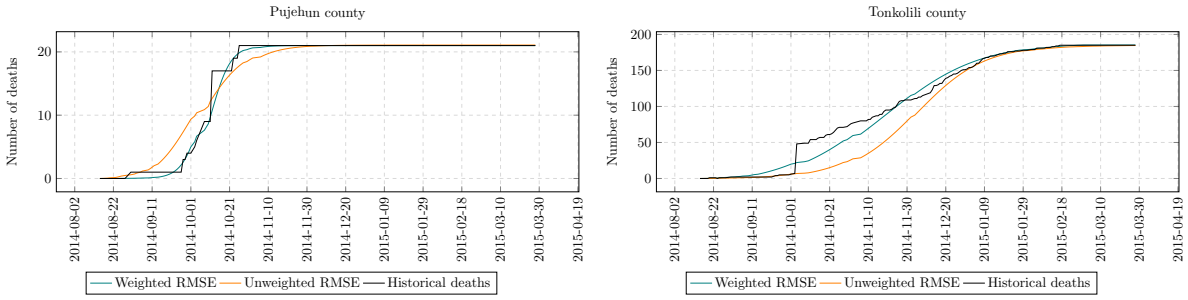

FIGURE 5.26: *Calibrated experiment of the SEIQRDB model for Pujehun and Tonkolili county*

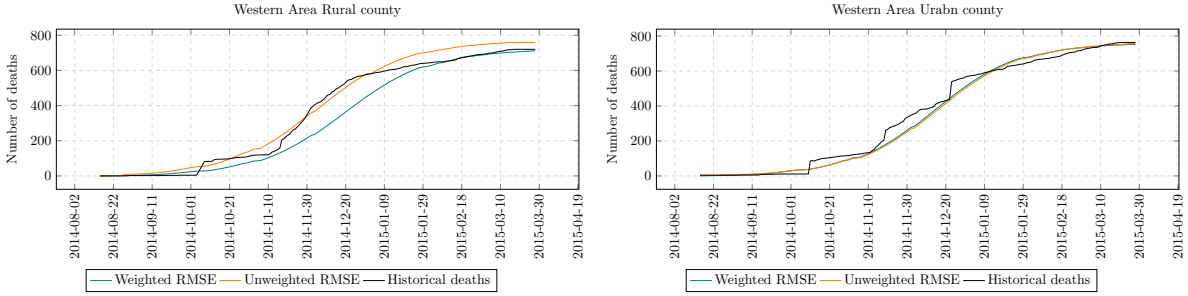

FIGURE 5.27: *Calibrated experiment of the SEIQRDB model for Western Area Rural and Urban county*

5.3 Sensitivity analysis

Sensitivity analysis is defined as the process of investigating the relationship between the input and output variables of complex models [64]. Through recalculating the outcome of a model under alternative input assumptions the behaviour of the model may be better understood. Sensitivity analysis is used in a number of ways, such as identifying critical, threshold or break-even values of the optimal criteria, testing model robustness, evaluation of parameter sensitivity, investigating sub-optimal solutions and increase understanding of the model for communication purposes [64, 64]. A number of methods for sensitivity analysis is mentioned in literature, from the simplest one-at-a-time approach in which only one input variable is varied over the uncertainty range while all other variables are kept at the baseline value, to more complex approaches such as the Fourier amplitude sensitivity test where the model is represented by the Fourier series using a single frequency variable, allowing for univariate sensitivity analysis. Both a single- and multi-parameter evaluation sensitivity analysis approach is used in this study where a single as well as a combination of parameters are varied over a range of uncertainty.

5.3.1 Single-parameter evaluation

Following the validation process of §6.2, a sensitivity analysis was performed on the various parameters relating to the intervention strategies. By increasing and decreasing each parameter incrementally with 5% for 20 interval points, the resulting number of deaths are compared to test the influence of the specified parameter on the epidemic.

The initial conditions chosen for the sensitivity analysis are given in Tables 5.7 and 5.8, where Table 5.7 represents the initial conditions for the counties initially introduced with the Ebola disease and 5.8 represents the counties in which the Ebola disease has not initially been introduced

to, respectively.

Parameter	Initial condition
Susceptible	N-E_0-I_0-D
Exposed	1
Infected	1
Quarantined	0
Recoveteal	0
Dead	Number of deaths of first date
Buried	0

TABLE 5.7: Initial conditions for populations in which disease is introduced at $t = 0$ for the SEIQRDB-model.

Parameter	Initial condition
Susceptible	N
Exposed	0
Infected	0
Quarantined	0
Recoveteal	0
Dead	0
Buried	0

TABLE 5.8: Initial conditions for populations in which disease is not introduced at $t = 0$ for the SEIQRDB-model.

The parameter values used for the sensitivity analysis are presented in Table 5.9, and the migration values given in Table 5.1 are used.

Country	β_1	β_2	qE	qI	f_1	f_2	f_5	υ
Sierra Leone	0.71	0.88	0.25	0.25	0.40	0.32	0.81	0.2

TABLE 5.9: Calibrated parameter values used within SEIQRDB model Sierra Leone.

Vaccination trails were initiated outside the data time period used for the model and with limited data available on the number of vaccinations and effectiveness thereof. An approximated vaccination coefficient was used for the simulation experiment sensitivity analysis. The vaccination coefficient is defined to be:

$$\upsilon = c \times \rho$$

where c denotes the per capita contact tracing rate and ρ the probability of vaccination. With a ring vaccination approach begin modelled, only close contact individuals traced from quarantined individuals are vaccinated. If it is assumed that the probability of being vaccinated is 1, the vaccination coefficient, υ, would then be the per capita contact tracing rate. The 2005-2010 census report of Sierra Leone states the average household size is 5.6. If a single member of the household becomes infected the remaining 4.6 individuals are classified as the close contacts of the infected individual and would therefore be traced and vaccinated. The vaccination coefficient which represents the per capita contact tracing rate is then chosen to be $\frac{1}{4.6} = 0.21$. Though this may not be a accurate representation of the rate at which individuals were vaccinated during the 2014 Sierra Leon outbreak, this provides a means to effectively investigate the impact of vaccination as a intervention strategy during an Ebola outbreak.

The intervention strategies investigated are mainly focused on decreasing the exposure of the disease and effectively decrease the total number of deaths. Therefore by increasing intervention strategies a decrease in the exposure rates β_1 and β_2 may possibly be observed. The change in the number of deaths in the steady state due to variations in β_1 and β_2 is presented in Figure 5.28.

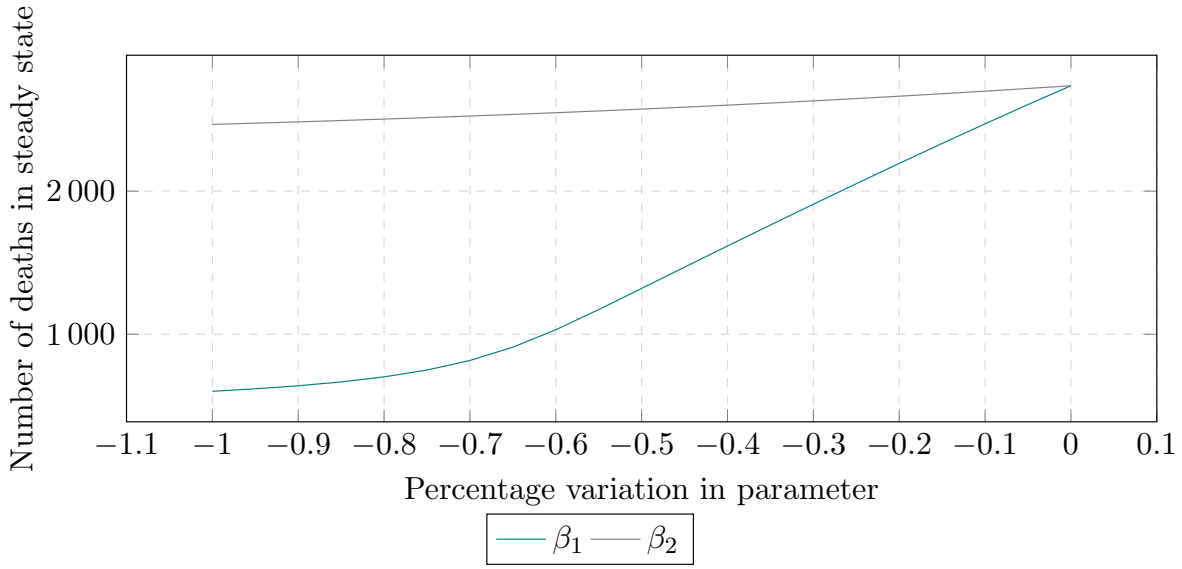

FIGURE 5.28: *Number of deaths in steady state due to variations in parameters β_1 and β_2.*

It may be observed from Figure 5.28 that variations in β_1 have a greater impact on the number of deaths in the steady state than the variations in β_2. By decreasing β_1 and β_2 with 5% from the initial calibrated values, a decrease of 5% in the number of deaths in the steady state due to the change in β_1 compared to a 0.69% decrease in the number of deaths in the steady state due to change in β_2, is observed. A greater decrease of 50% from the base value would result in a decrease of 57.15% in the number of deaths in the steady state due to change in β_1, with only a 6.43% decrease in the number of deaths in the steady state due to change in β_2. These results indicate that intervention efforts should be focused on decreasing β_1. It may be noted that the number of deaths in the steady state is less sensitive to changes in both parameter values beyond a decrease of 60% from the base value. This could be due to the effect of the exposure coefficient decreasing in relation to the population size which remains constant. Such a decrease is hardly likely achievable as this would require that either β_1 or β_2 become smaller than 0.1.

