Marburg:
Medical Consequence Assessment
DRAFT

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Background

The Project BioShield Act of 2004[1] provides the Department of Health and Human Services (HHS) the authority to accelerate the research, development, purchase, and availability of priority medical countermeasures to protect the U.S. population from the effects of chemical, biological, radiological, and nuclear (CBRN) threat agents. Implementation of Project BioShield is addressed by the Office of Public Health Emergency Medical Countermeasures (OPHEMC) enterprise strategy, which describes the responsibilities and interactions between the Department of Homeland Security (DHS) and the Department of Health and Human Services.

A primary responsibility of DHS is the development of agent-specific Material Threat Assessments (MTAs) that describe plausible, worst case, attack scenarios. Given the potential exposures described in the MTAs, a key responsibility of HHS under the BioShield legislation is to ensure that adequate biomedical countermeasures are available in the Strategic National Stockpile (SNS) to provide for the emergency public health security of the United States in the event of a biological attack or other public health emergency.

The draft HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) strategy specifies the use of modeling in addition to subject matter expertise in order to evaluate potential medical countermeasure strategies and public health response capabilities. Previous HHS initiatives, in support of the PHEMCE strategy, have included the use of models to estimate the number of casualties expected to occur as a result of an attack scenario, given the availability of medical countermeasures that might be included in the SNS, and the time taken to distribute the countermeasures.

Objective

The objective of the present study is to provide an initial and approximate model-based estimate of the medical consequences of a Marburg attack on New York City. There are no policies for post-exposure prophylaxis (PEP) in the event of a Marburg outbreak. Currently, the efficacy of medical treatment of Marburg patients is unclear. Thus, a sensitivity analysis of medical efficacy will examine the impact of medical treatment during the early stages of symptomatic disease.

In addition to providing a basis for informing potential SNS countermeasure requirements, the results contribute to a more quantitatively-oriented discussion of public health response capabilities and requirements. Furthermore, the results may assist in the identification of important basic research gaps.

Marburg Background

Exposure and Infection

The causative agent for Marburg hemorrhagic fever is the *Marburg virus*, which is a member of the genus *Filoviruda*e. Two members of the virus family have been identified, Marburg and Ebola. Marburg is a RNA virus, which is encased in a lipid envelope.[2] The disease is named for Marburg, Germany, which is the site of the first recorded outbreak of the virus in 1967. Thirty-one people were infected by the disease. The virus was carried by green monkeys sent to a laboratory where the virus was taken from the animals' kidney cells for use in making vaccines. Seven of the 31 infected people died.[3]

Marburg hemorrhagic fever is part of a group of hemorrhagic fever viruses that are thought to reside in animals or arthropod vectors.[4] There is limited knowledge about transmission of viral hemorrhagic fever (VHF) viruses since they occur sporadically outside of a laboratory environment and the disease is often well underway when surveillance is initiated. Infection is assumed to occur by direct contact with body fluids, contact with infected animals, or small particle aerosolization.[5] Confirmed transmission of the disease via aerosolization has been noted in a laboratory setting using an animal model. Airborne transmission involving aerosolization of VHF viruses to humans was considered a potential explanation in one incident, but the mode of transmission was not determined.[6] Most VHF is found in Africa, Asia, or the Middle East. An exception is Dengue fever, a mosquito borne VHF, which is found in the Americas and the Pacific region.

Infection from Marburg virus leading to symptoms may only require a few virons (1-10).[7] The Popp strain of the Marburg virus was under investigation when a Russian researcher, Dr. Nikolai Ustinov, accidentally sustained a needle stick while working with research animals and subsequently died from the disease. The strain of Marburg that infected Dr. Ustinov was found to have an ID_{100} of 1-5 particles.[4]

A deliberate, aerosol release of Marburg is considered a possible bioterrorism strategy.[14]

Diagnosis

Marburg VHF infections often present with a prodromal period involving multiple somatic complaints that include severe headache, high fever, abdominal pain, and cramping. Diagnosis of infection in the laboratory, according to guidelines established by the World Health Organization (WHO), includes the positive isolation of the filovirus (in a BSL-4 laboratory), positive skin biopsy (immunohistochemistry), or positive polymerase chain reaction (PCR). At present, laboratories at the Centers for Disease Control and Prevention (CDC) and United States Army Medical Research Institute for Infectious Disease (USAMRIID) are the only U.S. facilities capable of conducting a confirmatory diagnosis of VHF.[4]

