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VALUE OF INFORMATION ANALYSIS IN EBOLA MANAGEMENT

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Abstract

Over fifty mathematical models have been published to project the number of cases and the success of epidemic intervention strategies in the 2014 West African Ebola outbreak. Structural and parametric uncertainties exist between and within models, making it challenging to quantitatively rank the utility of intervention tools. Without a formal method of comparison, policymakers are forced to subjectively decide which models should dictate decision-making. Value of information (VOI) analysis, commonly used in economics and resource management, quantifies the extent to which decision-making is hampered by such uncertainties, thus providing guidance as to how to prioritize future information gathering. We focused on one of the most established models and performed a two scenario analysis to explore the uncertainties about hospital and funeral transmission and to demonstrate the utility of value of information analysis to address parametric uncertainties. We implemented a stochastic simulator using the Gillespie exact algorithm on a six compartment SEIHFR model introduced by Legrand *et al* [1]. We found that decreasing community transmission is universally most effective at minimizing case count and mortality. Public health policy in the 2014 Ebola outbreak should likely have targeted community transmission more intensely through awareness campaigns, distribution of household protective kits, and by encouraging self-quarantine.

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Chapter 1

An Overview of Ebola

Overview

The Filoviridae family consists of three of the most deadly and poorly understood single-stranded negative RNA viruses, including cuevavirus, marburgvirus, and ebolavirus. Ebolavirus causes Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever. The genus *Ebolavirus* contains five species: *Zaire ebolavirus, Sudan ebolavirus, Taï forest ebolavirus* (previously known as *Côte d'Ivoire ebolavirus), Bundibugyo ebolavirus*, and *Reston ebolavirus*. Four of the strains are known to infect humans. *Reston ebolavirus* was only documented in primates when infected monkeys were imported to Reston, Virginia from the Philippines. Eighteen countries have encountered EVD through laboratory contamination or zoonotic spillover.

Disease Progression

EVD is transmitted via blood and bodily fluids such as mucous, urine, vomit, semen, and saliva. After exposure, individuals will not exhibit symptoms during an incubation period between 2 and 25 days [2]. Once patients develop symptoms, they are considered infectious to others. Patients will most commonly present fever, diarrhea, fatigue, joint/muscle/abdominal pain, and vomiting [3, 4]. Most infected individuals will seek medical attention between three and seven days after symptoms develop. Initial symptoms of EVD are frequently mistaken for other tropical diseases such as malaria and dengue [5]. Differentiation occurs when EVD patients enter the terminal hemorrhagic phase, which includes internal hemorrhaging, subcutaneous bleeding, and the vomiting of blood [4]. Time to death is dependent on the subtype but on average half of Ebola patients will succumb to the virus in seven to eleven days [3]. Dehydration is the most common cause of death due to severe vomiting and diarrhea. Although there is no difference in infection rates for gender or age, patients over 40-years-old are more likely to succumb to the virus [3]. There is no known cure for Ebola. Vaccine development is underway but none are available on the market. Currently, health care workers treat symptoms and focus on rehydrating patients.

Historical outbreaks

The first two documented outbreaks of Ebola in humans occurred simultaneously in 1976 near the Ebola River in the Democratic Republic of Congo (DRC), formerly known as Zaire, and in Sudan near the DRC border [6, 7]. The Zaire outbreak had a mortality rate of 89% and is the namesake of the *Ebola zaire* subtype. Similarly, *E. sudan* caused a 53% mortality rate in Sudan. Sudan also hosted the third outbreak in 1979. Both the 1976 and 1979 outbreaks began with cotton factory workers [8]. The 1979 Sudan outbreak had a higher mortality rate (66%) than the previous one, but it affected fewer people.

After these initial three outbreaks, fifteen years passed before Ebola was seen in humans again. Ebola re-emerged as a new strain in the Ivory Coast in 1994 when a scientist was infected while autopsying a wild chimpanzee [9]. This is the only case of *Taï forest* documented in humans and the first case found in West Africa. *E. zaire* reappeared in Gabon in 1994 when three gold-miner camps in the forest were exposed to the virus. When the miners became infected and sought medical treatment, they spread the virus to the local hospital and its nearby inhabitants, causing a

second round of infection [10]. The Zaire virus also appeared in the DRC in 1995 and mirrored the 1976 outbreak, exhibiting an 81% mortality rate. Transmission occurred primarily in the two town hospitals and drove the persistence of the outbreak [11]. Again in 1996, *E. zaire* infected people in Gabon when village children handled a chimpanzee carcass they found in the forest [12]. Gabon hosted a third outbreak at the end of 1996, which began when hunters contracted the virus while in the forest. This was the first recorded outbreak with a notable geographic distribution. The hunters sought traditional medical treatment, exposing and infecting local healers. The healers, in turn, infected nearby villages, whilst a doctor naively traveled from Gabon to South Africa, where he infected a healthcare worker who succumbed to the virus days later. The October 1996 Gabon outbreak lasted 6 months and affected Gabon and South Africa [12].

No infections were noted between 1997 and 2000. In 2000, Uganda recorded the largest Ebola outbreak to that date with 425 cases [13]. *E. sudan* was responsible for the epidemic and continued its trend of lower mortality rates than *E. zaire* (40.7%). Not a year passed before Gabon was victim to *E. zaire* again in a series of independent outbreaks between October 2001 and March 2002 [14]. Hunters were implicated as the source of the outbreak and continued to reintroduce the virus through the handling of infected wildlife. The next outbreak occurred in the Republic of Congo in late 2002. Once again, a mining camp had interacted with wild carcasses and dispersed the virus to villages in the vicinity [15]. The number of cases began trending downward with the 2003 and 2004 outbreaks in the Republic of Congo and Sudan, respectively [16, 17]. The 2004 outbreak was the smallest recorded Ebola epidemic with only 17 cases.

After no outbreaks for three years, Ebola reemerged in 2007 with outbreaks in Sudan and Uganda [18]. *Bundibugyo ebolavirus* was first recorded in the 2007 Uganda outbreak with the lowest historical mortality rate of 25% [19]. *Zaire ebolavirus* came out of hiding in 2008 in the DRC with a slightly lower mortality rate (47%) than was previously recorded for the Zaire subtype [20]. Another infection-free period ensued between 2009 and 2011. A string of small outbreaks in Uganda and DRC caused by the Sudan and Bundibugyo subtypes, respectively, occurred in 2012 [21].

Two independent outbreaks coincided in 2014, both caused by *Zaire ebolavirus*. The DRC was home to the smaller and shorter of the two outbreaks, affecting 69 people and lasting four months [22]. The other outbreak accumulated more cases than the sum of the historical outbreaks and persisted from December 2013 through early 2016 when the final cases were recorded. The 2014 West Africa Ebola outbreak was globally televised and classified as an international public health emergency. Cases were recorded in ten countries, but the foci of the epidemic were in Guinea, Liberia, and Sierra Leone. Over 28,500 people contracted the virus, and over 11,300 people had succumbed to the disease as of March 31, 2016 [23].

In addition to direct mortality, the outbreak lead to a complete breakdown of public health infrastructure. The interruption of routine vaccinations for communicable disease such as measles is predicted to leave thousands of children susceptible in the coming years [24]. The expected number of measles cases is anticipated to rise by 100,000 in a year and a half. This could create up to 16,000 deaths due to measles as an indirect consequence of the Ebola outbreak. The Ebola epidemic was an immediate international public health crisis, but its indirect impact in public health may also be seen for years to come.

Table 1.1: Ebola outbreaks have occurred intermittently since 1976. The majority of historical outbreaks have been concentrated in Sudan, the Democratic Republic of Congo, and Uganda. They have been caused by a variety of suspected hosts. However, the most recent outbreak in Guinea, Sierra Leone, and Liberia surpassed previous impacts of Ebola and reached unprecedented case counts.

Year	Site of Outbreak	Suspected Source of Infection	Strain	Case Count	Mortality Rate
1976	DRC (Zaire)	Unknown	Zaire virus	318	88% [6]
1976	Sudan	Bats	Sudan virus	284	53% [7]
1979	Sudan	Bats	Sudan virus	34	65% [8]
1994	Ivory Coast	Chimpanzee	Ivory Coast virus	1	0% [9]
1994	Gabon	Wildlife	Zaire virus	52	59% [10]
1995	DRC	Wildlife	Zaire virus	315	81% [11]
1996	Gabon	Chimpanzee	Zaire virus	37	57% [12]
1996	Gabon	Chimpanzee	Zaire virus	60	75% [12]
2000	Uganda	Unknown	Sudan virus	425	53% [13, 25]
2001	Gabon	Gorilla/Antelope	Zaire virus	65	82% [26]
2002	Republic of Congo	Wildlife	Zaire virus	143	89% [15]
2003	Republic of Congo	Unknown	Zaire virus	35	82% [16]
2004	Sudan	Unknown	Sudan virus	17	41% [17]
2007	Sudan	Unknown	Sudan virus	264	71% [18]
2007	Uganda	Unknown	Bundibugyo virus	149	25% [19, 25]
2008	DRC	Fruit bats	Zaire virus	32	47% [20]
2012	Uganda	Unknown	Sudan virus	11	36.4% [21, 25]
2012	DRC	Unknown	Bundibugyo virus	36	36.1% [21]
2012	Uganda	Unknown	Sudan virus	6	50% [21, 25]
2014	DRC	Unknown	Zaire virus	66	74% [22]
2014	Liberia, Guinea, and Sierra Leone	Bats	Zaire virus	28646 (as of 3/31/16)	40% [23, 5]

Zoonoses and Spillover Events

Zoonotic spillover events occur when humans become infected with an animal disease. Such spillovers are responsible for three of every five infectious diseases [27]. Bacteria, viruses, fungi, and parasites are responsible for zoonotic diseases such as avian influenza, severe acute respiratory syndrome (SARS), malaria as well as Ebola. Ebola does not maintain a robust chain of transmission in humans and requires zoonotic spillover events to initiate what are normally short, stuttering

chains of transmission. Most of the historical Ebola outbreaks occurred through direct contact with wildlife. The most commonly documented infected animals were gorillas, chimpanzees, and duikers. During human Ebola outbreaks, there was a marked decline in these animal populations [14]. High decomposition rates in equatorial forests usually prevents human interaction with wildlife carcasses, but in the 2001 Gabon outbreak, 64 animal carcasses were reported by villagers, some of which tested positive for Ebola virus [14]. This rare occurrence suggests high death rates for large mammal populations in the vicinity, mirroring the human outbreak. Surveillance of nearby animal populations known to contract Ebola could aid in the prediction and prevention of Ebola outbreak and limit the risk of human exposure.