The changes in the number of deaths in the steady state due to variations in the parameter values for infection rate, recovery rate, death rate, recovery rate in quarantine and death rate in quarantine are presented in Figure 5.29

It may be observed in Figure 5.29 that the number of deaths in the steady state is relatively unresponsive to small changes in $\gamma, \mu_I, y_I, \mu_Q$ and y_Q which established confidence in the chosen parameter values based on the average of values for each parameter found within literature. An increase of 5% of γ, μ_I and μ_Q would result in an increase of 3.66%, 0.51%, and 1.54% in the number of deaths in the steady state, respectively. An increase in 5% in y_I and y_Q would result in a decrease of 1.26% and 1.45% in the number of deaths in the steady state, respectively. A decrease of 5% in γ, μ_I and μ_Q would result in a decrease of 3.69%, 0.523% and 1.53% in the number of deaths in the steady state, respectively. A decrease in 5% in y_I and y_Q would result in an increase of 1.22% and 1.45% in the number of deaths in the steady state, respectively. The unresponsive nature of the number of deaths in the steady state to small changes in $\gamma, \mu_I, y_I, \mu_Q$ and y_Q allows for a marginal error range in which parameter values could be chosen such that the effect of the over or under estimation of the parameter values would be seen as relatively insignificant in the total number of deaths observed in the country.

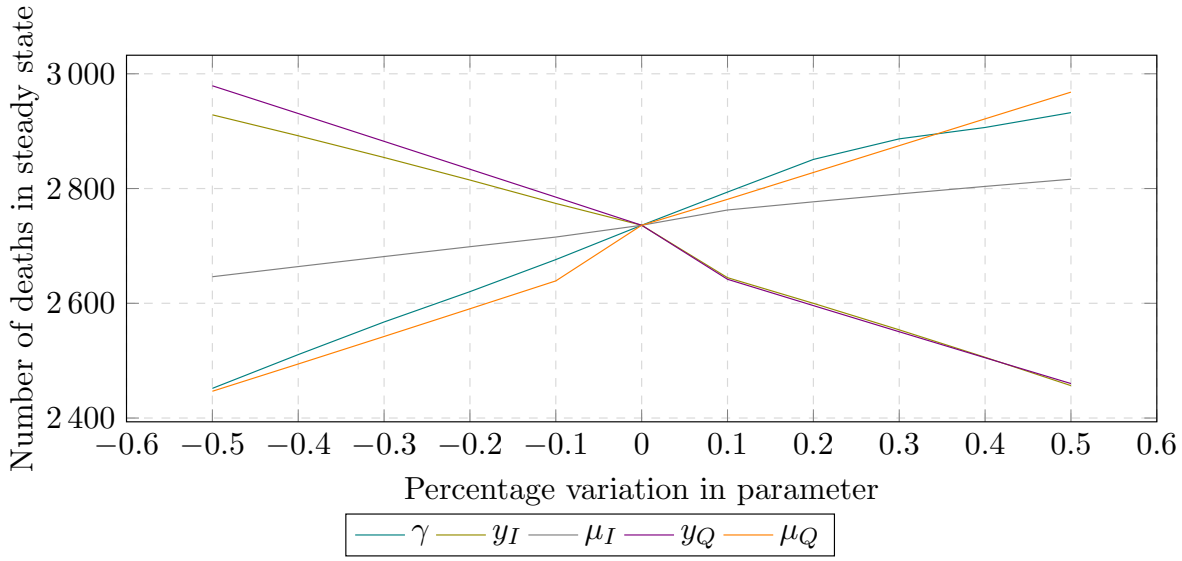

FIGURE 5.29: *Number of deaths in steady state due to variations in disease parameters.*

The changes in the number of deaths in the steady state due to variations in the parameter values for contact tracing, quarantine, safe burials and vaccination are presented in Figure 5.30. It may be observed in Figure 5.30 that the vaccination coefficient, υ, has the greatest impact on the total number of deaths. Both rates of quarantine of exposed, q_E, and infected, q_I, individuals were more effective than the proportion of individuals quarantined from exposed, f_1, and infected, f_2. This indicates that the time it takes to quarantine individuals are more important than the number of individuals quarantined. Therefore efforts focused on reaching exposed individuals sooner should be increased.

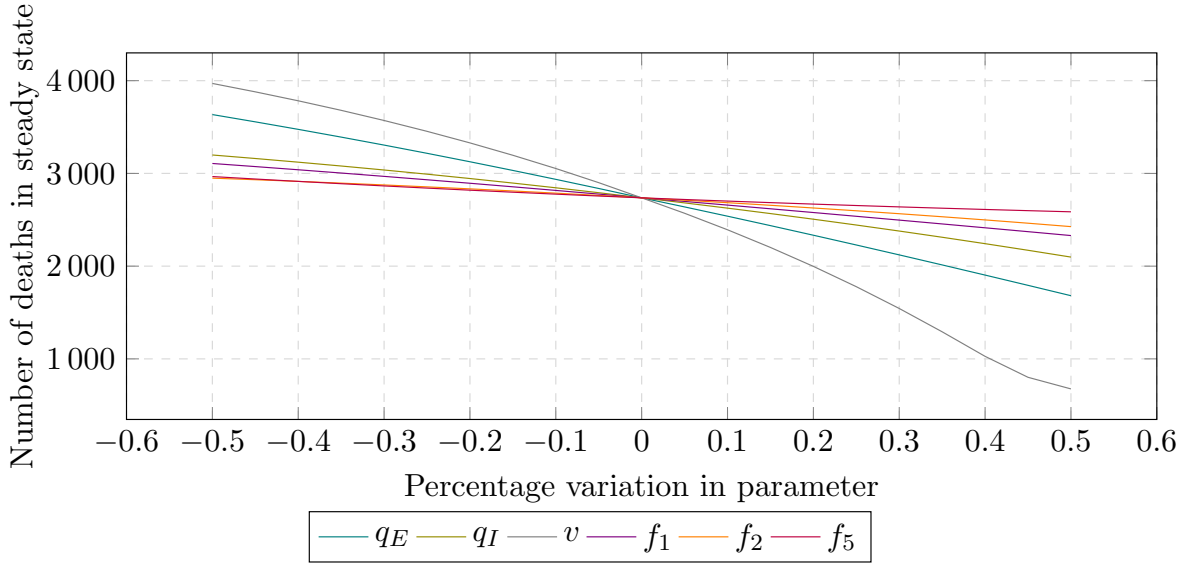

FIGURE 5.30: *Number of deaths in steady state due to variations in intervention strategy parameters.*

Increasing the υ by 5% yielded a decrease of 6.08% in the number of deaths observed in the steady state, compared to the base value. Further increasing υ by 50% from the base value

decreased the number of deaths in the steady state by 75.30%. A 50% increase in υ translates to a close contact individual of a quarantined individual will be traced and vaccinated within 3.33 days. This would be a challenging mark to achieve with limited resources, insufficient healthcare workers to administrate the vaccination and logistical challenges of finding all contacts especially if no national identification system is in place, contacts have no address or are referred to by nicknames. In spite of all these practical complications, an effective implementation of contact tracing and vaccination administration would cause a significant decrease in the number of deaths due to Ebola. If a decrease of 5% in the vaccination rate is experienced, it would result in a increase of 5.64% in the number of deaths in the steady state. A further decrease of 50% from the base value would yield an increase of 31.07% in the number of deaths in the steady state. A 50% decrease in υ translates to a close contact individual of a quarantined individual to be traced and vaccinated within 10 days. It may, however, be observed that the number of deaths in the steady state is less sensitive to the decrease of υ from the base value compared to the sensitivity of the number of deaths in the steady state due to an increase in υ.

The rate of quarantining exposed, q_E, and infected, q_I, individuals has the second most significant effect on the number of deaths in the steady state, after υ. By separately increasing q_E and q_I with 5% from its base value a decrease of 3.58% and 1.99% is observed in the number of deaths in the steady state, respectively. A further increase of 50% from the base value of q_E and q_I, separately, yields a decrease of 38.56% and 23.35% in the number of deaths in the steady state, respectively. This translates to exposed individuals contacted and quarantined or infected individuals quarantined within 3.33 days. This would be a challenging mark to achieve with many logistical challenges faced within a third world country such as Sierra Leone, such as weak infrastructures and poorly maintained roads. Though the engagement of the community would be the key to a successful implementation of contact tracing and quarantining individuals. Separately decreasing q_E and q_I with 5% from the base value would cause a increase of 3.55% and 1.977% in the number of deaths in the steady state, respectively. A further decrease of q_E and q_I, by 50% from the base value would yield a increase of 24.70% and 14.44% in the number of deaths in the steady state, respectively. This translates to exposed individuals contacted and quarantined or infected individuals quarantined within 10 days. Comparing the number of deaths in the steady state at the 50% increased q_E or q_I value from the base level to the 50% decrease q_E or q_I value from the base level indicates the number of deaths are more sensitive to the increased q_E or q_I values than the decreased q_E or q_I values.