Incubation

The reported time from exposure to Marburg virus until development of first symptoms varies. The overall range is two to17 days with a median time of three to seven days[32] or five to seven days.[8,9,10,11,12] Incubation times may be significantly shorter for needle stick or intravenous transmission of the virus. Contagious viral shedding has been reported to occur in semen and breast milk for up to 12 weeks during the recovery/convalescence period.[4]

Symptomatic Disease

The target of Marburg VHF infection is the vascular system. In early infection, patients exhibit high fever, watery diarrhea, headache, flushing, petechial rash, or conjunctival injection. Secondary symptoms will present as the solid organs are infected by the virus. Hepatic dysfunction, bleeding diathesis, hemorrhage and resulting hypovolemic shock occur as well. The patient may also demonstrate progressive deterioration in mental status and other neurological symptoms.[4,14]

Death is typically preceded by severe blood loss and shock and usually occurs within six to nine days following the onset of illness.[14,15] In the most recent activity of illness related to Marburg virus, the 2004-2005 Angola outbreak, most deaths occurred within three to seven days of symptom onset.[3] Case fatality rates for VHF agents have been reported to vary from 21% (1967 Germany/Yugoslavia outbreak) to 90% (2004-2005 Angola outbreak).[16]

Consequences

In order to assess the consequences of an intentional Marburg virus release, the outcomes measured in the model include the number of infections, casualties, deaths, and recoveries. Given a set of exposures, the initial step in the analysis is the calculation of the number of people who become infected, based on their level of exposure. In the absence of medical countermeasures, infected persons will progress through the disease process, from incubation through symptomatic/contagious disease to recovery or death.

People are defined as “casualties” if they develop symptomatic disease. This group represents the population that becomes ill and, thus, represents the demand on the medical system. The measured outcomes are dependent on the speed of the medical countermeasure response.

Countermeasures

Currently, no commercial vaccine exists for the Marburg virus. Limited laboratory trials using Marburg-like virus particles have been undertaken with guinea pigs and have demonstrated protection from the virus.[17] No human trials, however, have been performed. Researchers have also shown initial success in developing a live attenuated recombinant vaccine based on recombinant vesicular stomatitis virus (rVSV) in a primate model. These studies have shown promising results, and data suggest that this vaccine can be used as a preventive measure as well as for post-exposure treatment.[18,19]

Future development and use of one of the vaccines mentioned above or development of an additional vaccine is uncertain. In addition, effective drug therapy for treatment of Marburg is unavailable at this time.[26] Therefore, the only medical countermeasure modeled in this study is the use of supportive care in response to an intentional release of Marburg virus. Details of this countermeasure are described below.

Supportive care

Supportive care is the primary treatment for Marburg VHF infections. Treatment consisting of aggressive Intensive Care Unit (ICU) measures, including administration of intravenous (IV) fluids and mechanical ventilation, has been reported to lower the fatality rate.[9] Other treatment approaches include replacing lost blood, important blood proteins, and clotting factors by transfusion of blood and fresh frozen plasma. Use of the anticoagulant heparin has been proposed but is controversial because the effects of heparin on illness resulting from Marburg infections are also unknown. Ribavirin, an antiviral used for respiratory infection, has been shown to be effective only in Lassa fever or New World arena virus infections and is not considered a viable treatment option for Marburg virus.[14,20] The efficacy of supportive care in the early disease state is debatable. One study suggests that early supportive care, as observed in the Marburg, Germany outbreak, could save lives (22% mortality).[9] The study also cites two examples from the 2005 Angola outbreak: a 5-year old girl in shock and unconscious was saved with aggressive fluid rehydration; and a woman who recovered from a four-day coma during which she received adequate maintenance fluids.