Large mammals are prominent carriers of Ebola but are not suspected to be the reservoir species. Bats serve as a natural reservoir, or long-term host, for a number of emerging infectious diseases such as SARS, Hendra virus, Nepa virus, and rabies. Three fruit bat species, the hammer-headed fruit bat (*Hypsignathus monstrosus*), Franquet's epauletted bat (*Epomops franqueti*), and the little collared fruit bat (*Myonycteris torquata*), appear to exhibit asymptomatic Ebola, suggesting their suitability as reservoir [28]. Similar suspicions were raised in the 2007 DRC outbreak. Transmission chains were traced back to the capture and consumption of migratory fruit bats [29]. To date, we still know too little about bat biology to conclusively named bats as the reservoir of Ebola, but it is known that bats are the reservoir of the related zoonotic Marburg filovirus [30].

Transmission Venues

Interaction with an infected animal is the crucial first step in Ebola primary infections and usually occurs in forests where interaction with wildlife is more common. There have also been recorded outbreaks in cotton factories, where bats were noted to be present. After the initial case, Ebola usually spreads in three main venues: in the community/home, in the hospital, and at funerals.

An infected individual will often return home after initial exposure. After symptoms develop, his or her entire family may be exposed to the virus. A family member will usually become the caretaker of the infectious loved one. Because Ebola spreads through contact with bodily fluids, Ebola is highly contagious within a household. When the loved one desires medical attention or becomes too ill to care for, the infected individual travel to nearby hospital for admittance. Hospitals can be a journey away; when a sick family member travels, community members outside the immediate family are also exposed to the virus.

Nosocomial infections are a cause for concern in Ebola outbreaks. Initially, Ebola patients exhibit flu-like symptoms that can easily be mistaken for other infections such as malaria. The additional precautions to prevent secondary infections necessary for an Ebola patient will not be taken for the first hospitalized cases during an outbreak. Health care workers (HCWs) are highly at-risk for infection due to the frequency of interactions with the patient. HCWs can also spread the virus to other susceptible patients in the hospital as well as their own families in the community. Despite hospital care, Ebola can easily claim the lives of half of infected individuals.

Secondary cases also occur during traditional burial practices. Traditional funeral practices in many African countries include touching, kissing, and washing of the deceased by immediate family members [31]. A paternal aunt or elder female in the patrilineal line is responsible for washing and preparing the body. During the service, all attendees are welcome to touch the body

as a final goodbye. Given that the viral load is highest at death, this makes burials the most contagious venue for Ebola infection.

Ebola Management

The unprecedented outbreak in 2014-2016 left public health management with little direction. A range of interventions were suggested and enacted with varying success. To curb the impact of the outbreak, interventions targeted the three primary transmission venues.

Personal protective equipment (PPE) was mandated for HCWs to prevent contraction and spread of the virus. However, PPE is extremely limiting. Due to the high temperatures in West Africa, one to three hour time limits were placed on HCWs wearing PPE [32]. This restriction controls the number of patients receiving care within each time window. Thus, there were not enough HCWs to provide the same level of continuous care as when these precautions were not taken. In particular, the use of PPE limited the level of rehydration patients could receive [3]. Rehydration is vital to lowering mortality rates.

Extensive travel to the hospital was considered a burden on the sick and unnecessarily exposed community members to the virus. Ebola treatment units (ETUs), which were equipped with rapid diagnostic kits, functioned as emergency Ebola-care facilities with the goal to reduce the time from symptom presentation to isolation [32]. Lack of hospital space was an increasing issue with the outbreak. Estimates for the number of necessary hospital beds exceeded those available and pledged by the United States [33]. ETUs were built to curb this issue and make medical care more readily available.

Another tactic used for public health management was community awareness through educational campaigns [34]. Public education about the epidemic aimed to make community members more likely to perform preventative behaviors and self-quarantine to prevent contraction or spread of the virus. Community cooperation allowed for more efficient and effective healthcare. People feared that they would contract Ebola from a hospital when they visited for non-Ebola treatment. This fear motivated individuals to avoid medical treatment altogether, for both Ebola and non-Ebola cases, leaving Ebola cases in the community to drive up community transmission [35]. To curb community transmission, UNICEF issued household protective kits which contained PPE, disinfectants, and instructions on proper disposal [36].

Due to the indigenous culture, funerals presented a major opportunity for virus transmission. Health agencies attempted to thwart funereal transmission by regulating burial practices. Bodies were placed in leak-resistant bags by trained professionals donning PPE [37]. Burials occurred at at least two meters depth in a cemetery in the absence of family members.

While all management practices are likely to have been important in stemming the epidemic, it is unknown which action(s) were more important and why. Demographic and spatial heterogeneities cause some of the uncertainty in intervention. Resolving this uncertainty may be important for a prompt, effective response in future outbreaks.

Chapter 2

Determinants of Epidemic Size

The Basic Reproductive Number, R_0

Epidemiologists estimate the transmission potential of a directly transmitted disease through its basic reproductive number, R_0. R_0 describes the number of secondary cases caused by a single introduction into a completely susceptible population. Several factors affect the basic reproductive rate such as the rate of contact within a host population, the duration of infectiousness, and the probability of transmission while infectious. These factors are utilized to quantify R_0 through many approaches, including model-based approaches and detailed model fitting [38]. Assuming exponential, density-dependent infections, the simplest relationship is the transmission rate times the infectious period [39]. For endemic immunizing infections, R_0 is also related to the mean age of infection. Anderson and May estimated that R_0 is approximately equal to the ratio of mean life expectancy and the mean age of infection [40].

For an infection to spread in a population, R_0 must be greater than 1. In other words, a primary case must transmit to more than one person, on average, for a disease to circulate. If R_0 is less than one, the transmission will die out. Frequently, the goal of epidemic management is to force R_0 below its critical threshold to discourage disease persistence, but sometimes epidemiologists focus on the effective reproductive ratio, R_E instead. R_E is a similar quantity to R_0. R_E is the mean number of secondary cases in a partially immune population and is a more realistic estimate during an ongoing outbreak. When a disease grows without density dependence, the effective reproductive ratio is approximately equal to the basic reproductive ratio ($R_E \simeq R_0$) [41]. The level of immunity within a population can also slow disease transmission. If one half of a population is immune or not susceptible to a disease, R_E becomes one half of R_0.

Depletion of Susceptibles

Transmission to susceptible individuals is crucial to the persistence of every epidemic. Thus, management can focus on reducing the prevalence of susceptibles or on reducing transmission to new susceptibles. When a fraction of $1/R_0$ of all of the susceptibles have been infected, an epidemic will begin to recede. Once most susceptible individuals have become immune, the virus cannot effectively transmit to the remaining viable hosts. This creates an initial exponential rise in the number of infected individuals and then a subsequent fall as individuals recover or are removed from the susceptible pool. For acute, highly infectious diseases to persist in a population, there is a critical threshold of susceptible individuals known as critical community size (CCS). CCS is vital for the persistence of measles as well as other infectious diseases [42]. If the number of susceptibles falls below the CCS, the disease cannot effectively transmit and will fade out. This type of fadeout is known as a susceptible bottleneck.

Another cause of loss of persistence is the transmission bottleneck. Transmission bottlenecks occur when transmission is interrupted, and the disease cannot come into contact with susceptible individuals. Small stochastic fluctuations in transmission can remove all the pathogens from the system. Due to the lack of a vaccine, forcing a susceptible bottleneck is nearly impossible unless Ebola emerges in a highly immune population. Instead, public health management focuses on interrupting transmission through a transmission bottleneck by attempting to bring R_E below 1.

Final Epidemic Size

The final epidemic size is dependent on the basic reproductive number and the size of the population. Infections will accumulate exponentially for $\frac{logN}{R_0}$ generations until susceptible individuals are depleted [41]. If transmission is density-dependent, the generation time will be longer than the density-independent case, meaning that the epidemic will take longer to deplete the susceptibles. In a simple epidemic, we expect the epidemic to grow to approximately as e^{-R_0} (as long as R_0 is around two). However, the distribution of final epidemic sizes is most similar to e^{-R_0} toward the end of the epidemic, due to disease-induced mortality [43].

The 2014 Ebola Outbreak

A detection failure and delayed response are frequently blamed for the uncharacteristic size of the 2014 West Africa Ebola epidemic. Ebola had never been detected in West Africa before 2014, so intial cases were not recognized until significant transmission had occurred. The three foci of the epidemic, Guinea, Sierra Leone, and Liberia, had recently stabilized after political unrest or civil wars, which left damaged healthcare infrastructure in its wake. Hospitals did not have the resources or space to treat the cases that flooded their doors. Health care workers were also in shortage, limiting the number of patients that could be treated even further.

Population mobility reignited cases across borders. People move freely across borders in search of food or work, as most people in Guinea, Sierra Leone, and Liberia live in a state of poverty. The porous borders allowed for constant reintroduction of disease despite heavy intervention in any single area. Large households increase epidemic risk and may have contributed to the spread of Ebola in West Africa [44]. With effective household quarantines, the effect of household size may be mitigated.

The response to the 2014 West Africa outbreak was too little and too late. Funding for vaccine development came months into the outbreak and resulted in minute progress. Few Ebola vaccines have even entered Phase I of human clinical trials [45]. Additionally, educational campaigns attempted to raise community awareness of the Ebola epidemic by citing its danger and seriousness. The campaigns were partially effective in educating the public of preventative measures but made some people wary of seeking medical treatment at all.