When the base values of the proportion of exposed, f_1, and infected, f_2, individuals are increased by 5%, a decrease of 1.42% and 0.94% in the number of deaths in the steady state is observed, respectively. A further increase to 50% from the base value would yield a decrease of 14.87% and 11.34% in the number of deaths in the steady state, respectively. This translates to 60% of exposed individuals are quarantined at a rate of q_E or 45% of infected individuals are quarantined at a rate of q_I. The proportion of individuals quarantined is dependant on the available capacity of health facilities. Without proper planning and preparations for an emergency response to an Ebola epidemic, the demand for bed capacity in health facilities could be crippling. Implementing a strategic plan with well thought through infrastructure could increase the rate of quarantine and effectively increase the rate at which capacity is made available in health facilities. Separately decreasing f_1 and f_2 with 5% from the base value would cause a increase of 1.45% and 0.936% in the number of deaths in the steady state, respectively. A further decrease of f_1 and f_2 by 50% form the base value would yield a increase of 11.92% and 7.20% in the number of deaths in the steady state, respectively. This translates to 20% of exposed individuals are quarantined at a rate of q_E or 15% of infected individuals are quarantined at a rate of q_I. Similarly to the quarantine rates, the number of deaths in the steady state is more sensitive to the increased values of f_1 and f_2, respectively, than the decreased values.

The proportion of deaths safely buried, f_5, had the least significant impact on the number of deaths in the steady state over the 21 variations of the parameter value. Increasing the f_5 with 5% from the base value, decreased the number of deaths by 0.65%. A further increase in f_5 of 50% from the base level yielded a 5.51% decrease in the number of deaths. This translates to all of the deaths are safely buried per day. Due to traditional belief systems, family members are reluctant to hand over deceased family members to health workers, causing this mark to be challenging to reach. By involving the community in the burial process and persuading them by being transparent and open when explaining the procedure, a successfully implemented safe burial intervention may be more probable. Decreasing f_5 by 5% of the base value increases the number of deaths in the steady state by 0.71%. A further decrease by 50% of the base value would yield an increase of 7.73% of the number of deaths in the steady state. This translates to 40% of the deaths begin safely buried. The population based modelling approached used struggled to fully encompass the complexity of the burial ceremonies within the greater epidemic system. It is observed from literature and the reports found on the outbreak of Sierra Leone in 2014, that unsafe burials had a significant impact on the spread of the disease which is contrary to the results of the model. This is due to the model providing an averaged exposure coefficient, β_2, which is dependant on the number of contacts made by a susceptible individual with unsafe buried individuals and the probability of exposure to the disease. The calibrated values for each of these components of the exposure coefficient is a collective representation of numerous scenarios. These scenarios differ significantly in the combination of probability of exposure and contact rate. The movement of individuals in the model is limited to the fixed migration patterns set per day, which restricts the model to accurately investigate the clustering of individuals for a period of time, such as a burial ceremony, and the dispersion thereafter causing further exposures. For a greater understanding of the explicit impact of safe burials as an intervention strategy on a disaster system, an individual based modelling approach is recommended.

5.3.2 Multi-parameter evaluation

According to the WHO, a package or combination of intervention strategies may prove to be more successful than single intervention strategy. Following the sensitivity analysis of the single intervention strategies, combinations of the most effective intervention parameters are tested. The initial conditions and calibrated parameter values stated in §5.3.1 are used. From the sensitivity analysis of the single intervention strategies it was observed q_E, q_I and υ were the most effective towards lowering the number of deaths in the steady state and is therefore used for further sensitivity analysis. Each intervention is ranged from a 50% decrease to a 50% increase from its base value and run in combination with one another. The change in the number of deaths in the steady state is calculated for each combination of variations, with the results displayed in a 3D plane in Figures 5.31 - 5.32.

The first combination consists of a contact tracing and quarantine of exposed individuals intervention and a vaccination intervention. The change in the number of deaths in the steady state due to combinational variations in q_E and υ could be seen in Figure 5.31.

As expected the combination of intervention strategies q_E and υ is most effective the case where both parameters are increased by 50% from their base values. This would translate to exposed individuals being traced and quarantined within 3.33 days, as well as close contact individuals being vaccinated within 3.33 day. A decrease of 80.61% is observed in the number of deaths in the steady state at a 50% increase in both parameters from their base values. Various combinations of q_E and υ could be implemented as an effective combination of intervention strategies. Based

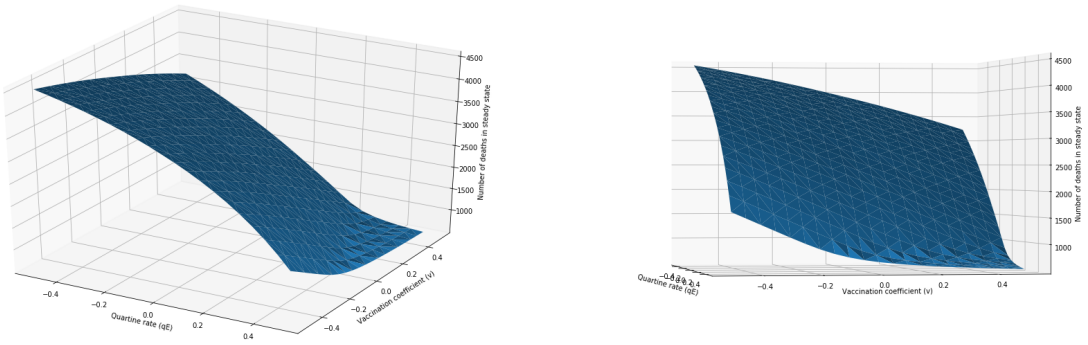

FIGURE 5.31: *The number of deaths in steady state due to variations is q_E and υ.*

of the single intervention strategy sensitivity analysis, the number of deaths is regarded as most sensitive to variations in υ and therefore suggests to initially focus on improving vaccination administration followed by quarantining of exposed individuals.

The second combination consists of a quarantine of infected individuals intervention, q_I, and a vaccination intervention, υ. The change in the number of deaths in the steady state due to combinational variations in q_I and υ could be seen in Figure 5.32.

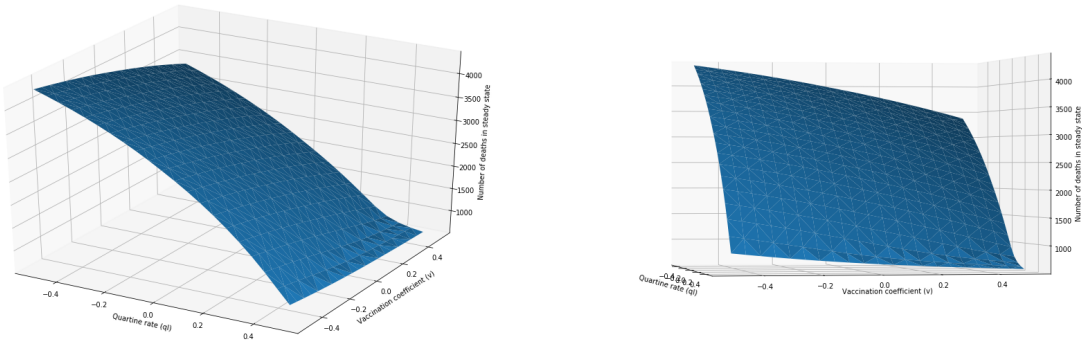

FIGURE 5.32: *The number of deaths in steady state due to variations is qI and υ.*

The combination of intervention strategies q_I and υ is most effective in the case where both parameters are increased by 50% from their base value. This would translate to infected individuals being quarantined within 3.33 days, as well as close contact individuals would be vaccinated within 3.33 day. A decrease of 79.02% is observed in the number of deaths in the steady state at a 50% increase in both parameters from their base values. Comparing the decrease in number of deaths in the steady state for both combination intervention strategies, indicates contact tracing and vaccinations would have a greater impact. This is expected as the number of deaths in the steady state show to be more sensitive to both vaccination and contact tracing in the single intervention sensitivity analysis compared to quarantine of infected individuals. It may also be noted for both combinations of interventions, the number of deaths in the steady state become less sensitive for values increased above 25% from the base values.

The advantage of implementing a combination of intervention strategies is the greater outcome achieved with smaller efforts compared to focussing all efforts on a single intervention and still achieving a lower outcome. By increasing q_E, q_I and υ each 50% from their base level would yield a decrease of 82.75% in the number of deaths in the steady state. This decrease would

not be achievable by any single intervention strategy and therefore confirms a combination of intervention strategies proves to be more successful than a single intervention. A 50% increase in the quarantine rate of exposed and infected individuals would translate to quarantining and vaccinating these individuals within 3.33 days. This is a challenging mark to achieve but with sufficient volunteers and resources, the significance of the effect of an increase in the combination of intervention strategies could not be overlooked.

Contact tracing plays an influential role in both the quarantine and vaccination of exposed or infected individuals. An increase in efforts to trace exposed or infected individuals would result in an increase in both quarantine and vaccination efforts. In the scenario where limited resources are available to be distributed amongst various interventions, it would be most strategic to prioritise improving contact tracing efforts as this allocation would also improve quarantine and vaccination effort.

5.4 County quarantine scenario testing

In addition to the sensitivity analysis, the impact of three quarantine intervention scenarios were considered, namely a focused county quarantine of six counties excluding Western Area Rural and Western Area Urban, a focused county quarantine of eight counties including Western Area Rural and Western Area Urban, and a nationwide quarantine.

5.4.1 County quarantine as an intervention strategy

The government of Sierra Leone imposed a three day lock down between 19 and 21 September 2014, in which individuals were restricted to their respective counties [82]. During this time 28 500 trained community workers and volunteers moved among designated counties to educate individuals on prevention measures as well as to tracedany unreported cases. More than 80% of targeted houses were reached with 150 new cases identified.