Infection Control Barriers

During the largest, most recent outbreak of the Marburg virus in Angola, the disease spread rapidly among people exposed to infected body fluids during home care or at funerals. The dangerous use of home-based injections was also identified as a major cause of the outbreak's spread. There was confusion regarding protocols required to contain the spread of disease and distrust of the existing healthcare system. Both factors contributed to the large number of individuals who died during the outbreak.[21]

Person-to-person disease transmission requires close contact with an infected individual (i.e., contact with body fluids) and does not typically occur during the incubation period. This transmission takes place more often with a high virus concentration, which typically occurs in the later stages of infection.[22] Body fluid barrier precautions should be strictly followed in order to prevent transmission of Marburg virus. In addition, the CDC reports that standard contact, and droplet precautions should be observed when Marburg infection is assumed or confirmed. Patients with respiratory infections should wear masks; while caretakers and others in close contact with an infected person should wear gloves, gowns, face masks, and eye protections. Furthermore, nonessential personnel should not enter the room of an infected individual.[23] In addition, the use of invasive procedures should be minimized in order to prevent iatrogenic transmission of the disease. This may be difficult, particularly in the ICU setting.[24]

Response Policies

Given the non-medical countermeasures associated with the Marburg VHF disease, public health officials and decision makers should develop response countermeasure policies that minimize the impact of the disease from a biological attack. This study uses modeling to examine the effectiveness of these non-medical countermeasure response policies.

Public Information/Social Distancing

One factor that helped control the Angola outbreak was public information programs aimed at informing the general population of ways to reduce the risk of infection.[9] The model in this study assumes that the public alters its behavior patterns, including self-imposed social distancing, after the public information programs have begun. This effect decreases the R_0 value associated with an outbreak.

Nosocomial Infection Reduction

Nosocomial and household transmission of Marburg has been observed.[25] Upon identification of a suspected or confirmed case of Marburg, medical personnel should use appropriate personal protective equipment (PPE). Airborne and contact precautions should be strictly adhered to.[25] Additionally, strict isolation protocol within hospitals should be utilized to prevent additional infection. Although airborne transmission is considered rare with all viral hemorrhagic fevers, including Marburg, the CDC, WHO, and the Working Group on Civilian Biodefense recommend physical and respiratory separation for all suspected and confirmed cases.[27,28,29]

Upon confirmation of the first Marburg case, the model assumes that hospitals employ isolation of Marburg patients, and that medical personnel will use PPE and barrier protocols and that this reduces the risk of secondary infections within the acute care setting.

Marburg Model

Exposure and Primary Infection

In this study model, the number of people exposed by the intentional release of the Marburg virus was calculated from the MTA report.[30] At the beginning of the simulation, the city population, *X*, is partitioned into two groups: Incubation, and Susceptible. The number of people in these groups may change over the course of the model run, but the initial population partition is described below:

- Primary Infections – Those in the Incubation group are those exposed and infected with primary infections resulting from the initial Marburg agent release. Number of primary infections is based on ID_{50} = 0.5 organism and probit slope = 1.28. Exposed people are partitioned into appropriate exposure bins based on the infectious dose. For *y* persons exposed to *ID(x)*, the number infected is *P(x,y)*.

$$P(x, y) = y\frac{x}{100}.$$

The number of people in the primary infections group is the combination of all people from the different exposure bins:

$$\#\ \text{Incubation} = \sum_{\forall x \in ExpBin} P(x, y)$$

where *ExpBin* is the set of exposure bins and y is the number of people exposed to *ID(x)*.

- Susceptible – The remaining city population is placed in the Susceptible group:

$$\#\ \text{Susceptible} = X - \#\ \text{Incubation}$$

where *X* is the total city population.

Secondary Infection

In addition to the initial exposure, secondary transmission can occur between contagious individuals and susceptible individuals within the population. The rate of the secondary transmission is affected by (1) the infectiousness of the disease, (2) the susceptibility of the population, and (3) the level of contact between contagious and susceptible individuals.

When the illness requires the need for hospitalization, close contacts may be further reduced. This model provides a coarse granularity in assessing the level of contact. Movement of population around the city is beyond the scope of the model, but contact rates are adjusted for movement from the general population the hospital setting.

