Handling Hantavirus: a Mathematical Analysis
Problem 2

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November 2015

Contents

1 Summary

We began by modeling the progression of the disease in a single patient. We then constructed a model of how people to seek medical attention, both before and after our press report is released. Finally, we consider the scenarios in which we have a limited quantity of antibiotics, and the effect this will have on our distribution strategy.

To model progression of this virus, we broke the infection into two distinct stages. The first begins at infection and doubles the virus population every hour until at least 1 million copies of the virus are present in the body, at which point the immune system becomes active and slows replication. When a person is infected with a single copy of the virus, this phase takes approximately 20 hours. The second phase begins at this point, and continues until there are 1 trillion copies of the virus in the body, at which point they die. In this phase the virus replication rate is 150% per hour, and 200,000 copies of the virus are killed every hour.

Additionally, at any point in the second phase we allow for the introduction of antibiotics, after which the model changes to include the death of 500 million copies of the virus every hour. We conclude that anyone treated between 0 and 35 hours after infection can be cured with a single hour of antibiotic treatment, and that after 35 numbers the number of doses required to cure a patient increases rapidly until approximately 38 hours. At this point, antibiotics can no longer completely eradicate the infection, and the patient will die even with treatment. An untreated individual at this stage will die 20 hours later (roughly 60 hours after infection).

To predict the behavior of the public, we consider two models. The first is the uninformed public: we model the time between infection and seeking medical attention as a uniform distribution between the onset of symptoms at 20 hours from infection, and the death of the patient at 60 hours from infection. From this, we model the number of patients we expect to treat in a month using a Poisson distribution with parameters tuned by data from previous Hantavirus outbreaks and studies on the reporting of flu-like symptoms.

The second model considers an informed public following guidelines outlined in our press release: we urge people to seek medical attention if they experience fever and myalgia for 7 hours or more, and model the time between infection and seeking medical attention as a beta distribution between 20 hours and 60 hours with a mean of 28 hours after infection. This places patients in a relatively safe timeframe to be treated with minimal antibiotics, but also allows time for symptoms from unrelated conditions to go away with conventional medication, as well as allotting plenty of time for both travel and triage.

The final model for the public uses a mixture of the uninformed and informed models, where the mixture ratio is based on the proportion of the public reached by our press release. Our general solution is to administer antibiotics to anyone presenting flu-like symptoms if they report they began feeling ill either that day or the day before. If they their symptoms do not subside, we continue administering antibiotics until they reach a cutoff determined by the availability of antibiotics. Based on our model of the disease and models of the public, we recommend an initial cutoff of 5 shots per person, and discuss alternate cutoffs that can be used, with an eye towards maximizing how many treatable people we can cure given a set supply of antibiotics. After this cutoff number, if the patient's symptoms have not subsided, we recommend hospitalization, as the patient is much more likely to have the flu than to have a terminal case of the Hanta virus, although hospitalization would be appropriate in either case.

2 Introduction

In our report, we provide a deterministic model for the spread of the disease in one patient. We provide guidelines for the medical response unit based on the severity of the outbreak and on the supply and demand for the antibiotic. We set up several regimes of administering the cure and provide a recommendation for switching the regimes. Our non-technical summary is based on a press release from WHO (see Appendix B).

3 Assumptions

In our model, we made the following assumptions:

1. People present with some subset of flu-like symptoms. We can evaluate the probability that they have the Hanta virus given the symptoms listed in [1]. Inherent in this assumption are the following decisions: which symptoms to we consider, which probability distribution to use and what cutoffs to implement.

2. People imprecisely report onset of symptoms: they might not be able to pinpoint the hour. People might also wait for days until reporting the symptoms, as reported in [2]. We will ask broad questions to categorize the patients, with some medical cutoffs.

3. Person-to-person transmission is a rare event [3]. Therefore, potentially infected patients need not be isolated from the general population.

4. The number of copies of the Hanta virus during the initial infection does not affect the course of treatment. Since we can only detect the disease when the patients are showing symptoms, the precise time elapsed from the infection until showing symptoms is not crucial.

5. The immune system responds immediately once the number of the copies of the virus in the body reaches or exceeds one million. In addition, the immune response immediately subsides if the number of copies present in the body drops below one million. While in real life it would take longer for the immune system to react, the antibiotic is strong enough that our results do not fundamentally depend on this assumption. However, we also assume that the antibiotics take effect immediately.

6. Cases of Hantavirus are not geographically independent. The disease is spread primarily by rodents[4], so cases are likely to cluster in the same geographic region.

7. The course of illness is deterministic rather than stochastic - we do not include randomness in our model of the progression of the disease. This assumption makes our model less realistic, but a rough approximation suffices for the purpose of the broad categorization of patients.