By regulating the movement between counties, the Ebola virus disease could be localised in various areas of Sierra Leone to prevent further spread of the disease in the country. A sensitivity analysis was done to the time at which such a quarantine was implemented. After a specified number of deaths in the county is observed the quarantine strategy is implemented and the effect of each specified number of deaths to be reached before county quarantine is initialised, on the total number of deaths in the country is evaluated. The same initial conditions and calibrated parameter values stated in §5.3.1 are used to initialise the simulations. The quarantine of a county is simulated by stopping the migration flows to and from the county under quarantine, as long as the number of deaths in the county exceeds the initialisation count. This may be seen as an extreme measure and unrealistic approach, though to accurately investigate the effect of migration patterns on the spread of the disease, all inflows and outflows of the quarantined county is halted. After a county has been placed in quarantine, contact tracing, quarantine, safe burials and vaccinations are implemented as calibrated from the patterns observed in the county data.

Three simulations are executed to compare various scenarios of county quarantine implementation. The visual representations of the three scenarios may be seen in Figure 5.33 to 5.35, where the blue dots represent a county not under quarantine and the orange dot indicates a county placed in isolation.

Throughout the duration of the epidemic, a total of six counties were isolated due to high rates

of new cases observed within the counties. The six counties isolated were Bombali, Kenema, Kailahun, Moyamba, Port Loko and Tonkolili, where both Kenema and Kailahun were the epicentres of the disease during the initial stages of the epidemic. The first scenario simulated is the effect of the variation of the number of deaths observed in each of the 6 specified counties before initialisation of county isolation on the total number of deaths in the country (see Figure 5.33).

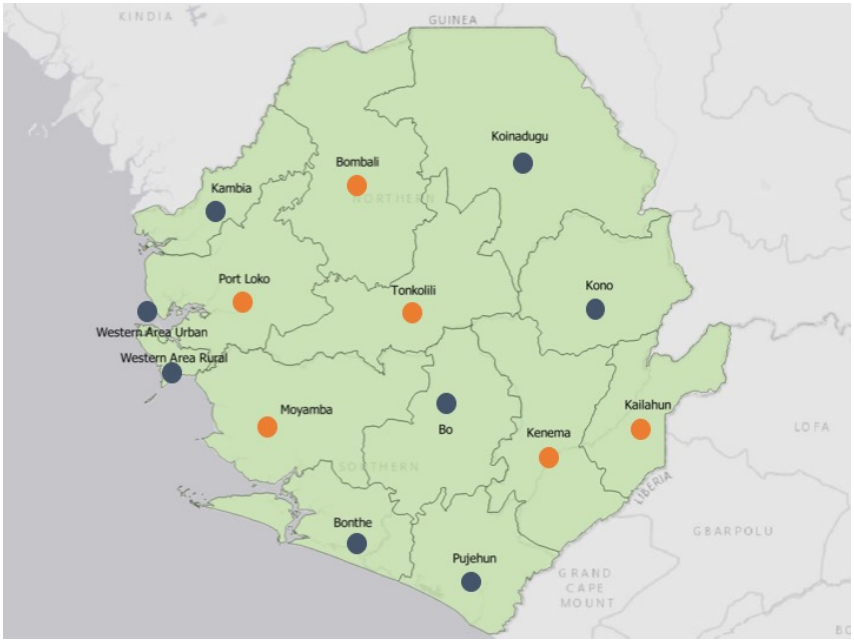

FIGURE 5.33: *Visual representation of the county quarantine strategy implemented.*

By early September 2014, Freetown became the epicentre of the epidemic. Though the highest rates of new cases in the country were observed from Western Area Rural and Western Area Urban, both counties were never isolated. Internal quarantine of infected individuals and the homes were implemented but restrictions to and from these counties were not. The second scenario simulated is the effect of variations of the number of deaths observed in each of the eight counties, including Western Area Rural and Western Area Urban, before initialisation of county quarantine (see Figure 5.34).

The final scenario simulated is the effect of the number of deaths observed within any of the 14 counties before initialisation of county quarantine (see Figure 5.35).

This scenario is seen as a nationwide county quarantine strategy. The simulated output for all three scenarios may be observed in Figure 5.36, with the dashed line representing the number of deaths without county quarantine intervention.

County specific quarantine excluding Western Area Rural and Western Area Urban

The total number of deaths in the country is observed to be less sensitive to changes in the number of deaths observed in the 6 specified counties before initialisation of county quarantine for the range 10 to 60 deaths observed. Thereafter the total number of deaths in the county exponentially increases as the number of deaths observed in the 6 specified counties before initialising county quarantine. A decrease of 26.75% is observed in the total number of deaths in the country given 10 deaths are observed in a county before initialising county quarantine. After observing 100 deaths in a county a 19.41% decrease in the total number of deaths in the

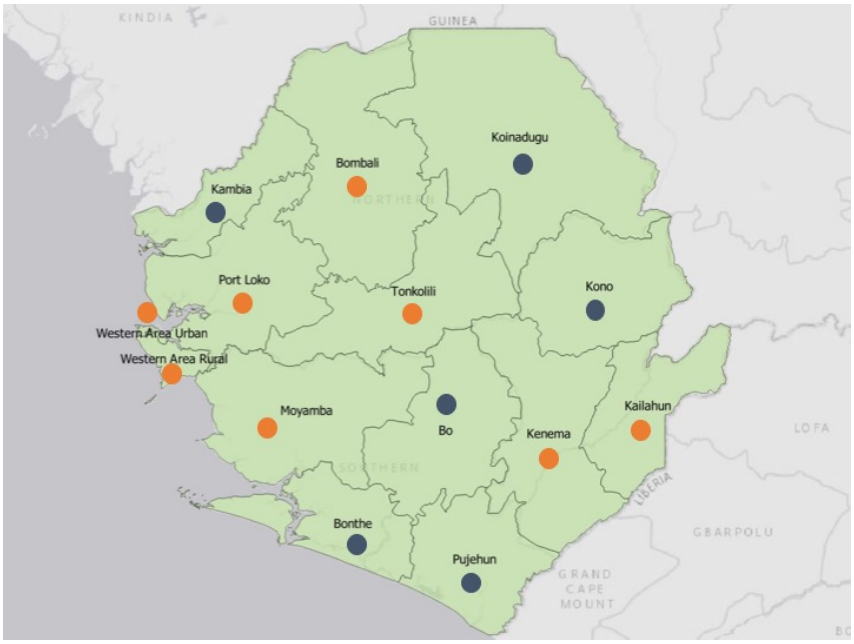

FIGURE 5.34: *Visual representation of the second county quarantine experimental simulation.*

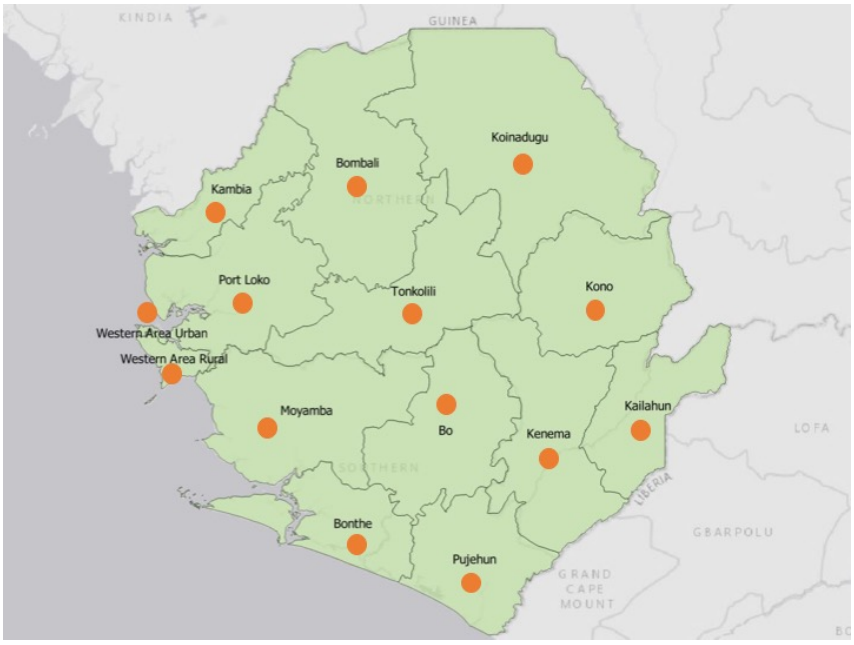

FIGURE 5.35: *Visual representation of the third county quarantine experimental simulation.*

country is observed after county quarantine initialisation. As expected the smaller the specified number of deaths to be reported before initialising county quarantine the greater the decrease in the total number of deaths in the country are.