Chapter 3

Value of Information Analysis

Adaptive Management

Public health management during ongoing epidemics is frequently affected by uncertainties, which limit management success. Two prominent types of uncertainties exist: those we can resolve through learning and those we cannot [46]. Aleatory (stochastic) uncertainties encompass uncontrollable environmental variation. Epistemic uncertainties characterize a lack of information on how a process occurs. These latter uncertainties can be resolved through further investigation into the state of the system.

During an outbreak, we usually attempt to resolve uncertainties by assessing prior epidemics and management approaches. However, the most relevant and predictive information is collected as the epidemic progresses. Retrospective analyses can also mislead uncertainty resolution if an active outbreak is drastically different from historical records, as in the case of the 2014 Ebola outbreak relative to the 24 previous outbreaks. To achieve the most beneficial management, active data collection can be incorporated into adaptive management models.

Adaptive management integrates science and policy by incorporating active data collection into decision-making during management. This efficiently guides resource allocation and information gathering to resolve uncertainties and maximize benefit. Adaptive management is a structured, decision-making framework that iteratively updates under dynamic, uncertain outbreak conditions.

Value of information (VOI) analysis is a technique, commonly used in economics [47], which quantifies the extent to which decision-making is hampered by uncertainties, providing guidance as to how to prioritize future information gathering. The VOI analysis provides an objective, quantitative indication of the most effective strategy to direct public health decision-making in the midst of an epidemic [48].

Expected Value of Perfect Information Analysis

Expected value of perfect information (EVPI) analysis quantifies the objective value of resolving uncertainties prior to decision implementation [48]. This structured framework guides the efficient allocation of resources and information gathering to inform decision-makers. EVPI compares the cost/benefit of having perfect information about the resolved uncertainties to the cost/benefit of the current information. In other words, EVPI analysis is the comparison of the optimum of the average values, which are weighted expectations across competing models, and the average of the optimum values contingent on each model. EVPI analysis evaluates all possible model and management combinations in terms of their ability to achieve a stated objective. Each model in the comparison is weighted based on the likelihood of it being the most realistic model:

$$\text{EVPI} = \sum_k p_k (\underset{i}{opt} C_{ik}) - \underset{i}{opt} \sum_k p_k C_{ik} \tag{3.1}$$

This model denotes p_k as the probability model k is the most realistic model such that $\sum_k p_k = 1$. The optimum across the i interventions is represented by $\underset{i}{opt}$, and C_{ik} is the cost/benefit of each action.

EVPI analysis can also evaluate policy robustness under different management objectives. During the course of an epidemic, multiple simultaneous objectives may recommend contradicting

management interventions or objectives may switch. For example, in the 2014 West Africa Ebola outbreak, the minimization of caseload and the minimization of mortality were of utmost importance. In another possible scenario, in an early outbreak, public health administration may strive to minimize the probability of a major epidemic. If a threshold is passed and the epidemic appears to have entered the major regime, the objective will likely then switch to the most prominent problem at hand.

Heterogeneities Cause Uncertainty

Demographic and spatial heterogeneities exist even within a single epidemic outbreak. As in the 2014 Ebola outbreak, transmission rates varied amongst venues and countries. Uncertainties in transmission rates makes it difficult to develop and enact targeted management when the crucial transmission venue (i.e. in the hospital, in the community, or at funerals) has not been identified. If management is misdirected, unnecessary resources are lost, and the epidemic staggers on longer than it could. By incorporating adaptive management into active policy decision-making, we can make more confident decisions through uncertainty resolution.

In particular, nosocomial and funeral transmission in the 2014 Ebola outbreak were highly variable across space and demographics. Different parameterizations drove drastically different caseload and mortality projections, making policy decisions difficult. We here study the uncertainty in these parameters through the EVPI framework.

Chapter 4

Mathematical Models of Infectious Disease

Why Do We Model?

People use models every day to make decisions about their lives. Most people would look at an expensive car and come to the conclusion that they could not afford it. An individual's budget is a model for their income allocation that they can use to predict the consequences of buying something too expensive. Models can be a means for evaluating plausible outcomes when testing could be expensive, dangerous, or impossible, but there are numerous reasons models are developed. Models can streamline the empirical experimentation process through identification of important variables and key hypotheses. Some models represent general patterns and trends that seem too complex to visualize. During infectious disease epidemics, models can test how a system will behave under different management interventions, identify management that optimizes an objective, and guide decision-making where action cannot wait for more detailed information.

Models are an important tool in infectious disease ecology. Infectious disease dynamics are commonly modeled to provide predictions for caseload, mortality rates, and the efficacy of vaccines [49, 50]. Policymakers use disease models for optimizing vaccine protocols, resource allocation, and the identification of important management parameters.

Approaches to Modeling

Modeling schemes in epidemiology take many forms such as compartment, network, branching process, or agent-based models. Compartmental models are the most common approach to modeling disease dynamics and treat disease stages as discrete states. The standard epidemic compartmental model is the Susceptible-Infected-Removed (SIR) model (Figure 4.1). Initially, everyone in a population of size N is susceptible (S) to the disease. The susceptible individuals are exposed to the infectious agent and become infected (I) with the disease at a rate β. Infected individuals are then removed (R) from the system by death or recovery in $1/\gamma$ days. The closed SIR model assumes the epidemic happens so quickly that susceptible recruitment may be ignored. Compartmental models also assume random mixing within the population, meaning that every individual has the same probability of contracting the disease. This framework is the building block for all compartment models.

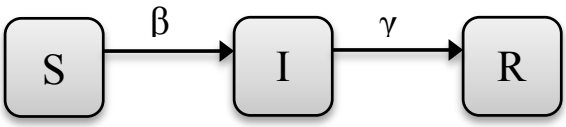

Figure 4.1: The closed SIR model prohibits natural introduction or removal of individuals from the system and assumes that every individual has the same probability of contracting the disease. Disease is transmitted at a rate β from infected individuals (I) to susceptible individuals (S). Once a person is infected, they are removed from the infected class through recovery or death in γ days on average.

$$\begin{aligned} \frac{dS}{dt} &= \frac{-\beta SI}{N} \\ \frac{dI}{dt} &= \frac{\beta SI}{N} - \gamma I \\ \frac{dR}{dt} &= \gamma I \\ N &= S + I + R \end{aligned} \tag{4.1}$$

An expansion of the SIR model is the SEIR model (Figure 4.2). This framework includes a separate state for individuals who have been exposed (E) to the infectious agent but have not yet become infectious. The SEIR model is most commonly used when there is a notable latent period in the disease process which creates a lag between exposure and infection.

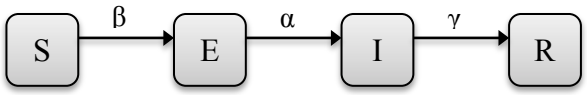

Figure 4.2: The SEIR model differs from the SIR model by the inclusion of an exposed class. After a susceptible individual (S) interacts with an infectious person and becomes infected, he or she is considered to be exposed (E) until becoming infectious themselves (I). Infectious individuals either recover or succumb and are removed (R) from the system.

$$\begin{aligned} \frac{dS}{dt} &= \frac{-\beta SI}{N} \\ \frac{dE}{dt} &= \frac{\beta SI}{N} - \alpha E \\ \frac{dI}{dt} &= \alpha E - \gamma I \\ \frac{dR}{dt} &= \gamma I \\ N &= S + E + I + R \end{aligned} \tag{4.2}$$

Modeling the 2014 Ebola Outbreak

When the 2014 Ebola outbreak began reaching unprecedented caseloads, over 55 models, ranging complexity and approach, were published. Caseload and mortality projections are key for predicting epidemic size and guiding management, but there was prominent disagreement between models. Caseload projections ranged from five thousand to over a million cases [49, 51, 52]. Structural differences also infiltrated the model space. Thirty-seven of the published models were variations of an SEIR framework, whereas the remaining 18 were less similar (branching pro-

cess, spatial models, etc.). This extreme variability amongst models complicated the management decision-making process.

The SEIHFR Model

We examined the model published first by Legrand et al. [1] for the 1995 Kitwit, DRC and 2000 Gulu District, Uganda outbreaks and refurbished by Rivers et al. [49] for the 2014 West Africa outbreak to explore uncertainties between nosocomial and funeral transmission rates.

Legrand *et al*. built on the standard SEIR model to create the SEIHFR model. The additional *H* and *F* represent hospital and funeral states, respectively. Historically, Ebola outbreaks have three main arenas for transmission: in the home or community, in the hospital, and during burial rituals. To encompass the differing transmission venues, separate compartments are included for hospitals and funerals. Thus, Legrand *et al*.'s [1] model consists of six compartments with individuals classified as: 1) susceptible individuals (S) that can be infected with Ebola by coming into contact with an infected individual; 2) exposed individuals (E) that have been infected but are not yet infectious; 3) living infected individuals (I) that have contracted Ebola virus and are infectious to others but have not been hospitalized; 4) hospitalized individuals (H) that have contracted Ebola virus and are infectious; 5) individuals who have died from Ebola virus (F) and can still infect others through the funeral process; 6) removed individuals (R) that are no longer infectious to others (cured or buried). Figure 4.3 is a schematic representation of the model.