Factors that impact the number of secondary infections:

- Infectiousness: An R_0 value of 1.38 was derived by fitting data from the Angola Marburg outbreak in 2005.[34] An alternate value of 0.4 was also examined at the request of HHS Subject Matter Experts (SMEs). We assume that people in the late disease are three times more contagious than people in the early disease state because people in the late disease state shed more virus.
- Level of contact: The two levels of contact modeled in this study are contacts in the general population and hospitalized contacts. General population contacts interact freely with general population and spread disease. Hospitalized contacts are those that infect others in hospital settings, and this level of contact is dependent on isolation efficacy and PPE/barrier efficacy.
- Public information awareness: This describes the behavior pattern of the general public after the initiation of public information non-medical countermeasures. People interact normally before public information counter measures are initiated. After the public information campaign is initiated, people change their behavior to reduce their probability of becoming infected. By fitting data from the 2005 Angola outbreak,[34] we calculated that the R_0 value was reduced by 40.6% after the public information campaign, from 1.38 to 0.82. We use 40.6% as a reduction factor after public information has begun. Thus, for the alternate value of R_0 = 0.4, the public information lowers the R_0 value to 0.16.

The number of secondary infections is based on the fraction of susceptible people in the population, the number of contagious people, how long they've been contagious, the severity of the disease, and how isolated the contagious population is:

$$\text{\# secondary infections} = \frac{\#Susceptible}{X}\left(C_G T_G + C_H T_H \lambda_H\right)$$

where X is the total city population, C_G is the number of contagious people in the general population, T_G is the probability of transmission of the people in the general population, C_H is the number of contagious people hospitalized, T_H is the probability of transmission of the people in the hospital, and λ_H is the isolation factor for those people in the hospital. Note that those people in the general population do not have an isolation reduction factor.

Medical Intervention

No prophylaxis countermeasures for the Marburg virus are currently available. Medical countermeasures consist of treatment of symptomatic persons. This model considers the non-medical countermeasure of public information programs aimed at informing the general public about how to reduce the risk of transmission.

The Compartmental Model

The progression of people during a Marburg outbreak can be depicted by a compartmental model. Each major medical state in the disease progression is represented by a model state. At each time step, all people in the population belong to one state which describes their disease state and the level of medical care they are currently receiving. Transitions between states represent changes in medical conditions. For each transition, a probability and a trigger event determine the rate at which people transition from one state to the next. As the model proceeds, the transition of people among states, represents disease progression or changes in medical care. Transitions are triggered by three possible events: (1) exposure to the biological agent, (2) completion of an interval of time, or (3) medical intervention.