From the data it was estimated that an average of 40 deaths were observed within the various counties at the point of county quarantine implementation. The simulation experiment suggests that a decrease of 26.46% in the total number of deaths may have been possible if the county quarantine could be maintained. Given that the average number of deaths observed in a county before implementation of county quarantine was 30 deaths, a decrease of 26.63% was observed

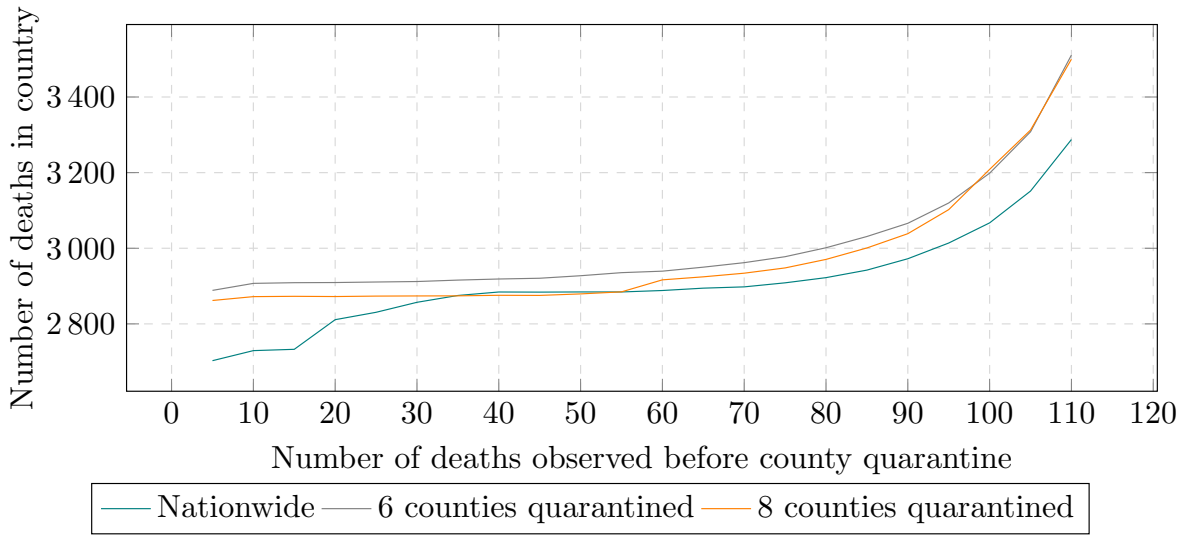

FIGURE 5.36: *The total number of deaths in Sierra Leone due to variations in the county quarantine initialisation points.*

in the total number of deaths in the country. A decrease of 26.59% and 26.55% was observed at 20 and 10 deaths, respectively. The decrease in the total number of deaths observed in the country given fewer number of deaths observed in each county, is not as significant as expected, however, an increase in the number of deaths observed has a more significant impact for values greater than 70. This suggest that county quarantine is most effective before the number of deaths reach 70.

County specific quarantine including Western Area Rural and Western Area Urban

Similar to the county specific quarantine excluding Western Area Rural and Western Area Urban intervention, the total number of deaths in the country after including Western Area Rural and Western Area Urban in the county specific quarantine intervention is less sensitive to the changes in the number of deaths observed before county quarantine implementation within the range 10 to 55 deaths. For 60 or more deaths observed within a county before initialisation of county quarantine, the total number of deaths observed in the country increases exponentially. A decrease of 27.22% is observed in the total number of deaths in the country given 10 deaths are observed in a county before initialisation of county quarantine. After observing 100 deaths in a county a mere 19.16% decrease in the total number of deaths in the country is observed after county quarantine initialisation. As expected the smaller the specified number of deaths to be reported before initialising county quarantine the greater the decrease in the total number of deaths in the country are.

Comparing the county quarantine strategy including Western Area Rural and Western Area Urban to the intervention strategy excluding Western Area Rural and Western Area Urban, it was observed that a smaller total number of deaths in the country was observed for all specified deaths observed before county quarantine smaller than 95, Thereafter the total number of deaths observed in the country strive to the base scenario of no interventions of 3 969 deaths. This is to be expected since decreasing the average mobility within the country would directly decrease the total number of deaths observed within the country.

Nationwide quarantine

As expected the smaller the specified number of deaths to be reported before initialising county quarantine, the greater the decrease in the total number of deaths in the country. With ten as the specified number of deaths the decrease in total number of deaths in the country is observed to be 26.69%. Compared to the specified number of deaths of 100 merely decreasing the total number of deaths in the country by 10.97%. It may be noted the total number of deaths in the country is less sensitive to changes in the specified number of deaths before initialising county quarantine for values between 5 and 70. Thereafter the total number of deaths in the country strive to the base scenario of 3 969 deaths in the country. These results indicate that a rapid quarantine response of counties would be more successful.

A decrease of 27.26% in the number of deaths in the country after implementing a nationwide county quarantine state with an average death toll of 40 per county. If the lockdown measures were implemented at an average of 30 deaths per county, a decrease of 27.39% would have been observed in the total number of deaths in the country. Similarly, implementing the nationwide lockdown of counties if an average 20 and 10 deaths per county were observed would yield a decrease of 29.10% and 31.17%, respectively. Though the decreases in the total number of deaths observed in the country given fewer number of deaths observed in each county is not as significant as expected, it still remains evident an earlier response of county quarantine would yield a more favourable outcome.

Comparing all three scenarios it becomes apparent that the greater the number of counties quarantined, the greater the restriction of mobility within the country and therefore the greater the decrease observed within the total number of deaths in the country. Scenario 1 and 2 had an average decrease in the total number of deaths observed in the country over all number of deaths observed before county quarantine of 24.28% and 25.02%. A nationwide county quarantine intervention strategy led to an average decrease of 26.68% over all variations of number of deaths observed before nationwide quarantine. Although movement restrictions are implemented among counties the prevention of further spread of the disease within each county remains subject to the effectiveness of other implemented intervention strategies and community responsiveness. Therefore to effectively combat further spread of the disease a combination of movement restrictions among counties and intra-county specific interventions should be effectively executed.

5.5 Bed capacity scenario testing

During the peak of the epidemic in September 2014 more than 500 new cases were reported per week which decreased in February 2015 to less than 100 confirmed cases per week [96]. After announcing the Ebola epidemic in West Africa to be a public health emergency of international concern during August 2014, a significant increase in response efforts to control the rapidly spreading disease was seen. The effect of these increased response efforts were only observed by late November of 2014 due to delays in the set up of the ETCs. The timeliness and focus of the international response efforts in Sierra Leone was widely criticised to have fallen behind the epidemic curve [41, 46]. In Figure 5.37 the national bed capacity for Sierra Leone is given as a ratio of the number of available beds in ETC per case.

The WHO estimated at the height of the epidemic in September 2014, a substantial demand of 532 treatment beds were required with merely 37% of confirmed cases isolated and treated within ETCs [91]. Observed from Figure 5.37, a significant increase in the number of beds per case was observed in late November of 2014. The number of new cases per week greatly

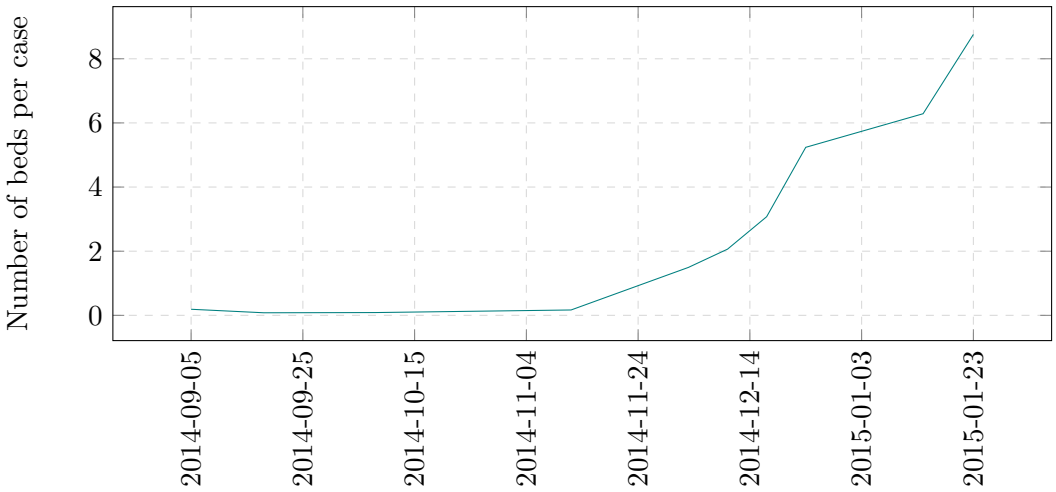

FIGURE 5.37: *The national bed capacity for Sierra Leone as the number of operational beds in ETC per case.*

decreased with the increase in intervention efforts leading to the WHO reporting sufficient bed capacity available to isolate and treat each new case by 3 December 2014 [92]. The number of beds surpassed the demand exponentially thereafter, increasing the number of beds per new case from 1.9 in mid December 2014 to 8.75 beds per new case in January 2015 [92]. The effectiveness of the increased bed capacity undoubtedly played a role in the turn of the disease's curve, however the significance of the increase in the interventions strategy's influence is yet to be determined.

Investigation of the timeliness and magnitude of an increased bed capacity intervention may provide a greater understanding of the effectiveness of bed capacity as an intervention strategy for future prevention planning of an Ebola outbreak. Adapting the model presented to encompass a capacity to the quarantine intervention allowed for such an investigation. Three scenarios of bed capacity implementation were simulated to evaluate the impact of the magnitude of an increased bed capacity intervention, the timeliness of implementing an increased intervention effort and various distribution strategies of limited bed capacity on the number of deaths in the country.

5.5.1 Evaluation of the change in size of an increased bed capacity effort

To evaluate the effect of various sizes of increased bed capacity efforts the model was adapted to effectively simulate the proposed scenarios. If the number of individuals quarantined for a specific county was over the set capacity, the quarantine count was set to the specified capacity and the excess individuals were moved to the infected state where they would follow the natural progression of the disease. Each county was assigned a similar quarantine unit with a specified bed capacity which varied over the range of 5 to 60 beds. Since the model was calibrated without any limitations to quarantine, the number of deaths observed in the calibrated model is chosen as the upper limit of the range in which the bed capacity is varied. It was noted that the model with limited bed capacity in quarantine reached the same number of deaths as the unlimited bed capacity model at the capacity of 60 beds per quarantine unit for the 14 counties, relating to 840 beds in the country. The effect of the change in the bed capacity for each county on the number of deaths observed in the country, is seen in Figure 5.38.