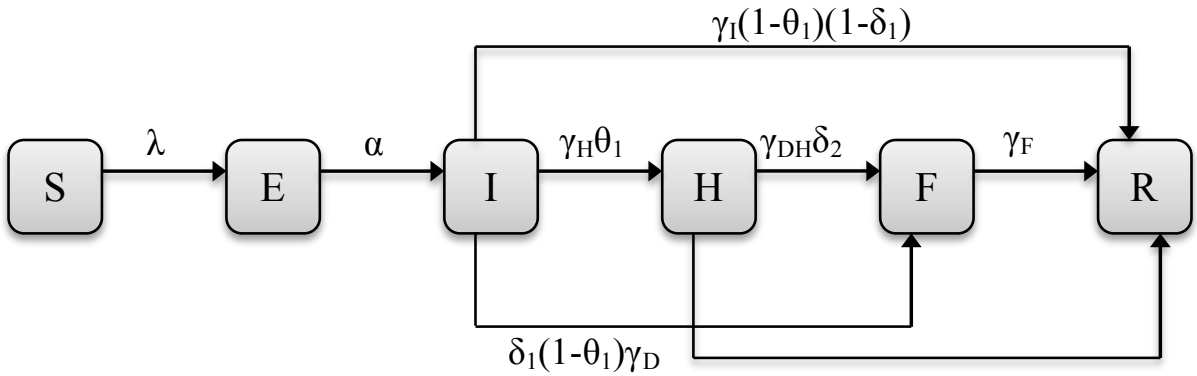

Figure 4.3: Susceptible individuals (S) are exposed to EVD at a rate λ. After a latent period of $1/\alpha$ days, exposed individuals (E) become infectious (I) to others. Once infectious, $\theta\%$ of individuals will seek medical attention (H) at a rate γ_H. The remaining $(1-\theta)\%$ will either succumb to the illness at a rate δ_1 and enter traditional funeral proceedings (F) in $1/\gamma_D$ days, or recover (R) at a rate $(1-\delta_1)\gamma_I$. A hospitalized individual can either die at a rate $\delta_2\gamma_{DH}$ or recover in $1/\gamma_{IH}$ days. All dead individuals are buried in $1/\gamma_F$ days and are removed from the system.

In terms of parameterization, susceptible individuals (S) are assumed to be exposed to EVD at a rate λ, where λ is the composition of the transmission from infectious, hospitalized, and funeral states. Explicitly, $\lambda = \frac{\beta_I I+\beta_H H+\beta_F F}{N}$. Each interaction of a susceptible individual with an infected

individual is represented by a different transmission rate, depending on whether transmission occurs in the community (β_I), hospital (β_H), or at a funeral (β_F). After exposure, individuals (E) become infectious (I) after an average latent period of $1/\alpha$ days. The latent period for Ebola ranges between 2 and 25 days [2]. Infectious individuals diverge into three pathways. Some of the sick ($\theta\%$) seek medical attention in $1/\gamma_H$ days on average. If hospitalized, individuals succumb to the illness at a rate $\delta_2\gamma_{DH}$. The case fatality ratio for hospitalized individuals is defined as δ_2. Hospitalized individuals are only hospitalized for $1/\gamma_{DH}$ days on average before they die or recover in $1/\gamma_{IH}$ days. From the infectious state, individuals that were not hospitalized ($(1-\theta)\%$) move into the funeral class at a rate $\delta_1\gamma_D$. The case fatality ratio for unhospitalized cases is defined as δ_1. On average, individuals enter the funeral state in $1/\gamma_D$ days. Recovery is also possible for unhospitalized cases in $1/\gamma_I$ days. Funeral proceedings last $1/\gamma_F$ days on average before individuals are completely removed from the system. In its deterministic form, the detailed equations governing the system is the following set of six coupled ordinary differential equations (ODEs).

$$\begin{aligned}
\frac{dS}{dt} &= -\frac{\beta_I SI + \beta_H SH + \beta_F SF}{N} \\
\frac{dE}{dt} &= \frac{\beta_I SI + \beta_H SH + \beta_F SF}{N} - \alpha E \\
\frac{dI}{dt} &= \alpha E - [\gamma_H\theta_1 + \gamma_I(1-\theta)(1-\delta_1) + \gamma_D(1-\theta)\delta_1]I \\
\frac{dH}{dt} &= \gamma_H\theta_1 I - (\gamma_{DH}\delta_2 + \gamma_{IH}(1-\delta_2))H \\
\frac{dF}{dt} &= \gamma_D(1-\theta_1)\delta_1 I + \gamma_{DH}\delta_2 H - \gamma_F F \\
\frac{dR}{dt} &= \gamma_{IH}(1-\delta_2)H + \gamma_I(1-\theta)(1-\delta_1)I + \gamma_F F
\end{aligned} \tag{4.3}$$

We are interested in parametric uncertainty for nosocomial (β_H) and funeral (β_F) transmission on caseload and mortality. Community transmission is harder to estimate and was not selected for use in this analysis. It is appropriate to examine this system within a stochastic framework. Including stochasticity in the model accounts for the demographic stochasticity naturally seen during the epidemic.

Chapter 5

Methodology

Overview

Over 50 models have been published about the 2014 outbreak, each with its own parameterization and structure. To investigate the effect of uncertainty in funeral transmission and hospital transmission on management recommendations, we consider a single model with two versions. The original model parameterization was identified as Model I. Model II was the same model framework with the parameter values of funeral transmission and hospital transmission switched. Reflecting on the level of uncertainty surrounding the transmission rates, the simplest comparison was to switch the rates between the transmission venues. We examined the contrasting models under two objectives, minimization of caseload and minimization of mortality, using the EVPI framework in Liberia and Sierra Leone. Liberia and Sierra Leone are similarly located in West Africa but have very different economics, governments, and demographies.

Parameterization

Rivers *et al.* [49] published their paper early in the epidemic, so extensive information about the model parameters was not available. Instead, model fitting was informed by the Uganda outbreak in 2000, and the most recent data from the 2014 outbreak was given a preferential weighting [49]. Rivers *et al.* performed the model parameterization by fitting the outbreak data to the deterministic system of equations through least squares optimization. The optimizer was limited by the range of validity for each parameter. For example, probabilities were constrained between zero and one.

As seen in Table 5.1, parametric differences exist between Liberia and Sierra Leone in terms of magnitude. Because the parameters are fitted values, a level of uncertainty surrounds each estimate. Additional parametric uncertainty is attributed to the data. The parameterization developed by Legrand *et al.* [1] for the 2000 Uganda outbreak served as seed values for the optimization but the 2014 West Africa outbreak behaved very differently to the outbreak in Uganda; it is unlikely that the parameters were similar overall. The most recent outbreak data at the time was also used to fit the model, but parameters are not static. Throughout an epidemic with no intervention, there is a level of dynamicity in the parameters. The 2014 outbreak was also heavily affected by underreporting and misdiagnosis, which can skew case counts and mortality rates.

Within each country there are spatial and demographic heterogeneities. Because transmission interruption is a target for public health management, we are interested in resolving uncertainties between hospital and funeral transmission. To do this, we created a two scenario situation where Model I is the original model parameterization. Model II has the same parameterization but now the fitted values for hospital transmission (β_H) and funeral transmission (β_F) are switched.

Table 5.1: Rivers *et al.* fit the model parameters using data from the early 2014 Ebola epidemic using least squares optimization. The R_0 values were estimated using next generation methods.

Parameter	**Liberia Fitted Value**	**Sierra Leone Fitted Value**
Size of the Population	10,000	10,000
Number of Index Cases	1	1
Contact Rate, Community (β_I)	0.160	0.128
Contact Rate, Hospital (β_H)	0.062	0.080
Contact Rate, Funeral (β_F)	0.489	0.111
Incubation Period ($1/\alpha$)	12 days	10 days
Time until Hospitalization ($1/\gamma_H$)	3.24 days	4.12 days
Time from Hospitalization to Death ($1/\gamma_{DH}$)	10.07 days	6.26 days
Duration of Traditional Funeral ($1/\gamma_F$)	2.01 days	4.50 days
Duration of Infection ($1/\gamma_I$)	15.00 days	20.00 days
Time from Infection to Death ($1/\gamma_D$)	13.31 days	10.38 days
Time from Hospitalization to Recovery ($1/\gamma_{IH}$)	15.88 days	15.88 days
Fraction of Infected Hospitalized (θ)	0.197	0.197
$\theta_1 = \frac{\theta[\gamma_I(1-\delta_1)+\gamma_D\delta_1]}{\theta[\gamma_I(1-\delta_1)+\gamma_D\delta_1]+(1-\theta)\gamma_H}$	0.053	0.073
Case Fatality Ratio (δ)	0.50	0.750
Case Fatality Ratio, Unhospitalized (δ_1)		
$\delta_1 = \frac{\delta\gamma_I}{\delta\gamma_I+(1-\delta)\gamma_{DH}}$	0.47	0.609
Case Fatality Ratio, Hospitalized (δ_2)		
$\delta_2 = \frac{\delta\gamma_{IH}}{\delta\gamma_{IH}+(1-\delta)\gamma_{DH}}$	0.39	0.542
Basic Reproductive Ratio, R_0	2.53	1.93

Management Interventions

We explored the impact of four management interventions on the outbreak. We assumed that each management action resulted in a 25% effect as seen in Table 5.2. The interventions range in complexity, cost, and clarity. Community behavior change is modeled through a **decrease in community transmission** (β_I), but there is significant difficulty in enacting and measuring efficacy of community interventions. This may be the least socially feasible intervention proposed. Theoretically, individuals should have a higher rate of survival in the hospital where they can be treated. To model **increased hospital recruitment**, we increased the proportion hospitalized (θ). Rehydration should theoretically result in fewer deaths, so we modeled this by **decreasing the hospitalized case fatality ratio** (δ_2). Finally, due to the risk that funeral proceedings present, we modeled the regulation of burial practices by **decreasing funeral transmission** (β_F). This reduction could be

achieved in a number of ways such as requiring HCWs to wear PPE, keeping the family of the deceased a safe distance away, prohibiting manipulation of the body after death, etc.

Table 5.2: Four management actions (increased hospitalization, increased community awareness, more rehydration, and regulated funeral proceedings) were explored and assumed to have a 25% intensity (i.e. an increase or decrease, as appropriate, for that parameter). The altered parameters and their new fitted values are shown. The R_0 for each model was estimated using next generation methods.