8. The Hantavirus is susceptible to the antibiotic and does not evolve resistance to the medicine at the time scales under consideration. If this virus were resistant to the antibiotic, we would have no way of treating the patients.

9. People tend to report flu-like symptoms over a similar time scale regardless of region. We assume that despite cultural and economic differences between regions, patients experiencing the same symptoms are going to seek medical help on similar time scales. We are assuming this due to limited data on the specific area a medical unit will need to be deployed to.

10. Regional statistics are similar to reported ones. We are assuming that the Hanta virus is causing symptoms similar to the ones documented during the 1993 outbreak described in [1].

11. During the time period in which Hantavirus can still be cured by antibiotics, symptoms are indistinguishable from those of the flu or other flu-like diseases. This assumption allows us to cast a wide net and catch as many potential cases of Hantavirus as possible.

4   Model of the Disease Progression

The disease functions in two distinct phases. The first begins at infection and continues until the virus has reached 1,000,000 copies in the body, at which point the immune system becomes active and slows the growth of the virus. The second phase begins at this point, and continues until the patient reaches 1 trillion copies of the virus in the body, at which point they die.

4.1   Phase 1

Examining the first phase in more detail and using the assumption that the model of the disease described in the problem statement is accurate, we see that the virus will double in population every hour. Thus, we can calculate the number of copies of the virus in the patient at a given time by the formula $V = V_0 * 2^t$, where V_0 is the number of copies of Hantavirus the person was initially infected with and t is the time since infection in hours. Using this formula, we can also calculate how long after infection people will begin to show symptoms. Notably, larger initial populations can lead to drastic reductions in time between infection and the beginning of immune response. (figure 1).
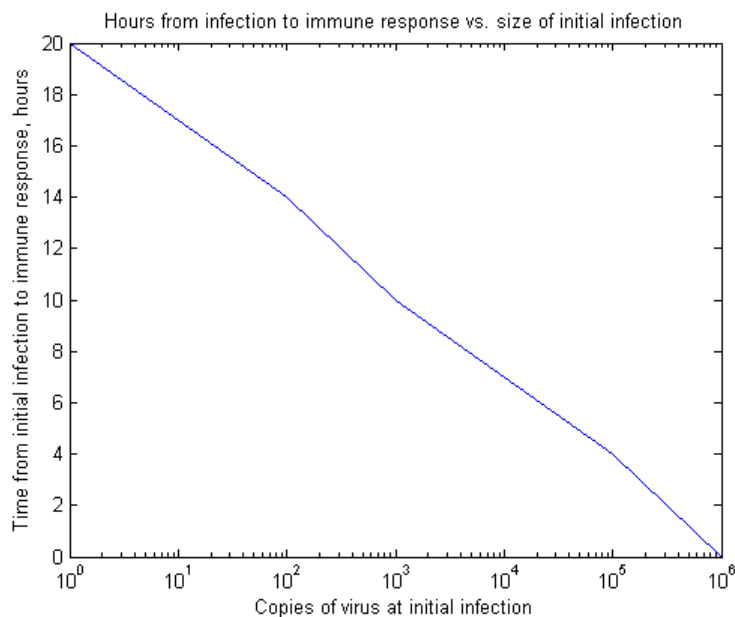

Figure 1

   If a person is infected with a single copy of the virus, they will have approximately 20 hours until the second phase of the disease begins. If they are infected with more copies initially, they will have less time, following the graph of figure 1.

4.2   Phase 2

The second phase of the disease begins when at least 1,000,000 copies of the virus accumulate in the body. At this point, immune response begins, both slowing the growth of the virus and presenting symptoms which we can use to treat the disease. Left untreated, this will give patients approximately 20 hours until 1 billion copies accumulate in the body and they can no longer be saved, and approximately 20 hours after that until they die. Thus, left untreated, the virus will progress from an initial infection to death over the course of approximately 60 hours (figure 2).

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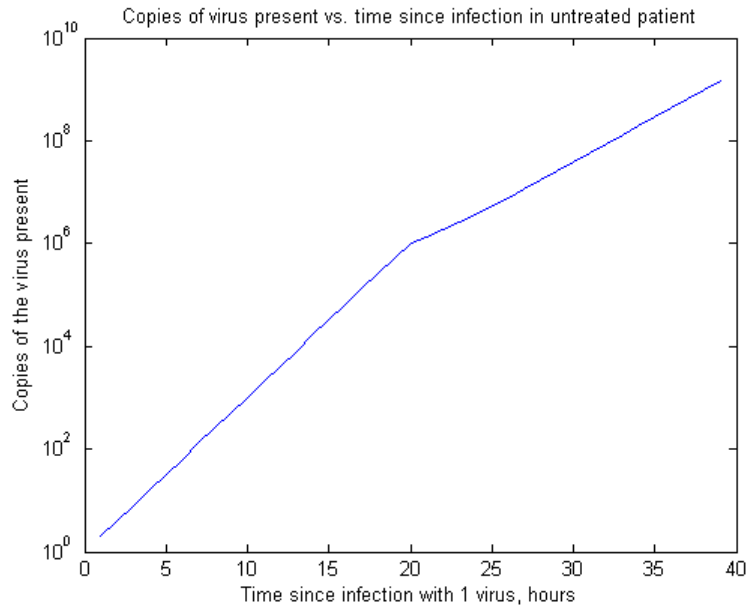
Figure 2