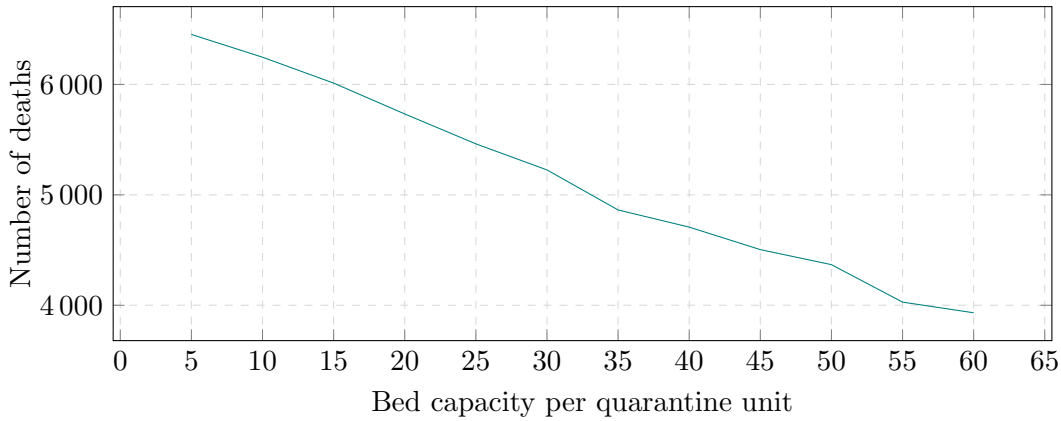

FIGURE 5.38: *The effect of variation in the bed capacity of the quarantine in each county on the number of deaths observed in Sierra Leone.*

As expected, the total number of deaths in the country decreases as the bed capacity increases. As the capacity of each county's quarantine increases more exposed and infected individuals are placed within quarantine and removed from the natural progression of the disease, increasing their chance of recovery. With a capacity of 5 beds per county quarantine unit, relating to 70 beds for the country, a total of 6 452 deaths are recorded. This would be a relatively easier mark to achieve as community centres or households could be utilised for such small number of treatment beds. The bed capacity of 5 beds per county quarantine unit was used as the comparison intervention to all other bed capacity increased values. Given that each county's quarantine capacity is doubled to 10 beds per county, relating to 140 beds for the country, a 3.3% decrease in the total number of deaths in the country is observed. With a further increase to 35 beds per county quarantine unit, a 32.69% decrease in the total number of deaths of the country is observed. A capacity of 35 beds per county, relating to 490 beds for the country, was reported by the WHO as sufficient capacity to quarantine all new cases by December 2014. This was unique to the time of the epidemic, as the peak was already reached and the number of new cases per week was decreasing. A 64.12% decrease in the total number of deaths in the country is observed with a capacity of 60 beds per county. This translates to 840 beds for the country, which is smaller than the reported number of treatment beds in Sierra Leone for March 2015. The implementation of a quarantine intervention cannot be considered as an effective strategy to control an Ebola epidemic without considering the restrictions to resources, location and time of implementation, although the considerable influence on the number of deaths observed in the country could not be denied.

5.5.2 Evaluation of the change in timeliness of an increased bed capacity effort

The epidemic reached its peak by September 2014, at which time ETC reached their capacities and turned patients away [45]. Delays in implementation of an increased bed capacity intervention resulted in further falling behind the epidemic curve, leading to ETC beds being underutilised by January 2015 [45]. The simulation model was adapted to evaluate the influence of timely implementation of effective intervention strategies. The number of days before a quarantine intervention is implemented is varied between 1 and 105 days, which relates to opening a quarantine facility in each county with a set capacity on the 9th of August 2014 compared to opening a facility on the 30th of November 2014. The days before a quarantine intervention is

implemented it is assumed the quarantine intervention is to be 0, to effectively investigate the influence of a delayed intervention implementation. In Figure 5.39 the effect of a delay in the implementation of a quarantine intervention on the total number of deaths in the country can be seen.

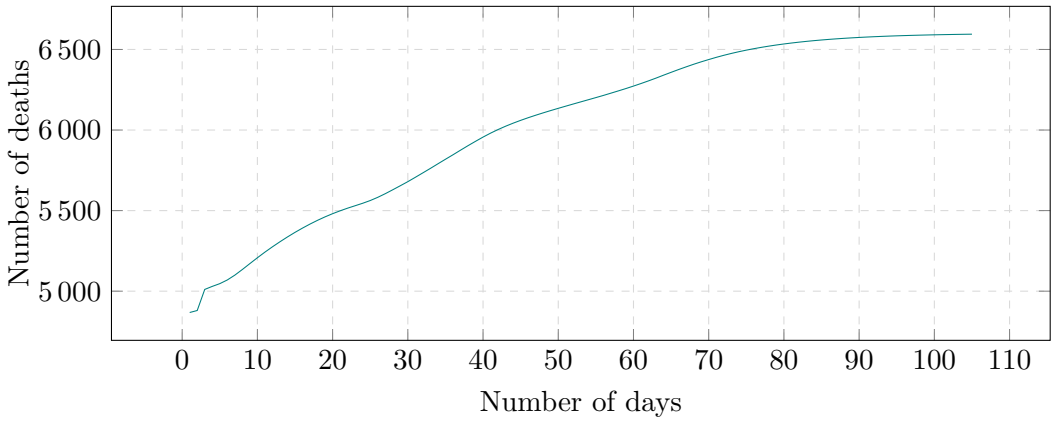

FIGURE 5.39: *The effect of variation in the implementation of an increased bed capacity intervention strategy on the number of deaths observed in Sierra Leone.*

As expected an increase in the number of days before an quarantine intervention is implemented would cause an increase in the total number of deaths observed in the country. With a delay of two weeks an increase of 8.79% deaths were seen. This may seem as a relatively small increase though it relates to more than 460 lives. A delaying of 30 days after the start of the epidemic would result in an increase of 14.29% in the total number of deaths in the country. The total number of deaths exponentially increase as the number of days before implementing a quarantine intervention increase. After two months delay of quarantine, an increase of 26.19% in the total number of deaths in the country is observed, resulting in more than 1 700 additional lives lost. Timely implementation of intervention strategies is critical to effectively respond to a rapid changing and spreading disease. Given limited time and resources, a delayed intervention proves more effective than no intervention implementation, since no implemented quarantine would result in more than 6 600 deaths in the country.

5.5.3 Evaluation of the distribution of limited bed capacity

In the planning of an effective intervention strategy, it is critical to consider the distribution of resources and facilities. The proposed model is used to evaluate various scenarios of distributing ETC in an Ebola outbreak. These results may aid in the process of making vital decisions during a fast spreading disease epidemic. The WHO reported on 3 December 2014 that 500 treatment beds were sufficient capacity to isolate and treat all new cases. However due to uneven distribution of beds and cases, serious shortfalls remained throughout the country [93]. On 3 December 2014, 13 ETC were operational with a total capacity of 500 beds. Western Area Rural had 8 ETCs and the remaining 5 ETCs were distributed among Western Area Urban, Bo, Bombali, Kenema and Kailahun [93]. Three ETC scenarios are compared to the reported event of the WHO to establish a more effective distribution strategy of ETC. The visual representation of each strategy and the WHO's scenario may be seen in Figures 5.40 to 5.43, where the navy dots represent an ETC with an assigned bed capacity. The first strategy is to distribute the 500 beds evenly among the 7 counties with the highest populations (see Figure 5.41).

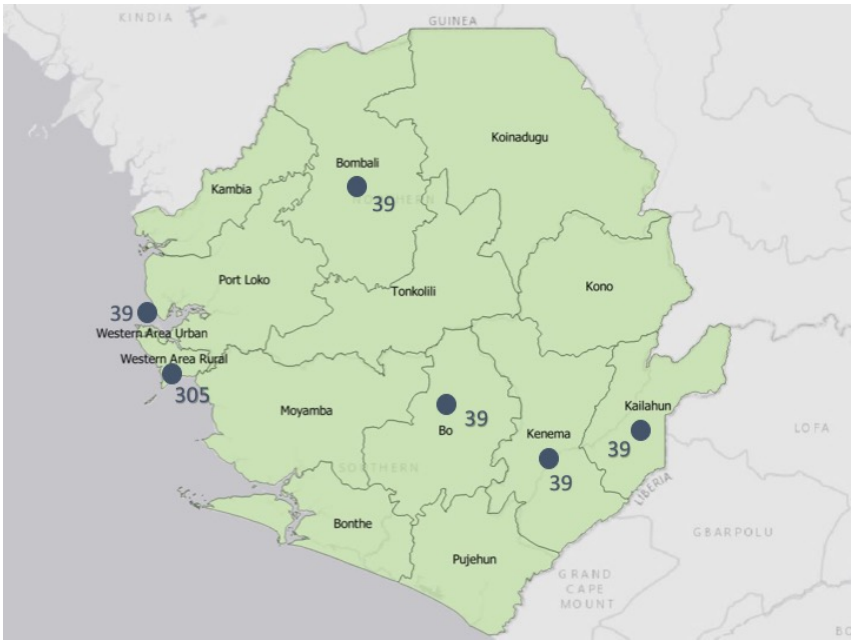

FIGURE 5.40: *Visual representation of the WHO's implementation of quarantine on 3 December 2014.*