Model	**Management**	**Parameter**	**Original Fitted Value**	**Modified Fitted Value**	R_0
		Liberia			**2.53**
Model I	Hospitalization	θ	0.197	0.246	2.48
	Community awareness	β_I	0.160	0.120	2.05
	Rehydration	δ_2	0.39	0.29	2.52
	Burial practices	β_F	0.489	0.367	2.41
Model II	No Management				3.04
	Hospitalization	θ	0.197	0.246	3.22
	Community awareness	β_I	0.160	0.120	2.56
	Rehydration	δ_2	0.39	0.29	3.06
	Burial practices	β_F	0.062	0.0465	3.03
		Sierra Leone			**1.93**
Model I	Hospitalization	θ	0.197	0.246	1.91
	Community awareness	β_I	0.128	0.096	1.57
	Rehydration	δ_2	0.542	0.407	1.94
	Burial practices	β_F	0.111	0.083	1.83
Model II	No Management				1.88
	Hospitalization	θ	0.197	0.246	1.87
	Community awareness	β_I	0.128	0.096	1.52
	Rehydration	δ_2	0.542	0.407	1.89
	Burial practices	β_F	0.080	0.060	1.81

Each intervention targets a different transmission pathway. Figure 5.1 illustrates which pathways are affected by each management action. The green arrow indicates management that directly targets transmission pathways. This includes community awareness and regulating burial practices. With these actions, our goal is to decrease the transmission rates. The oranges arrows represent the effect of hospital recruitment. Although this management does not directly stem transmission, it controls the dissemination of infected individuals. If the proportion hospitalized is high, then fewer sick individuals will remain in the community or transition to the funeral state. Theoretically, this management is best when hospital transmission is low. Finally, the blue arrows indicate the effect

of lowering the hospital case fatality ratio. When the ratio is decreased, more individuals should be funneled into the recovered state instead of the funeral state. Lowering the hospital case fatality ratio also has an indirect effect on the unhospitalized case fatality ratio (δ_1). When fewer people enter the funeral class, the risk of contracting Ebola decreases, leaving fewer people infected. In turn, fewer unhospitalized people will succumb to the virus if only because there are fewer people infected.

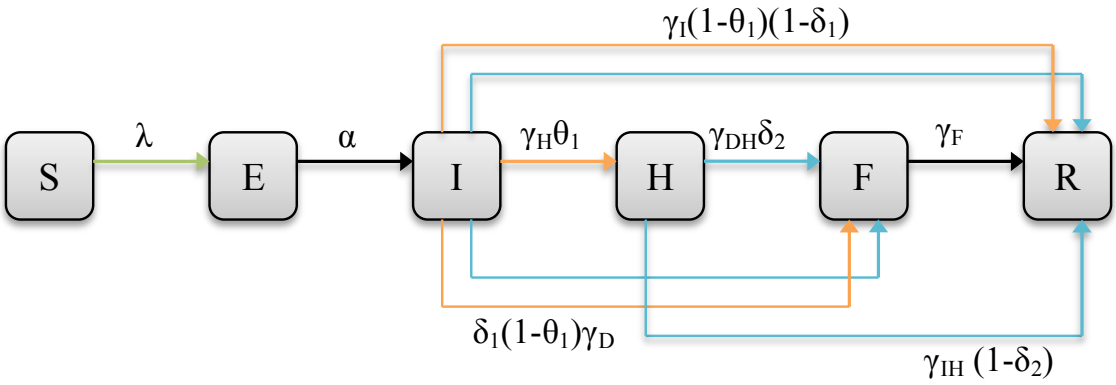

Figure 5.1: The SEIHFR transition pathways are affected by different management actions. Community awareness and regulating burial practices directly affect the transmission rates (green). The orange arrows represent the pathways affected by hospital recruitment. Changing the hospital mortality ratio affects the pathways in blue.

Stochastic Implementation

To use the EVPI framework, we estimated case load and death count under each model and management combination for each country. We chose to simulate the model stochastically in order to provide a range of possible epidemic trajectories. The average final case count and mortality count for each model/management combination were eventually compared in the EVPI table. We performed 1000 stochastic simulations on a population of 10,000 individuals.

Model simulations were performed using Gillespie's exact algorithm [53]. The elapsed time (transition) for each iteration was randomly picked from an exponential distribution with the parameter equal to the sum of the transition rates. A transition was randomly sampled from the possible transitions with a multinomial probability proportional to its relative rate. The counts in each compartment were updated accordingly. We assumed that parameters were fixed across simulations. All simulations were run in the open-source software R [54] using the code in the Appendix.

There are two prominent approaches to stochastic simulation: fixed-time and event-based algorithms. In a fixed-time Markov chain, the probability of moving from one state to the next is

fixed and independent of any transitions that occurred previously. It is a prospective approach which is blind to everything outside its current state. However, we chose an event-based approach. In an event-based stochastic algorithm, the transition probability is proportional to the number of individuals in each compartment at the given time. The particular transition and elapsed time are randomly generated, most frequently from an exponential distribution. Each state transition is calculated exactly, so each trial is an exact sample from the possible outcomes. The exact Gillespie algorithm [53] frequently becomes computationally intensive as only one transition occurs at each time step requiring, instead, the use of the τ-leap approximation [55] to address this problem. The τ-leap approximation for stochastic simulation is less computationally intensive and more efficient for larger systems as updating occurs less often. Although a margin of error exists the τ-leap aproximation is an excellent proxy for the exact Gillespie algorithm [55]. Because computational constraints were not an issue in this project, we chose to use the exact Gillespie algorithm.

R_0 Estimation by Next Generation Methods

The next generation method is the most general of several methods for calculating R_0 for compartmental models. In short, the next generation method framework allows R_0 to be calculated when there are multiple compartments of infected individuals because it accounts for difference in structure [56]. Models with underlying age or spatial structures can also use the approach to estimate R_0. To follow this method, two matrices are formed. The first, F, stores all of the new infections. V, the second matrix, is the vector difference between all loss of infection (V^-) and the gain of infection (V^+) between infected compartments (i.e. infections transferring compartments but not new infections). We take the partial derivatives of F and V with respect to the infected state variables to form two Jacobian matrices, f and v. R_0 is the maximum eigenvalue of the matrix product of f and v evaluated at the disease-free equilibrium.

For the SEIHFR model, we identify all new infections in the matrix F.

$$F = \begin{bmatrix} \frac{\beta_I SI + \beta_H SH + \beta_F SF}{N} \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

Next, we form V, which is the difference in the loss of infection and the transfer of infections between infected compartments. V takes the form:

$$V = V^- - V^+ = \begin{bmatrix} \alpha E \\ \gamma_I(1-\theta_1)(1-\delta_1)I + \delta_1(1-\theta_1)\gamma_D I + \gamma_H \theta_1 I \\ \gamma_{IH}(1-\delta_2)H + \gamma_{DH}\delta_2 H \\ \gamma_F F \end{bmatrix} - \begin{bmatrix} 0 \\ \alpha E \\ \gamma_H \theta_1 I \\ \gamma_{DH}\delta_2 H + \delta_1(1-\theta_1)\gamma_D I \end{bmatrix}$$

Now, we generate the Jacobian matrices for F and V by taking the partial derivatives with respect to the four infected states. The Jacobian matrices are 4×4 matrices of the form:

$$f = \begin{bmatrix} 0 & \frac{\beta_I S}{N} & \frac{\beta_H S}{N} & \frac{\beta_F S}{N} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$v = \begin{bmatrix} \alpha & 0 & 0 & 0 \\ -\alpha & (1-\theta_1)(1-\delta_1) + \delta_1(1-\theta_1)\gamma_D + \gamma_H\theta_1 & 0 & 0 \\ 0 & -\gamma_H\theta_1 & \gamma_{IH}(1-\delta_2) + \gamma_{DH}\delta_2 & 0 \\ 0 & -\delta_1(1-\theta_1)\gamma_D & -\gamma_{DH}\delta_2 & \gamma_F \end{bmatrix}$$

Finally, R_0 is the maximum eigenvalue of the matrix product of the two Jacobian matrices f and v. Explicitly, $fv^{-1}|_{dfe}$, where $dfe = \{S = 1, E = 0, I = 0, H = 0, F = 0, R = 0\}$.

Chapter 6

Results

To illustrate the expected value of perfect information (EVPI) framework, we performed 1000 stochastic simulations on a population of 10,000 individuals. We examined two differing scenarios, which weighed uncertainties of funeral contact rate (β_F) against the hospital transmission rate (β_H) under different objective functions in both Liberia and Sierra Leone.

The expected trajectory of the SEIHFR model takes the form shown in Figure 6.1. The total number of susceptible individuals will decay through time as the number of removed individuals is monotonically increasing. The four interior compartments (Exposed, Infectious, Hospitalized, and Funeral) exhibit initial exponential growth, reach their maximum, and decay to zero. How quickly the outbreak occurs will vary between stochastic realizations, so the peaks in the interior states will shift through time. Generally, every iteration will have a similar form.

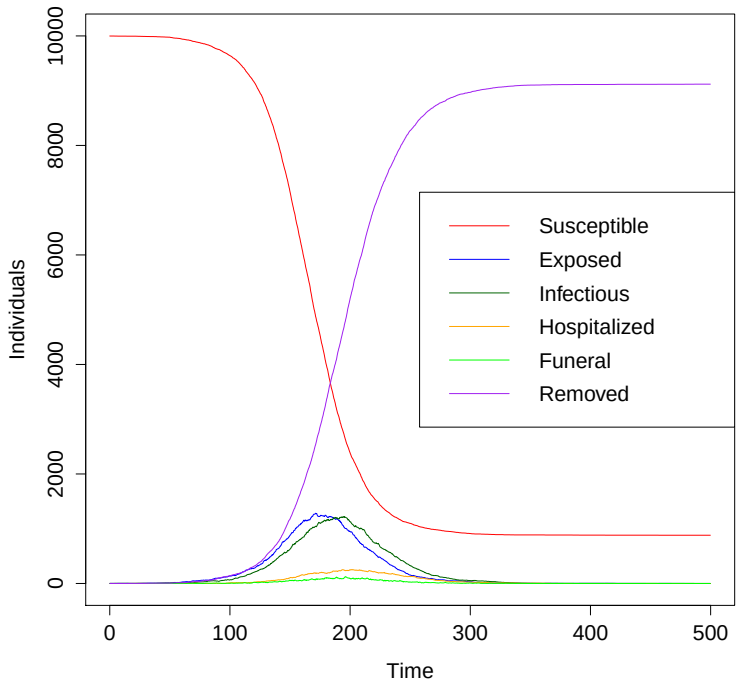

Figure 6.1: The susceptible compartment monotonically decreases as infection occurs. The four interior compartments (Exposed, Infected, Hospitalized, and Funeral) exhibit parabolic behavior through the introduction and removal of individuals from each compartment over time. The removed class grows monotonically by the accumulation of recovered or deceased individuals. In general, each simulation behaves similarly.