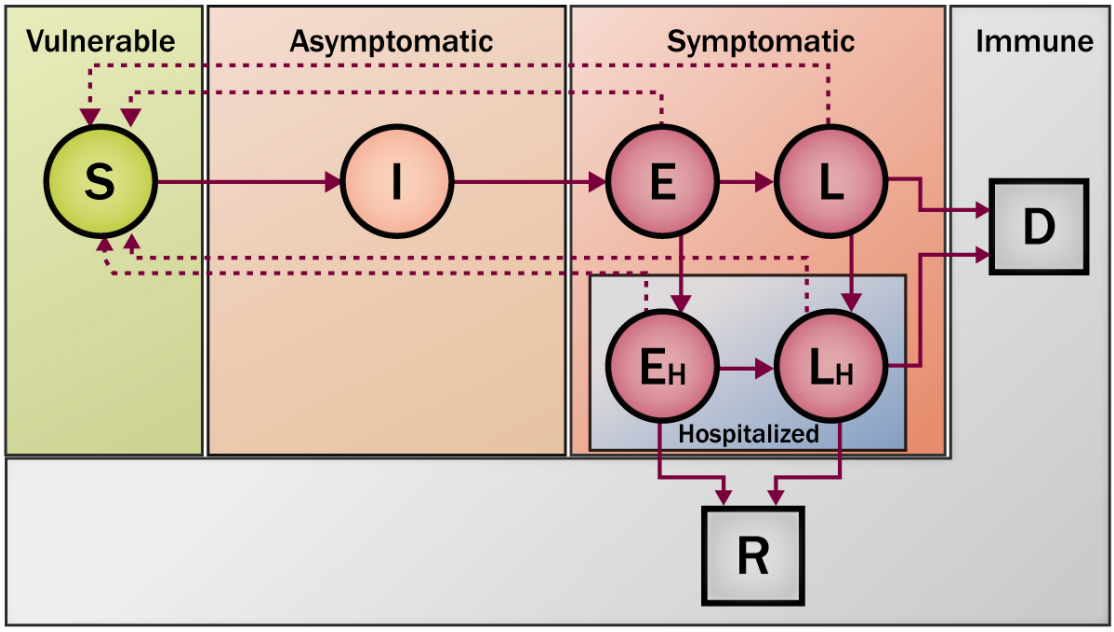

Figure 1: Marburg Model - Disease states and allowable transitions. The disease states are shown by circles, and the final states are shown by squares. The solid arrows indicate allowable transitions between the states. The dashed arrows indicate the influence the contagious state has on the susceptible states. Modeling states: S=susceptible to infection, I= incubation period, E=untreated early symptomatic period, L=untreated late symptomatic period, E_H=treated early symptomatic period, L_H=treated late symptomatic period, R=recovered, and D=dead.

States and Transitions

The states and possible transitions used in the model are depicted in Figure 1. The model consists of the following disease states:

- Vulnerable – The vulnerable states contain those who are at risk for a Marburg infection:
  - Susceptible (S) – This state contains those who have not been infected.
- Asymptomatic – The period of infection in which patients do not exhibit symptoms:
  - Incubation (I) – The initial stage of infection, known as incubation, where the patient has not become symptomatic but is infected with the virus.
- Symptomatic – The period of infection in which patients exhibit symptoms. There are four symptomatic states:
  - Untreated Early Symptomatic (E) – This is the initial untreated symptomatic state. This is a contagious state.
  - Untreated Late Symptomatic (L) – This is the final untreated symptomatic state. This is a contagious state.
  - Treated Early Symptomatic (E_H) – This state contains those that seek medical treatment early in the symptomatic stage of disease progression. This is a contagious state.
  - Treated Late Symptomatic (L_H) – This state contains those that are

receiving medical treatment late in the symptomatic stage of disease progression. This is a contagious state.

- Immune – The model has two final states into which the infected population must fall:
    - Recovered (R) – The recovered state contains those who became symptomatic and survived.
    - Dead (D) - Those persons who became symptomatic and died.

It is also assumed that hospitals follow standard isolation and PPE/barrier procedures, and that these procedures will reduce the probability that contagious persons in the hospital will infect others. The probability of infection is reduced 40.6% when isolation and PPE/barrier protocols are implemented.

Transitioning Through the Model

The model begins with the initial exposure. The initial exposure is uniformly distributed across the population. A fraction of the population that is initially exposed begins the model run in the Incubation (I) state, while the remainder of the population begins in the Susceptible (S) state.

At each time step in the model run, people may transition from one state to another. The possible transitions are described below:

- Susceptible (S)
    - $S \rightarrow I$: If susceptible people (S) are infected with Marburg (secondary infection), they may become infected and enter the incubation (I) state. The number of people who contract Marburg through secondary infections depends on the number of people in the contagious state and the level of isolation those contagious people employ.
- Incubation (I)
    - $I \rightarrow E$: The duration spent in the Incubation (I) state is log-normally distributed with a median time of 5 days, then people transition to the untreated early symptomatic (E) state.
- Untreated Early Symptomatic (E)
    - $E \rightarrow E_H$: Some untreated people (E) seek medical treatment and transition into medical care (E_H).
    - $E \rightarrow L$: Untreated people in early symptomatic (E) that do not seek medical treatment transition to untreated late symptomatic (L).
- Treated Early Symptomatic (E_H)
    - $E_H \rightarrow R$: Some people treated during early symptomatic (E_H) transition to recovered (R) without any further progression of the disease. The percentage of those that recover is subject to a sensitivity analysis.
    - $E_H \rightarrow L_H$: Treated people in early symptomatic (E_H) that do not recover transition to the treated late symptomatic (L_H) state.
- Untreated Late Symptomatic (L)

- $L \rightarrow L_H$: Some people in the late symptomatic stage (L) seek medical treatment and transition into medical care (L_H).
- $L \rightarrow R$: Some people untreated during late symptomatic (L_H) transition to recovered (R).
- $L \rightarrow D$: Some people untreated during late symptomatic (L_H) transition to dead (D).