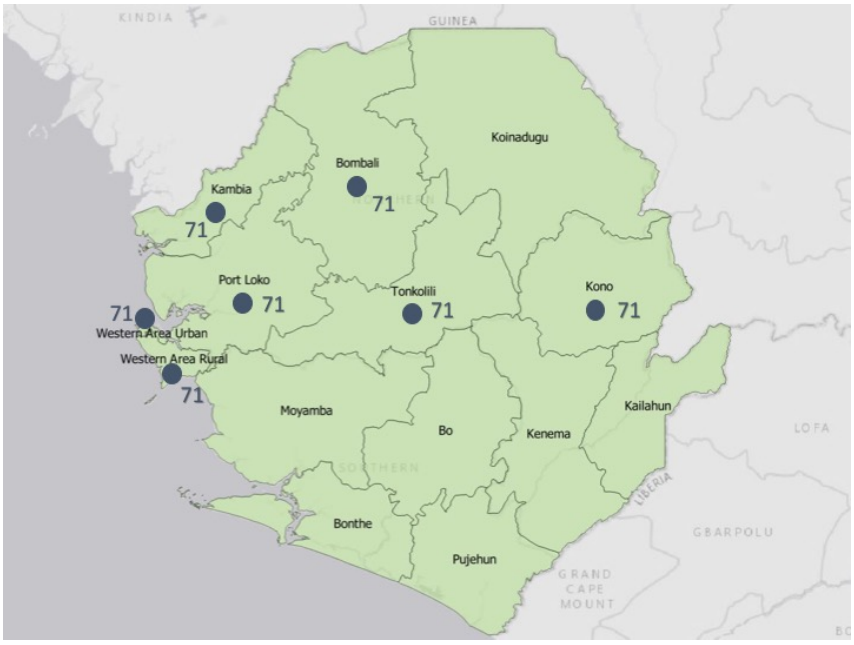

FIGURE 5.41: *Visual representation of the first county quarantine strategy under bed capacity restrictions.*

The argument for the approach is that a greater population size in a county would have a greater infection rate, due to a greater contact rate between infected and susceptible individuals. This approach however does not take into account whether the initial population of the county has a proportion of infected individuals present. Therefore the second strategy is to distribute the 500 beds among the 7 counties with the highest number of cases (see Figure 5.42).

This approach ensures a quicker removal of infected individuals from the susceptible population within a county, however, it restricts counties without an ETC to effectively remove infected individuals from their susceptible populations. The third strategy distributes the 500 beds

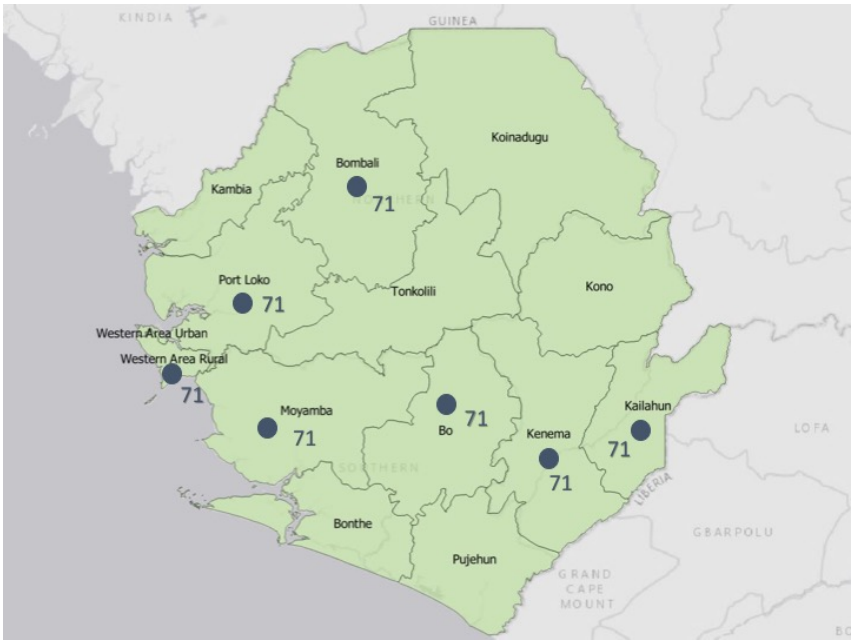

FIGURE 5.42: *Visual representation of the second county quarantine strategy under bed capacity restriction.*

evenly among the 14 counties, ensuring all counties have relatively similar access to isolation and treatment units to isolate and treat immediate cases (see Figure 5.43).

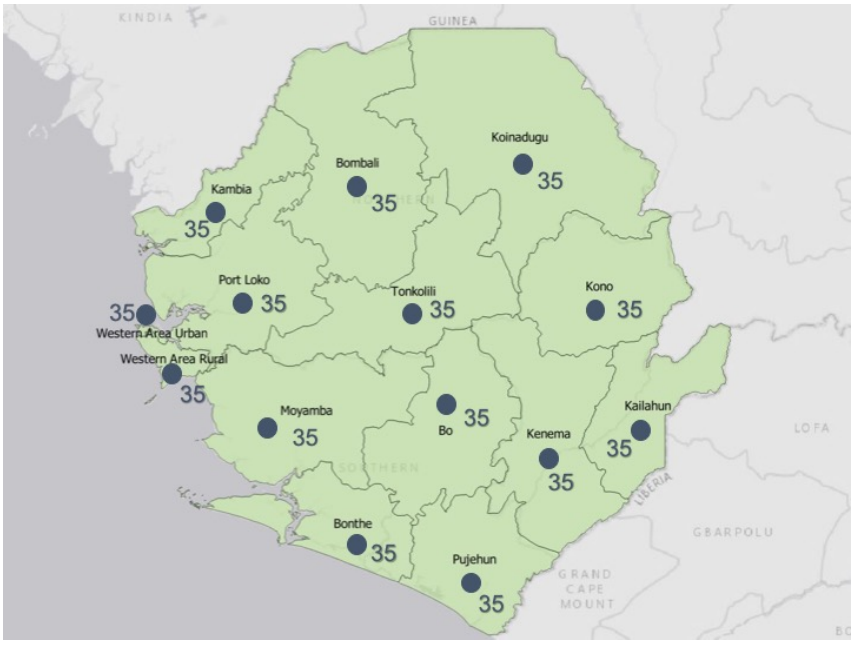

FIGURE 5.43: *Visual representation of the third county quarantine strategy under bed capacity restriction.*

The effect of the four ETC distributions strategies on the total number of deaths in country could be seen in Figure 5.44.

The reported event of the WHO resulted in 5 878 deaths in the country. Strategy 1 place ETC in Bombali, Kambia, Kono, Port Loko, Tonkolili, Western Area Rural and Western Area Urban

and resulted in a total number of 5 920 deaths in the country. Strategy 2 place ETC in Bo, Bombali, Kailahun, Kenema, Moyamba, Port Loko and Western Area Rural and resulted in a total number of 5 786 deaths in the country. The final strategy, strategy 3, place an ETC in each county with evenly distributed treatment beds and resulted in a total number of 4836 deaths in the country. Comparing the results it would be most effective to place an ETC in each county during an Ebola outbreak. Distributing facilities more evenly over the country would act as a secondary means to restrict movement among counties. Placing an ETC in each county allows for infected individuals to remain in their initial county and restricts migration to other counties in search of treatment. This would prevent hot spots of increased disease spread in a specific area due to infected individuals remaining more widely distributed rather than clustered in higher population counties. The possibility of infecting an uninfected population in an alternative county would also be decreased if infected individuals could find treatment in the county of their origin. Strategy 2 proved to be relatively more effective than the WHO reported event and strategy 1 in the total number of deaths in the country. Strategy 2 had a slower initial increase in number of deaths which is expected as already infected individuals in a county could be swiftly removed from the susceptible population. However, as the capacities of the ETCs are reached the remaining infected individuals who were not isolated and treated would cause an intensified spread within the county as well as cause infection in other counties as they search for treatment, resulting in a relatively similar total number of deaths as the WHO reported event and strategy 2.

The implementation of an intervention strategy is strongly dependant on the unique characteristics of the response situation, environment, social and economical status of the community and the willingness of the communities corporation. It can however not be overlooked the importance of a timely and well strategised intervention implementation to control the further spread of an infectious disease within an country.

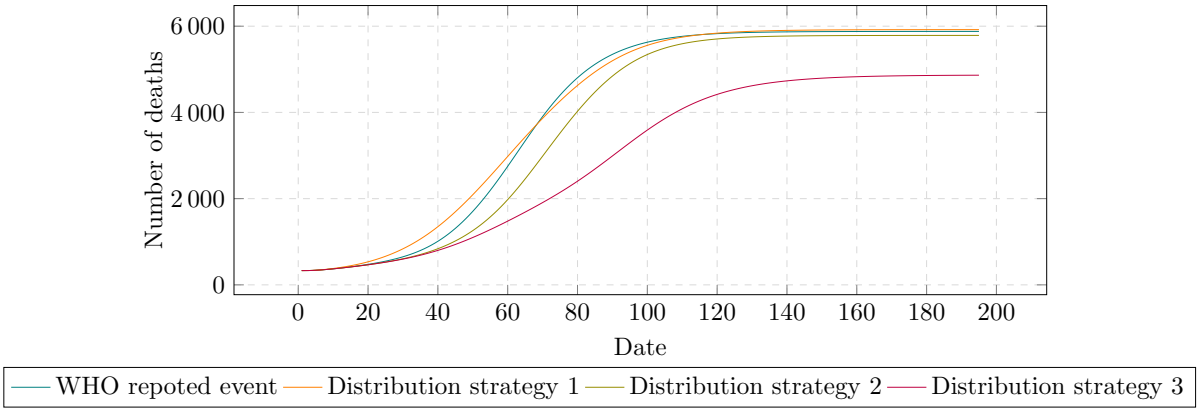

FIGURE 5.44: *The effect of four ETC distributions on the total number of deaths in Sierra Leone. The WHO implementation of 2014, distribution 1 where 500 beds are distributed among the 7 counties with the highest populations, distribution 2 where 500 beds are distributed among the 7 counties with the highest number of cases and distribution 3 where 500 beds are evenly distributed among the 14 counties of Sierra Leone*