Stochastic epidemics typically progress in one of two fashions. They either go extinct early leading to a 'minor epidemic' or progress to the susceptible bottleneck causing a 'major epidemic.' The likelihood of the two outcomes depends on R_0. A range of epidemic sizes were possible through the stochastic simulations of the model. Figure 6.2 illustrates the case count distribution for Liberia with no management imposed. Results for Sierra Leone were qualitatively the same. The majority of realizations resulted in a major outbreak (>8000 cases). However, under the SEIHFR structure and the current parameterization, the epidemic has a 34.4% chance of being a minor

epidemic. The caseload and mortality count distributions under the various management actions share similar distributions to this one.

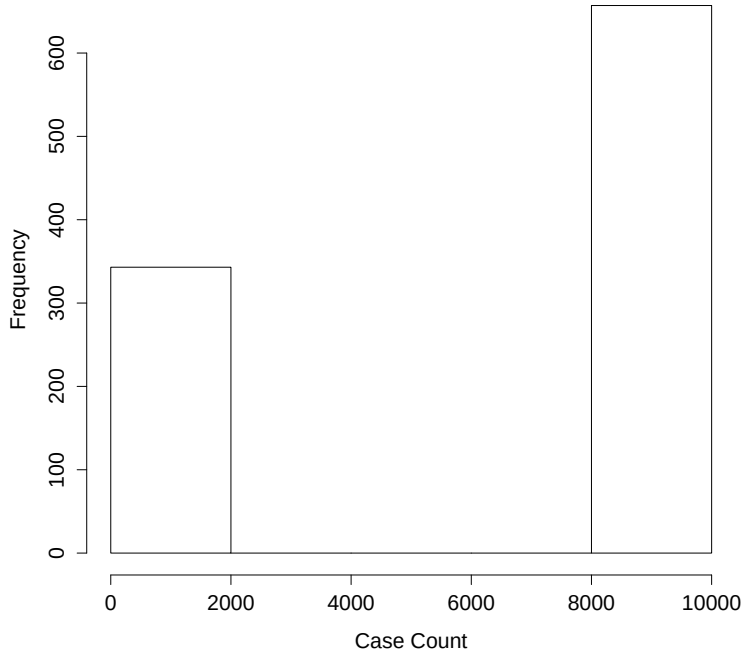

Figure 6.2: The distribution of case counts for Liberia with the original parameterization under no management shows a bimodal distribution. The majority of simulations resulted in a major epidemic with over 80% of the population becoming infected. Minor epidemics occurred 34.4% of the time.

Each cell in the EVPI table represents a unique combination of model and intervention. Under Objective 1: minimize caseload, each cell contains the projected average number of cases and range of cases under the model-intervention combination. Similarly, for Objective 2: minimize the number of deaths, the projected mean number of deaths and range of death counts is displayed. The four management actions most likely be practical are increased hospital recruitment (HOS), community transmission reduction (COMM), improved hospital treatment, specifically, rehydration (REH), and burial regulation (BUR). Each intervention is imposed on the contrasting models and contrasted with a control (ORIG) model with no management. Each model is weighted (W) to be equally likely.

Liberia

In Liberia, increasing community awareness is the most effective management to minimize caseload (Table 6.1). The average optimum (5001 cases) and the optimum average (5001 cases) are the same because both models indicate that decreasing community transmission is the dominant management. Therefore, management appears to be robust to parametric uncertainty.

In practice, decreasing community transmission has many modes of execution and it may be difficult to control and estimate the effect of those interventions. Considering this, if we remove community intervention from the possible management schemes, some uncertainty is resolved. The new model optima (shown in red) indicate differing optimal interventions. Model I is optimal under restricted burial practices whereas the Model II caseload minimizes under increased hospital recruitment. On average across the models, rehydration is most effective in minimizing case count. From this EVPI analysis, we can decrease our case count by 0.67% through resolving parametric uncertainties.

Table 6.1: **Objective 1: Minimize Caseload in Liberia** To minimize the number infected with EVD, the optimal universal intervention is community transmission. Because the models agree on the optimal management, further investigation is not needed. However, as increasing community awareness may be less easy to achieve and quantify, we can remove it from the framework and only compare the more direct interventions. In this scenario, the models disagree on the optimal management, and 0.67% of the population would be spared if additional information were gathered.

Liberia		W	ORIG	HOS	COMM	REH	BUR	**Optima**
Model 1		0.5						
	$\beta_H = 0.062$		5923	6042	**4996**	5771	5766	4996
	$\beta_F = 0.489$		(1, 9148)	(1, 9153)	(1, 8396)	(1, 9084)	(1, 9009)	
Model 2		0.5						
	$\beta_H = 0.489$		5936	5843	**5006**	5894	5940	5006
	$\beta_F = 0.062$		(1, 9627)	(1, 9713)	(1, 9344)	(1, 9660)	(1, 9620)	
	Average		5930	5943	**5001**	5833	5853	**5001**

As is common during an epidemic, multiple objectives may exist at a time. For instance, during an outbreak, policymakers may want to minimize the caseload or minimize the death count. If we view mortality minimization as a separate objective, we can apply the same EVPI framework (Table 6.2). The recommendation is again unanimous across models to minimize mortality: improve hospital care and rehydration. Thus, the value of perfect information is, again, zero. Based on the estimates for this particular time in the epidemic, the most effective universal management focus to minimize mortality overall is improving hospital infrastructure and treatment.

Table 6.2: **Objective 2: Minimize Mortality in Liberia** To achieve our objective, decreasing community transmission is unanimously the optimal action. Secondly, decreasing hospital case fatality is consistently the best suboptimal action.

Liberia		W	ORIG	HOS	COMM	REH	BUR	**Optima**
Model 1		0.5						
	$\beta_H = 0.062$		2964	3022	2498	**2370**	2882	2370
	$\beta_F = 0.489$		(0, 4722)	(0, 4649)	(0, 4305)	(0, 3808)	(0, 4583)	
Model 2		0.5						
	$\beta_H = 0.489$		2969	2922	2503	**2291**	2972	2291
	$\beta_F = 0.062$		(0, 4957)	(0, 4989)	(0, 4779)	(0, 3871)	(0, 4916)	
	Average		2967	2972	2501	**2331**	2927	**2331**

Sierra Leone

Although objectives may be ubiquitous for an epidemic, spatial heterogeneities affect model parameterization. Differences in parameterization can cause local- or state-level management differentiation. In the 2014 Ebola outbreak, models were parameterized at the country level with significant differences between countries. This is captured in the EVPI framework by examining Liberia and Sierra Leone data separately. Under Objective 1: Minimize Caseload (Table 6.3), the Sierra Leone table mirrors the first objective for Liberia (Table 6.1).

To minimize caseload in Sierra Leone, the models agree that decreasing community transmission is the optimum management action, so future information gathering is not needed. If we remove community intervention as a possible management as in the Liberia analysis, the optimal direct management approach is burial regulation (shown in red). As there is no conflict between model recommendations under the first objective, resources need not be spent on further surveillance in Sierra Leone.

Table 6.3: **Objective 1: Minimize Caseload in Sierra Leone** As in Liberia, reduction in community transmission is optimal for this objective. Ignoring the decrease in community transmission as the best action overall, in Sierra Leone, regulating burials is the best direct intervention. Information gathering is unnecessary due to the high level of agreement between the models on the optimal interventions.

Sierra Leone	W	ORIG	HOS	COMM	REH	BUR	**Optima**
Model 1	0.5						
$\beta_H = 0.080$		4394	4346	**2659**	5771	3712	2659
$\beta_F = 0.111$		(1, 8060)	(1, 7978)	(1, 6580)	(1, 9084)	(1, 7737)	
Model 2	0.5						
$\beta_H = 0.111$		4173	4186	**2012**	4323	3601	2012
$\beta_F = 0.080$		(1, 7844)	(1, 7815)	(1, 6360)	(1, 8133)	(1, 7702)	
Average		4284	4266	**2336**	4481	3657	**2336**

If we change our objective to minimizing mortality in Sierra Leone (Table 6.4), the common theme of reducing community transmission arises again. Additional information gathering can reduce mortality by 1.41% if we ignore community behavior change as a viable management. Model I is optimal under upregulated rehydration practices, whereas Model II minimizes the objective under downregulated burial transmission. The difference between the optimal average and the average optimum is 141 cases.

Table 6.4: **Objective 2: Minimize Mortality in Sierra Leone** To minimize mortality in Sierra Leone, reducing community transmission is the best action to take. If that is not feasible, there is a small level of uncertainty (1.41%) which can be resolved with additional information gathering.

Sierra Leone	W	ORIG	HOS	COMM	REH	BUR	**Optima**
Model 1	0.5						
$\beta_H = 0.080$		3296	3256	**1954**	2944	2980	1954
$\beta_F = 0.111$		(1, 6069)	(1, 6019)	(1, 4943)	(1, 5258)	(1, 5829)	
Model 2	0.5						
$\beta_H = 0.111$		3126	3136	**1470**	2747	2698	1470
$\beta_F = 0.080$		(1, 5951)	(1, 5894)	(1, 4717)	(1, 5217)	(1, 5773)	
Average		3211	3196	**1712**	2846	2839	**1712**

Chapter 7

Discussion

Discussion

The 2014 Ebola outbreak in West Africa drew global attention when the case and mortality counts began reaching unprecedented numbers. Liberia and Sierra Leone were among the three countries most affected by the outbreak. Significant heterogeneities existed between the locations, making management decision-making difficult. Over 50 epidemic models were published to aid public health management, but structural and parametric uncertainties among the models caused a range of caseload and mortality projections. By acknowledging the uncertainties about Liberia and Sierra Leone in an effort to minimize caseload and mortality, we demonstrated the utility of value of information analysis in directing information gathering during ongoing epidemics.