▪ Treated Late Symptomatic (L_H)
- $L_H \rightarrow R$: Some people treated during late symptomatic (L_H) transition to recovered (R).
- $L_H \rightarrow D$: Some people treated during late symptomatic (L_H) transition to dead (D).

Model Parameters and Assumptions

The model examines the progression of Marburg and the medical countermeasures for the case of New York City only, with no persons entering the city or leaving the city. Table 1 shows parameter values used within the Marburg model and the sources of each.

Table 1: Model Parameter Values

Parameter Description	Value	Reference
NYC Population	8,000,000	2005 Census[33]
Dose-Dependent Exposure/Infection		
ID_{50}	0.5 organisms	Bazhutin et al.[7]
Probit slope	1.28	Bazhutin et al.[7]
R_0	1.38	WHO[34]
	0.4	HHS SMEs
Incubation duration (log-normal, median time)	5 days	CDC[20] PHAC[32]
Symptomatic Durations		
Early Symptomatic	2 days	This study
Late Symptomatic	4 days	WHO[3]
Recovery Rates		
Untreated Late Symptomatic	10%	CDC[16]
Treated Early Symptomatic	*sensitivity analysis*	
Treated Late Symptomatic	19%	Jeffs[9]

Scenario

The scenario used in this study was taken from the plague MTA report produced for DHS.[30] Specific details of the simulated release are described in the classified MTA report.

The literature suggests that the number of virus particles necessary to infect people is extremely low.[4,7] Consequently, the model assumes the ID_{50} level is 0.5 organisms, the ID_{90} level is 5 organisms, and the dose-response probit slope is 1.28. In the analyses presented in this study, people are considered as exposed if they have inhaled at least five organisms (the smallest exposure level reported in the MTA). The different values for source strength greatly affect the number of people who are exposed by the intentional release, while the number of persons who become infected is dependent on the ID_{50} and the probit slope (Table 2). Under our modeling assumptions, more than 90% of exposed persons become infected.

Table 2: The number of exposed and infected persons assuming different source strengths.

		Number Exposed	Number Infected
Source Strength	10%	720,000	676,746
	75%	3,800,000	3,732,298

Results

Two critical modeling assumptions identified by HHS SMEs were the source strength associated with the release of the pathogen, and the average number of secondary infections caused by each contagious person (R_0 value). In the study, we examine a worst-case plausible scenario which assumes a source strength of 75% and an R_0 value of 1.38. An alternate scenario addressed in this study assumes a source strength of 10% and an R_0 value of 0.4.

We present an unmitigated base case with no post-exposure prophylaxis, in which people receive medical treatment in hospitals and either recover or die. In the worst-case plausible scenario, approximately 3.7 million primary infections caused 3.4 million secondary infections, and 6.4 million deaths (90% mortality). In the alternate scenario, 676,746 people were initially infected by the intentional release, while 541,826 secondary infections resulted. Of the 1.2 million people who became infected, the model predicts that approximately 1.1 million deaths (90% mortality) resulted.

Sensitivity Analysis

The sensitivity analysis focused on two factors: the effect of a public information non-medical countermeasure response, and the efficacy of medical treatment for people who enter the hospitals while in the early symptomatic stage of disease. Similar to mass prophylaxis campaigns, the effectiveness of public information non-medical countermeasures is dependent on how quickly the countermeasure can be initiated. In the sensitivity analysis, it was assumed that the public information programs could be initiated at 2, 3.5, 5, or 6.5 days after the Marburg release. The model examines the medical efficacy for people who enter the hospital while in the early symptomatic stage of disease, ranging from 10% efficacy (purely supportive care) to 60% (highly effective

medical care), with an intermediate value of 30%. The impact of these two factors on the number of infections and deaths is shown in Table 3and Table 4. In both scenarios, the number of secondary infections and deaths is reduced when the non-medical countermeasures can be initiated rapidly and when the medical efficacy during the early stage of disease is higher. An assumption of higher medical efficacy in the early stages of symptomatic disease reduces the number of secondary infections. This occurs because people recover in the early symptomatic stage, and they do not progress to the late symptomatic stage in which they would be more contagious.