4.3 Treatment

We have access to a powerful antibiotic that can kill 500,000,000 copies of the virus per hour in tandem with the immune system. This means we can save many of the patients with the Hanta virus, often with only a single hour of treatment. Unfortunately, anyone with over 1 billion copies of the virus is beyond saving with the antibiotics and will die. For those who have under 1 billion copies however, many will be saved with only a single dose of antibiotics (figure 3).

Figure 3

Not shown in the graph, the worst-case treatable patient will be a patient with just under 1 billion copies of the virus at the time of treatment. They will be cured after approximately 52 doses of antibiotics over 52 hours. Patients that begin treatment with just over 1 billion viruses will die after 69 hours of antibiotic treatment, as opposed to surviving for 20 more hours when left untreated.
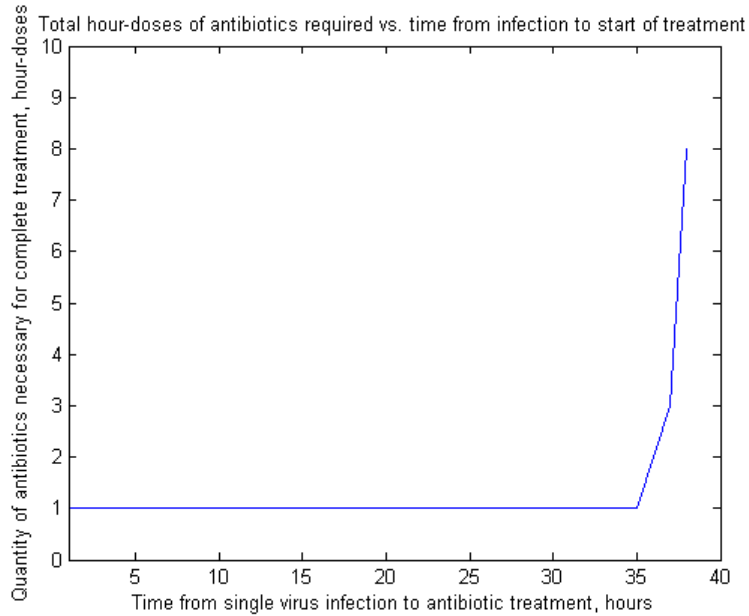
5 Medical Response Unit

We now turn to the problem of building a set of recommendations and guidelines for a medical unit tasked with handing a potential outbreak of Hantavirus. We assume that such a medical unit will be capable of the following:

- Appropriately trained staff - all members of the medical unit will have identical and sufficient knowledge of, and will follow recommended protocols for recognizing and handling suspected cases of Hantavirus

- Dedicated staff - the sole purpose of this medical unit is to handle potential cases of Hantavirus: they will not be tied up in other medical tasks at a time when their services are required to deal with a symptomatic individual

- All available equipment and supplies required for diagnosing symptoms and managing care is available - necessary equipment for diagnosing fever, myalgia, etc. is available and on-hand, along with all co-requisite medical equipment for sterilizing them and appropriately disposing of biohazards. In addition, all medical equipment necessary for managing care for terminally ill is also available and in ample supply.

- Antibiotic administered punctually and infallibly - all required doses of antibiotic will be administered to the necessary individuals every hour, on the hour, to completion of a recommended course of treatment.

- The shelf life of the antibiotic is not a factor over the time scales being discussed - the shelf life is sufficient for the drug to remain viable over the course of a single deployment.

5.1 Tuning the Response to the Percent of the Public Informed

The time of reporting into the hospital will vary depending on what percent of the public knows about the outbreak.

5.1.1 Completely Uninformed Public

According to the case study [1], in two months, 31 people were reported as suspected for Hantavirus. We assume that in populations similar to the Four Corners region of the US, the expected number of such patients in one month can be modeled with the Poisson distribution with parameter $\lambda = 31/2$.

$$\mathbb{P}(X = k) = \frac{\lambda^k}{k!}e^{-\lambda}.$$

This allows us to infer the number of doses we would need to supply to the local medical centers in the affected region, since the cdf of this distribution tells us how many doses we would need to be certain that 95 percent of the time we will have enough to provide appropriate care to affected individuals.