Across country and objective, decreasing community transmission is universally predicted to be most effective in minimizing caseload and mortality. This indicates that the most influential venue for transmission was the community. Although focusing on the decrease in community transmission may have had the greatest effect on the objective functions, a single intervention was not enough to drive R_0 below its threshold ($R_0 < 1$). R_0 can be indicative of epidemic size and virulence of the pathogen. Across R_0 values for the differing models and parameterizations (Table 5.2), enacting community awareness consistently minimizes R_0 relative to no management and the other interventions across each model's parameterization scheme and the differing objectives. This supports the conclusions drawn from the EVPI analysis.

The 2014 outbreak reached a caseload over 28,000 in early 2016, thousands below what was predicted in the absence of control. Most likely, there was dynamicity in the parameters caused by behavior change. Based on our conclusions from the EVPI analysis and R_0, we suspect that behavior change in the community, such as encouraging hand washing practices, self-quarantining, and the use of household protective kits was the most influential factor in driving the downturn of the epidemic. It is hard to conclude definitively that community behavior change was the cause of the stem of the epidemic because public health management enacted several interventions at once such as the erection of Ebola treatment centers (ETCs), the requirement of PPE for HCWs, and the regulation of burial practices. Although our analysis indicated that preventing community transmission was the best action to minimize case count, mortality count, and R_0, in reality, standards of care for Ebola needed to be maintained through other means of public health interventions.

The unanimity of the EVPI analyses directs the allocation of resources for public health management. Additional surveillance will not aid in clarifying the best management approach. Thus, funds, manpower, or supplies that had been directed to information gathering can to some extent be reassigned to a more efficient and effective purpose. The streamlining of resource allocation through incorporating adaptive management into policy decision-making could allow faster response time in an epidemic.

Throughout these EVPI tables, a 'blanket' intervention arises: the decrease in community transmission through awareness campaigns and behavior change. Although easily identified, enacting behavior change can be completed in many modes and may not have a single solution. Other factors such as time, monetary resources, and manpower may limit the scope of the intervention. These factors are not addressed in the EVPI analysis demonstration but should be considered for any active public health intervention. The EVPI analysis is also limited in its ability to acknowledge uncertainty. Uncertainties between hospital and funeral transmission are used in this example, but the EVPI analysis could be expanded to include community transmission, the hospital admittance

rate, or any other parameter around which uncertainty lies. Simultaneous objectives should also be considered. Public health management may aim to reduce caseload and mortality at the same time. The dual optimization may result in a greater efficiency and a faster epidemic downturn. There are plausible downsides to this approach. For example if you consider a dual optimization in Liberia, community transmission is the primary target but increasing hospitalization is a plausible secondary mode of action. When we acknowledge the uncertainty between hospital and funeral transmission, there is a possibility that improving hospitalization rates will actually make the epidemic worse. R_0 increases under Model II in Liberia from 3.04 under no management to 3.22 under hospitalization. Examining scenarios that optimize simultaneous objectives and understanding the effects management could have with respect to uncertainties could prevent a suboptimal management choice.

This demonstration of EVPI analysis illustrates its utility in disease outbreak management. For the specific models and scenarios explored here, directed action and the impacts of clarifying information differ between countries and objectives. There will always be uncertainty during ongoing outbreaks of Ebola and other diseases, but the application of EVPI analysis can guide resource allocation and information gathering.

Conclusions

The 2014 Ebola outbreak was a serious international public health crises of the modern day. Over 55 mathematical models were published in an attempt to aid public health management. Initial estimates of epidemic size varied substantially between a few thousand and over a million cases. The vast uncertainty in case load left public health management with difficult subjective decisions to make.

Value of information analysis acknowledges the uncertainty encapsulated by different models and quantifies it to direct information gathering. To explore the relative importance of uncertainty about hospital and funeral transmission, we examined an SEIHFR model built by Legrand *et al.* [1] and parameterized by Rivers *et al* [49]. We developed two versions of the model: the first with the original parameterization and the second with the fitted values for hospital transmission and funeral transmission switched. Our aim was to quantify uncertainty under two objectives, the minimization of case load and the minimization of mortality, by implementing one of four management actions. Increasing hospital recruitment, raising community awareness, improving rehydration within a hospital, and regulating burial practices were identified as four of the most feasible and straight forwardly modeled actions.

Using the expected value of perfect information framework, decreasing community transmission through public awareness campaigns universally minimized the objectives across countries and models. Additional surveillance to resolve the parametric uncertainty was unnecessary. When community transmission is not considered, some uncertainty remains. In future endeavors, public health management should consider doing dual optimization of objectives to achieve the greatest impact and efficiency.

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Appendices

R code

Exact Gillespie Algorithm

To use the exact Gillespie algorithm, the user must specify:

- `start`: the starting values
- `ratefun`: a rate function that returns a numeric vector of rates at which each event occurs. The inputs are the current state variables, parameters, and time
- `trans`: a matrix that indicates the changes in each state variable (column) that occurs when a particular event (row) occurs
- `pars`: a numeric vector of parameters
- `times`: a vector of times at which to evaluate the system

```
gillesp <- function(start,ratefun,trans,pars,times=0:50) {
  t0 <- times[1]                                    # set starting time
  ntimes <- length(times)
  X <- start                                          # set starting state
  res <- matrix (nrow=length(times),ncol=length(start), # result matrix
                 dimnames=list(times,names(start)))
  for(ctr in 1:(ntimes-1)) {                        # loop over reporting time
    res[ctr,] <- X
    while (t0 < times[ctr+1]) {
      rates <- ratefun(X,pars,t0)                   # calculate current rates
      if(all(rates==0)) break
      totrate <- sum(rates)
      elapsed <- rexp(1,totrate)                    # sample elapsed time
      which.trans <- sample(1:nrow(trans),size=1,prob=rates) # pick transition
      t0 <- t0 + elapsed                            # update time
      X <- X + trans[which.trans,]    # add transition values to current state
    }
  }
  cbind(times,res)
}
```

The rate function defines the inputs for the SEIHFR model. Black magic allows reference to states and pars by name.

```
ratefun.SIR <- function(X,pars,time) {
  vals <- c(as.list(pars),as.list(X))             # attach state and pars as list
  rates <- with(vals,                          # allow reference to states and pars by name
                c(exposure = (betaI*S*I + betaH*S*H + betaF*S*G)/N,
                  infection = alpha*E,
                  hospitalization = gammaH*theta1*I,
                  deathH = gammaDH*delta2*H,
                  funeral = gammaF*G,
                  recoveryI = gammaI*(1-theta1)*(1-delta1)*I,
                  deathI = delta1*(1-theta1)*gammaD*I,
                  recoveryH = gammaIH*(1-delta2)*H))
}
```

We name the state variables and transitions to make the code easier to read.

```
statenames.SIR <- c("S","E","I","H","F","R","D","C")
transnames.SIR <- c("exposure","infection","hospitalization",
                    "deathH","funeral","recoveryI",
                    "deathI","recoveryH")
```

Define the transition matrix. The rows indicate the particular events (i.e. exposure, death, etc.) and the columns indicate the state variables. Two extra compartments are included here to calculate the cumulative case and mortality counts.

```
trans.SIR <- matrix(c(-1, 1, 0, 0, 0, 0, 0, 0,
                       0,-1, 1, 0, 0, 0, 0, 1,
                       0, 0,-1, 1, 0, 0, 0, 0,
                       0, 0, 0,-1, 1, 0, 1, 0,
                       0, 0, 0, 0,-1, 1, 0, 0,
                       0, 0,-1, 0, 0, 1, 0, 0,
                       0, 0,-1, 0, 1, 0, 1, 0,
                       0, 0, 0,-1, 0, 1, 0, 0),
                     byrow=TRUE,
                     ncol=8,
                     dimnames=list(transnames.SIR,statenames.SIR))
```

Define the parameters as a 'named' vector.

```
# Liberia parameterization
pars.lSIR <- c(betaI=0.160, betaH=0.062, betaF=0.489, alpha=1/12, gammaH=1/3.24,
               gammaI=1/15, gammaD=1/13.31, gammaDH=1/10.07, gammaF=1/2.01,
               gammaIH=1/15.88, theta=0.197, delta=0.50, delta1=0.47,
               delta2=0.39, theta1=0.053, N=10000)
# Sierra Leone parameterization
pars.lSIR <- c(betaI=0.128, betaH=0.080, betaF=0.111, alpha=1/10, gammaH=1/4.12,
               gammaI=1/20, gammaD=1/10.38, gammaDH=1/6.26, gammaF=1/4.5,
               gammaIH=1/15.88, theta=0.197, delta=0.75, delta1=0.609,
               delta2=0.542, theta1=0.073, N=10000)
```

To execute the algorithm, call the function with the start variables and time defined.

```
G.lSIR <- gillesp(start=c(S=9999,E=0,I=1,H=0,G=0,R=0,D=0,C=1),times=seq(0,500,by=0.25),
                  ratefun=ratefun.SIR,trans=trans.SIR,pars=pars.lSIR)
```