Table 3: Impact of time to start non-medical countermeasures and medical efficacy for the worst-case plausible scenario.

Medical Efficacy in Early Symptomatic Stage	Time to start non-medical countermeasures (days)	Secondary Infections	All Infections	Dead
10%	2	2,275,012	6,007,310	5,404,921
	3.5	2,282,776	6,015,074	5,411,769
	5	2,328,971	6,061,269	5,452,610
	6.5	2,419,043	6,151,341	5,532,549
30%	2	2,118,867	5,851,165	4,270,139
	3.5	2,127,764	5,860,062	4,280,067
	5	2,179,999	5,912,297	4,336,409
	6.5	2,279,857	6,012,155	4,439,986
60%	2	1,871,676	5,603,974	2,413,642
	3.5	1,882,413	5,614,711	2,426,589
	5	1,944,374	5,676,672	2,497,387
	6.5	2,059,721	5,792,019	2,621,187

Table 4: Impact of time to start non-medical countermeasures and medical efficacy for the alternate scenario.

Medical Efficacy in Early Symptomatic Stage	Time to start non-medical countermeasures (days)	Secondary Infections	All Infections	Dead
10%	2	243,103	919,849	827,853
	3.5	244,549	921,295	829,142
	5	253,285	930,031	836,938
	6.5	271,000	947,746	852,779
30%	2	219,504	896,250	654,252
	3.5	221,014	897,760	655,985
	5	230,020	906,766	665,902
	6.5	247,947	924,693	684,567
60%	2	186,101	862,847	409,832
	3.5	187,700	864,446	412,192
	5	197,087	873,833	425,103
	6.5	215,308	892,054	447,851

Discussion

Requirements

The results of this study provide bounded estimates of the expected number of infections and deaths that may occur after an intentional Marburg virus release. The worst-case plausible scenario produces a very large number of initially infected people (3.7 million), 3.4 million secondary infections, and 6.74 million deaths in the unmitigated case. In contrast, the alternate scenario results in approximately 675,000 primary infections, 540,000 secondary infections, and 1.1 million deaths in the unmitigated case. The results of the sensitivity analysis show that the number of people who become infected (and will require medical treatment) may be reduced by 20-25%. Public health planners, however, are faced with planning a response for 1.2 million to 7.1 million people (unmitigated case) who will require medical treatment. This range may be reduced with additional basic research on the proportion of the virus that survives the aerosolization process (i.e. source strength). Basic research may narrow the estimated range for the source strength, which spans from 10% to 75% in this study. More accurate estimates of source strength can reduce the five-fold difference in the number of expected primary infections and provide a better estimate for public health planners.

This study examined the impact of a non-medical countermeasure based on a public information campaign. The results indicate that the effectiveness of non-medical countermeasures is also affected by how rapidly the program can be initiated. This is similar to mass prophylaxis campaigns for other bioagents. The model assumes that the combination of public information campaigns and procedures to reduce nosocomial

infections could reduce the number of secondary infections and deaths, relative to the unmitigated case. Public information is described as part of the responsibilities of HHS in the Emergency Support Function (ESF) #8, public health and medical services annex, of the National Response Plan. The annex states that HHS should "provide public health, disease, and injury prevention information that can be transmitted to members of the public who are located in or near areas affected."[35] The model did not explicitly describe how public behavior changes following the public information campaign, but it assumed that behaviors that put people at risk of becoming infected would be reduced. Thus, planning for effective public information campaigns prior to an attack could be a critical activity in terms of casualty reduction. Likewise, working with medical system personnel to ensure that proper barrier protocols and isolation protocols can be implemented in response to a biological attack is also crucial.