5.6 Chapter summary

The chapter opens with a brief discussion of the Ebola outbreak in Sierra Leone of 2014-2015 in §5.1. A geographical representation of the 14 counties and the population distribution of 2015

follows in §5.1.1. The data used for the model calibration is presented in §5.1.2, as well as a discussion on the number of reported cases and deaths for each county. The validation process of the model is discussed in §5.2. A calibration experiment was implemented on the proposed model through the use of a weighted RMSE approach, minimising the difference between the historical data and simulated data. The models parameters were estimated and proved to adequately replicate the patterns observed in the historical data. Both a single parameter and combination of parameters sensitivity analysis were conducted to investigate the influence of the specified parameters on the number of deaths observed in the country. The sensitivity analysis of both exposure rates indicated intervention efforts should be aimed at decreasing the communities exposure rate. The number of deaths were observed to be most sensitive to vaccination efforts, as the greatest decrease was observed in the number of deaths with increased vaccination rates. The sensitivity analysis with combinations of intervention parameters proved that a smaller effort in a combination of intervention strategies would have a greater impact on the number of deaths in the country than a greater effort of a single intervention. Finally concluding the chapter with various simulations experiments evaluating the effectiveness of intervention strategies in the Sierra Leone outbreak of 2014-2015 in §5.3 -§5.4. Evaluation of different quarantine approaches on a county level proved the greater the number of counties isolated the greater the more effectively the spread of the disease in the country is prevented. The success of an intervention strategy's implementation is subject to the resources available. Evaluating of the effect of quarantine under the limitations of bed capacity indicated the critical role of timely and well planned execution of intervention strategies.

CHAPTER 6

Conclusion

This chapter consists of a brief summary of the work presented in this study, as well as an overview of the main contributions of the study with respect to the mathematical modelling and analysis of the influence of interventions strategies on the Ebola epidemic. The chapter concludes with suggestions for possible future work to further this research.

6.1 Thesis summary

In the introduction of this study, the severity of the Ebola outbreak in Sierra Leone of late 2014 caused by the lack of knowledge and understanding of the disease was discussed, followed by a brief explanation of humanitarian crises. After emphasizing the importance of humanitarian logistics for a successful outcome of a humanitarian crisis, the necessary biological background of the Ebola virus disease was discussed, which provided the necessary foundations to model the interacting dynamics observed within the disease system and understand the assumptions made during the construction of the model in subsequent chapters (in fulfilment of Thesis Objective I). The various interventions strategies previously executed in an attempt to control the disease was provided, followed by the four phases of control and prevention strategies of an epidemic, as stated by the WHO. The chapter concluded with a brief outline of the Ebola epidemic in Sierra Leone of late 2014 followed by the informal problem description and the scope and objectives pursued in this study.

An overview of the mathematical background with respect to the modelling of infectious diseases with examples of such models applied to the Ebola epidemic and the limitations of those models, was discussed in Chapter 2 (in fulfilment of Thesis Objective II(i)). Previous models of the Ebola epidemic excluded various intervention strategies and to an extent disregarded the temporal spatial movement of individuals within the disease system. A metapopulation model with temporal spatial movement awareness was therefore required to investigate the influence of migration on the interacting dynamics of the Ebola epidemic.

Chapter 3 served as a literature review of computer simulation modelling fundamentals and best practices from literature (in fulfilment of Thesis Objective II(ii)). The chapter opened with the four prevalent simulation modelling paradigms observed in literature followed by a discussion of the advantages and disadvantages of simulation modelling. The typical twelve steps followed in the simulation modelling process was presented followed by various methods of verification and validation of simulation models. The chapter concludes with a brief overview of simulation modelling in the context of epidemiological systems.

A mathematical model for describing the spread of Ebola through a susceptible population was presented in Chapter 4 (in fulfilment of Thesis Objective III(i&ii)). The conceptual model was presented first, followed by a discussion of the implicit and explicit assumptions made within the model. Thereafter an overview of the model formulation was given accompanied by a discussion of the model parametrisation and the pseudocode of the software implementation. The chapter concluded with the verification of the model. The model was deemed valid after numerous simulation runs that verified that the model output was able to adequately replicate the interacting dynamics of an Ebola virus disease outbreak.

In Chapter 5 a case study was presented. The chapter opened with a brief discussion of the Ebola outbreak in Sierra Leone of late 2014, followed by a geographical representation of the 14 counties of Sierra Leone and their population distribution of 2015. The data used in the model application was presented with a brief discussion of each county's number of cases and deaths. The validation process of the model was presented (in fulfilment of Thesis Objective IV & V) followed by a set of simulation experiments investigating the impact of the various intervention strategies on the Ebola epidemic's interacting dynamics (in fulfilment of Thesis Objective VI). The sensitivity of the community exposure rate and the burial ceremonies exposure rate indicated that efforts should be aimed at decreasing the communities exposure rate. The sensitivity analysis of the various intervention parameters indicated that the number of deaths observed in the country were most sensitive to the rate of vaccination. It is therefore advised to prioritise the effective execution of vaccination efforts. A sensitivity analysis on sets of intervention parameters indicated a smaller effort in a combination of intervention strategies achieved similar results to a greater effort in a single intervention. A simulation experiment was executed to observe the influence of limited migration movement due to county quarantine on the spread of the disease in Sierra Leone. Evaluation of different quarantine approaches on county level indicated that the greater the number of counties isolated, the more effectively the spread of the disease is prevented. The chapter concluded with an evaluation of the effect of bed capacity within ETU on the number of deaths observed due to Ebola. Evaluation of quarantine under the limitations of bed capacity proved the critical role timely and well planned intervention strategy implementation play in the number of deaths observed in the country.

6.2 Main contributions

The main contributions of this study include:

1. *The development of a spatio temporal model describing the spread of Ebola in Sierra Leone*

A metapopulation modelling approach was applied to a case study of a population with migration factors determining the movement amongst geophysically separated regions. The model incorporated a set of intervention strategies of which various combinations of strategies have not yet been examined by previous studies. The detailed discussion of the implementation of the spatio-temporal model in PYTHON may also aid as a valuable foundation for future implementations of mathematical models describing similar infectious disease simulations.

2. *The evaluation of county quarantine on an Ebola virus disease epidemic*

The simulation model was used to investigate the impact of a county specific quarantine intervention strategy. Given the 14 counties of Sierra Leone, various scenarios of quarantine measures were simulated restricting the movement among counties and therefore preventing further spread of the disease throughout the country. A lack of such unique intervention evaluations is seen in literature.

3. *The evaluation of an effective quarantine intervention given limited resources*

The successful implementation of any intervention strategy is dependant on the resources available. Through the use of the simulation model developed, the influence of limited bed capacity within a quarantine intervention strategy implementation was investigated. Gaining better insight on the effect of timely and well strategies intervention strategies, may possibly aid future prevention planning of an Ebola outbreak.

6.3 Possible future work

In this section six suggestions are made with respect to possible future research pertaining to the development of simulation models describing the dynamics of infectious diseases and their associated performances, as well as the mathematical model describing the spread of Ebola in Sierra Leone proposed in this study.

Suggestion 8.3.1 The model framework presented in this study could be used to model various diseases, by which the model is tailored to the unique characteristics of the disease to investigate the impact of the proposed intervention strategies on the specified disease modelled.

Suggestion 8.3.2 In this study a closed system was assumed, therefore allowing no flux of individuals from neighbouring countries. Observed from various reports of the Ebola spread in Sierra Leone, this assumption is unrealistic and is therefore suggested a possible expansion of the proposed model could incorporate the migration of individuals to and from neighbouring countries.

Suggestion 8.3.3 To achieve a more accurate representation of the Ebola system, more intervention strategies may be included such as symptom treatment and awareness and educational campaigns. Incorporating all aspects of the Ebola system may aid in investigating efficient intervention combinations and ultimately result in a greater understanding of the interacting dynamics between the different compartments in the Ebola system. Consequently, a more efficient and focused approach to epidemic control may be achieved.

Suggestion 8.3.4 The model was calibrated using a weighted RMSE approach. The weights allocated to the historical data could be varied. Different allocations of weights could be evaluated to find the appropriate weights that result in calibrated values that best describe the patterns observed in the historical data.

Suggestion 8.3.5 The use of a self governing agent based modelling approach would allow for investigation of the behaviour response of the individuals within the population being modelled. The effectiveness of a set of interventions implemented, is strongly dependant on the cooperation of the community in which it is introduced. To successfully implement control and prevention strategies, the cultural, social and economical status of the community should be taken into consideration.

Suggestion 8.3.6 Investigate challenges arising due to resource limitations and develop cost effective strategies. Diseases such as Ebola tend to break out within highly populated developing countries that are greatly limited in resources. Finding an intervention strategy that would control the epidemic, as well as being cost-efficient given the limitation to resources, would be considered as a optimal solution.

Suggestion 8.3.7 Three quarantine distributions were investigated in this thesis. An additional distribution of bed capacity proportional to the total population distribution of the country could be investigated to establish the most effective distribution of beds during a limited resource

quarantine intervention strategy.

Suggestion 8.3.8 At the time of this study an accurate vaccination coefficient was not available and was estimated for the evaluation of the impact of vaccinations on the spread of Ebola in Sierra Leone. More information on the vaccination trials is needed in order to be able to accurately replicate the influence of vaccination as an intervention strategy.

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