To call the code within a stochastic framework, use an iterative loop and store the outputs for each realization.

```
G.lSIR.S <- array()
G.lSIR.E <- array()
G.lSIR.I <- array()
G.lSIR.H <- array()
G.lSIR.G <- array()
G.lSIR.R <- array()
G.lSIR.D <- array()
G.lSIR.C <- array()
```

```
for (i in 1) {
  G.lSIR <- gillesp(start=c(S=9999,E=0,I=1,H=0,G=0,R=0,D=0,C=1),times=seq(0,500,by=0.25),
                    ratefun=ratefun.SIR,trans=trans.SIR,pars=pars.lSIR)
  G.lSIR.S <- cbind(G.lSIR.S,G.lSIR[,"S"])
  G.lSIR.E <- cbind(G.lSIR.E,G.lSIR[,"E"])
  G.lSIR.I <- cbind(G.lSIR.I,G.lSIR[,"I"])
  G.lSIR.R <- cbind(G.lSIR.R,G.lSIR[,"R"])
  G.lSIR.H <- cbind(G.lSIR.H,G.lSIR[,"H"])
  G.lSIR.G <- cbind(G.lSIR.G,G.lSIR[,"G"])
  G.lSIR.D <- cbind(G.lSIR.D,G.lSIR[,"D"])
  G.lSIR.C <- cbind(G.lSIR.C,G.lSIR[,"C"])
}
```

Next Generation Methods for R_0 Estimation

To calculate R_0 for compartmental models, (1) identify the infected compartments. (2) Form a matrix F that contains all of the new infections.

```
F1 <- expression(betaI*S*I/N + betaH*S*H/N + betaF*S*F/N)
F2 <- 0
F3 <- 0
F4 <- 0
```

(3) Form $V^{-} as a matrix of the loss of infection.

```
Vm1 <- expression(alpha*E)
Vm2 <- expression(gammaI*(1-theta1)*(1-delta1)*I +
                    delta1*(1-theta1)*gammaD*I + gammaH*theta1*I)
Vm3 <- expression(gammaIH*(1-delta2)*H + gammaDH*delta2*H)
Vm4 <- expression(gammaF*F)
```

(4) Form V^{+} as a matrix of the transfer of infections between infected compartments (i.e. no new infections).

```
Vp1 <- 0
Vp2 <- expression(alpha*E)
Vp3 <- expression(gammaH*theta1*I)
Vp4 <- expression(gammaDH*delta2*H + delta1*(1-theta1)*gammaD*I)
```

(5) Form V as a matrix of the difference between V^{-} and V^{+}.

```
V1 <- expression(alpha*E - 0)
V2 <- expression(gammaI*(1-theta1)*(1-delta1)*I +
                   delta1*(1-theta1)*gammaD*I +
                   gammaH*theta1*I - (alpha*E))
V3 <- expression(gammaIH*(1-delta2)*H + gammaDH*delta2*H
                 - (gammaH*theta1*I))
V4 <- expression(gammaF*F - (gammaDH*delta2*H +
                               delta1*(1-theta1)*gammaD*I))
```

(6) Take the partial derivatives of F and V with respect to the infected state variables to form two Jacobian matrices f and v, respectively.

```
f11  <-  D(F1,"E"); f12  <-  D(F1,"I");
f13  <-  D(F1,"H"); f14  <-  D(F1,"F")
f21  <-  D(F2,"E"); f22  <-  D(F2,"I");
f23  <-  D(F2,"H"); f24  <-  D(F2,"F")
f31  <-  D(F3,"E"); f32  <-  D(F3,"I");
f33  <-  D(F3,"H"); f34  <-  D(F3,"F")
f41  <-  D(F4,"E"); f42  <-  D(F4,"I");
f43  <-  D(F4,"H"); f44  <-  D(F4,"F")
v11  <-  D(V1,"E"); v12  <-  D(V1,"I");
v13  <-  D(V1,"H"); v14  <-  D(V1,"F")
v21  <-  D(V2,"E"); v22  <-  D(V2,"I");
v23  <-  D(V2,"H"); v24  <-  D(V2,"F")
v31  <-  D(V3,"E"); v32  <-  D(V3,"I");
v33  <-  D(V3,"H"); v34  <-  D(V3,"F")
v41  <-  D(V4,"E"); v42  <-  D(V4,"I");
v43  <-  D(V4,"H"); v44  <-  D(V4,"F")
```

(7) Define the parameters and disease-free equilibrium.

```
 # Sierra Leone
S <- 1; E <- 0; I <- 0; H <- 0; F <- 0; R <- 0
alpha <- 1/10; gammaH <- 1/4.12; gammaD <- 1/10.38;
gammaI <- 1/20; gammaF <- 1/4.5;
gammaIH=1/((1/gammaI)-(1/gammaH));
gammaDH=1/((1/gammaD)-(1/gammaH));
theta1 <- 0.073; delta1 <- 0.609; delta2 <- 0.542;
betaI <- 0.128; betaH <- 0.08; betaF <- 0.111;
N <- 1;

 # Liberia
S <- 1; E <- 0; I <- 0; H <- 0; F <- 0; R <- 0
alpha <- 1/12; gammaH <- 1/3.24; gammaD <- 1/13.31;
gammaI <- 1/15; gammaF <- 1/2.01;
gammaIH=1/((1/gammaI)-(1/gammaH));
gammaDH=1/((1/gammaD)-(1/gammaH));
theta1 <- 0.053; delta1 <- 0.47; delta2 <- 0.39;
betaI <- 0.160; betaH <- 0.489; betaF <- 0.062;
N <- 1;
```

(8) Evaluate fv^{-1} at the disease-free equilibrium. R_0 is the largest eigenvalue of this matrix.

```
f <- matrix(c(eval(f11),eval(f12),eval(f13),eval(f14), # this forms a matrix
            eval(f21),eval(f22),eval(f23),eval(f24),   # each term had
            eval(f31),eval(f32),eval(f33),eval(f34),   #   previously be treated
            eval(f41),eval(f42),eval(f43),eval(f44)),  #   as separate entities
            nrow = 4, byrow = TRUE)
v <- matrix(c(eval(v11),eval(v12),eval(v13),eval(v14),
            eval(v21),eval(v22),eval(v23),eval(v24),
            eval(v31),eval(v32),eval(v33),eval(v34),
```

```
            eval(v41),eval(v42),eval(v43),eval(v44)),
            nrow = 4, byrow = TRUE)
max(eigen(f%*%solve(v))$values)
```

Academic Vita

RILEY O. MUMMAH

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EDUCATION

The Pennsylvania State University — University Park, PA
Master of Applied Statistics (Integrated Undergraduate/Graduate) — August 2014 – August 2016

The Pennsylvania State University — University Park, PA
Bachelor of Science in Biology (Ecology option), Schreyer Honors College — June 2012 – May 2016
Bachelor of Science in Statistics (Biostatistics option)
Bachelor of Science in Mathematics (Systems Analysis option)

RESEARCH EXPERIENCE

Student Research Experience (SRE) — Knoxville, TN
National Institute for Mathematical and Biological Synthesis (NIMBioS) — Summer 2015

Schreyer Honors College Thesis, Dr. Ottar Bjørnstad's lab — University Park, PA
The Pennsylvania State University — August 2014 to Present

Research Experience for Undergraduates, Dr. Christopher Griffin's Lab — University Park, PA
Applied Research Laboratory, The Pennsylvania State University — May 2014 to Present

Research Experience for Undergraduates — University Park, PA
Department of Mathematics, The Pennsylvania State University — Summer 2014

Research Assistant, Dr. Peter Hudson's Lab — University Park, PA
Center for Infectious Disease Control, The Pennsylvania State University — July 2012 to January 2013

RESEARCH PRESENTATIONS

Mummah, R. Diya Sashidhar, Jinchuan Wei, Hunter Rice, Lauren Parker, Alyson Marek, Shigetoshi Eda, and Vitaly V. Ganusov. Discriminating between alternative mechanisms of mycobacterial granuloma formation *in vitro*. Poster presentation at Undergraduate Research Forum at University of Tennessee, Knoxville, TN, July 2015

Mummah, R., Ottar N. Bjørnstad, Matthew J. Ferrari, and Katriona Shea. Value of Information Analysis of Ebola Management. Poster presentation at 13th Annual Ecology and Evolution of Infectious Disease Conference, Athens, GA, May 2015.

TEACHING EXPERIENCE

Undergraduate Chemistry Proctor — University Park, PA
The Pennsylvania State University — August 2013 to May 2016

Undergraduate Mathematics Proctor — University Park, PA
The Pennsylvania State University — August 2015 to May 2016

Grader for Mathematics Department — University Park, PA
The Pennsylvania State University — August 2015 to December 2015

Biology Tutor for the Student Services Support Program — University Park, PA
The Pennsylvania State University — January 2015 to May 2015

AWARDS

- Headings Scholarship — 2015 – 2016
  The Pennsylvania State University Eberly College of Science

- Sovereign Trust Trustee Scholarship — 2015 – 2016
  The Pennsylvania State University Schreyer Honors College
- Carrell Family Association Grant — 2014 – 2016
- Hammond Scholarship — 2014 – 2015
  The Pennsylvania State University Eberly College of Science
- Mu Sigma Rho (National Honorary Society for Statistics) — 2014 – Present
- George B. Doughman Memorial Scholarship — 2014 – 2016
  The Pennsylvania State University
- Travel Grant — 2015
  The Pennsylvania State University Schreyer Honors College
- Eberly College of Science Alumni Scholarship — 2014
  The Pennsylvania State University Eberly College of Science
- Student Enhancement Fund — 2014
  The Pennsylvania State University Eberly College of Science

OUTREACH

Expanding your horizons STEM career day for girls — University, PA
The Pennsylvania State University — 2014

COURSES & SKILLS

Significant coursework:

The Pennsylvania State University Applied Statistics
Multivariate statistics, regression, ANOVA, DOE, Design and Analysis of Clinical Trials, Survey Sampling

The Pennsylvania State University Biology
Populations & Communities, Molecules & Cells, Function & Development of Organisms, Tropical Field Ecology (field course in Costa Rica), Biology of Eco-Health (field course in Tanzania), Ecology of Infectious Diseases

The Pennsylvania State University Statistics
Regression, ANOVA, Applied Time Series Analysis, Nonparametric Statistics, Introduction to Probability Theory

The Pennsylvania State University Mathematics
Calculus & Biology I & II, Vector Calculus, Discrete Mathematics, Combinatorics, Real Analysis, Population Biology & Evolutionary Game Theory, Linear Programming, Linear Algebra

Skills

- Proficient in R, Matlab; Familiar with SAS