Comparison with Other Models

From an epidemiological point of view, Marburg is a relatively unstudied disease. Most recent research, such as that of Borchert, et al.,[36] involves surveys of case records, survivors, and close contacts to determine basic disease characteristics such as its reproductive number. Borchert, et al., derived a post-intervention reproduction number of 0.9 from the Marburg outbreak in the Congo of 1998 to 2000. The Congo outbreak was unusual in that outbreak was prolonged by repeated primary infections or transmissions from the unknown but presumed zoonotic source among the local gold mining population rather than widespread secondary transmission. From the larger data population of the Angola outbreak of 2005,[34] we derived an R_0 of 1.38 and a post-intervention reproductive value of 0.82.

Because of the similarities between Marburg and some species of Ebola such as Ebola-Zaire, and lacking substantive research into Marburg itself, Borchert, et al., used Ebola to validate their results. We will compare our model results to Ebola models for the same reason.

Chowell, et al., examined both the Congo 1999 and Uganda 2000 Ebola outbreaks to determine the basic pre- and post-intervention reproductive numbers for the respective outbreaks.[37] They created a basic compartmentalized model which was fitted to the outbreak data to investigate the effects of accelerating or delaying public intervention. They estimated R_0 to be 1.83 for Congo and 1.34 for Uganda pre-intervention, and reproductive numbers of 0.51 for Congo and 0.66 for Uganda post-intervention. It should be noted that their model did not include a population representing the effects of hospitalization on either survivability or transmissibility, and that the outbreaks upon which the model was based began with a very small number of infected people.

Intervention slowed and halted the outbreak through population education on basic barrier-nursing techniques, quarantine, and prompt burial or cremation of infected remains. Their model illustrates that a delay of two weeks in public intervention would approximately double the expected number of casualties from the outbreak. By adjusting our model to begin with a small number of initial infections (10 people) to mimic a

natural outbreak, we also found that a delay in initiating the public information campaign by two weeks would approximately double the expected number of casualties.

O'Regan and Moles created a system dynamics model to describe the same 2000 Uganda outbreak as a set of four village populations, each village with its own characteristics and approximately 1,000 individuals, and the regional hospital which served them.[38] The goal of their model was to use system dynamics to illustrate how information feedback regarding the state of the outbreak could modify the behavior of the population and, thus, the progression of the outbreak. These modifications in public behavior are similar in character to the impact of public information examined in our study. When people receive information (through feedback or public information), they change their behavior such that their effective R_0 is reduced.

Marburg Model Limitations

The model in this study assumes a closed population system. There is no population migration in the model. An increase in global travel patterns implies that short-term migration could have a real impact on containment efforts. In addition, there is no transfer of contagious people across the geographic boundaries of the system (e.g. emergency room transfers). Implicit in this choice is the assumption that the time scale of the migration effects on the population under consideration is very large compared to the disease dynamics.

We assume that there are unlimited and immediately available medical resources. Further we assume that Marburg is correctly diagnosed; that there is no shortage of medical personnel who are fully qualified to administer PEP and care for the sick, and their performance is unaffected by the outbreak. There is no vaccine available for Marburg and prophylactic antiviral therapy is not recommend for persons exposed to hemorrhagic fever viruses in the absence of clinical illness.[4] Instead, it is recommended that people thought to be exposed to the disease be placed under medical surveillance. We also assume that the outbreak will have minimal impact on city services and infrastructure.

The model does not consider demographic implications. Adverse side effects of medical countermeasures are not considered. HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) is committed to the needs of both general and special populations that may impact the efficacy of, or the ability to access, medical countermeasures. Modeling special populations such as children, the elderly, pregnant women, persons with immunocompromised conditions and persons with disabilities may offer insights into implications of a Marburg outbreak on these populations.[13]

The model includes a very simple characterization of behavioral response - the public information campaign induces a reduction of probability of infection in the susceptible population. The model, however, does not describe the explicit changes in behavior that causes this reduction.

Assumptions relating directly to the epidemiology of the disease include: the disease is dispersed homogenously, or the disease does not evolve (no passage or other strains etc.).

Since Marburg hemorrhagic fever is an emerging but uncommon disease in sub-Saharan Africa, the natural reservoirs and patterns of transmission are not well understood. We have chosen to model disease transmission only by human-to-human contact, there is no vector transmission, and no zoonosis.

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