5.1.2 Informed Public

Qualitatively, we expect that a larger proportion of patients with flu-like symptoms will report them in time to be treated and cured if the population is informed. Therefore, we recommend that we supply medical units with twice as many doses of antibiotics as we would expect to need to manage care in an uninformed population.

5.2 Modeling the Severity of Incoming Patient Condition

We assume that under normal circumstances, most people do not report to the medical facility with flu-like symptoms until two or more days of feeling sick (based on [2]). We assume that prior to our release, people would show up uniformly in the period when the virus can be stopped, starting at the time they begin to show symptoms.

In our press release, we will recommend that people seek medical attention 7 hours after they start showing symptoms. This number was chosen for a number of reasons. We do not want patients to report in at the first sign of flu-like symptoms in order to prevent some false positives. As long as people are administered the medicine within 14 hours of showing symptoms, they will only need one dose. Given transportation time up to 1 hour and 15 minute diagnosis time, this distribution will peak at approximately 28 hours after infection (8 hours after showing symptoms). In case of longer hospital waiting time, most people who report in after 7 hours of showing symptoms will still only need one dose of the antibiotic to be cured. We hope that after our press release, most patients will report within the window where one dose of the antibiotic will cure them completely.

5.3 Using the Beta Distribution

Our random variable is the time patients report to the medical facility with the symptoms in question. Since they can only report after showing symptoms up until the time the virus kills them, the time window in question is from 20 to 60 hours since being infected. Since the support of this random variable is bounded, we choose the beta distribution to model the probability distribution of patients reporting in with flu-like symptoms. We expect the mean of this distribution to land at approximately 28 hours since infection, and we expect the variance to be 1 hour. The variance will depend on the population density of the region and on the density of medical facilities in it, which could be determined when more information about the region is known.

The beta distribution takes in parameters α and β.

$$\mu = \frac{\alpha}{\alpha + \beta}$$

$$\sigma^2 = \frac{\alpha\beta}{(\alpha + \beta)^2(\alpha + \beta + 1)}$$

Substituting for μ and σ, with appropriate normalization, we obtain $\alpha = 1.08$, $\beta = 4.32$ and produce the following graph:
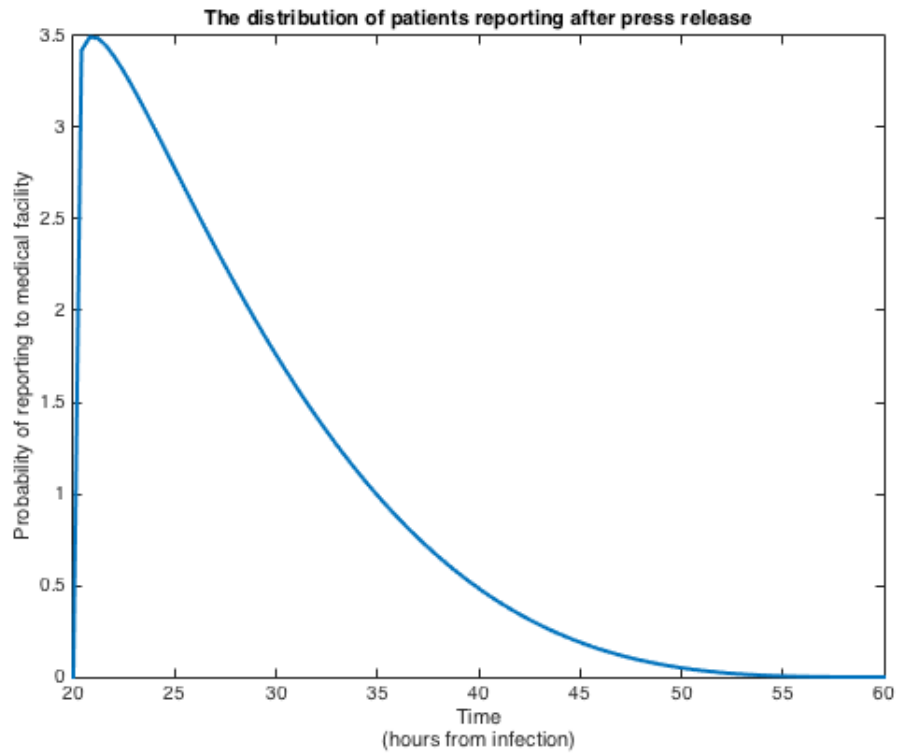
Figure 4

5.4   Tuning the Distribution to the Conditions

We assume that without the outbreak, people would report uniformly likely at random at a given time with flu-like symptoms.

Suppose we reach a proportion of people with our press release. Then let b be the fraction of people we reach, and let $a = 1 - b$. Then we would expect the probability distribution of people coming into the hospital to follow the mixture distribution of the uniform distribution and the beta distribution. The following graph presents how the distribution of patients coming depends on the choice of a and b.

Figure 5

As we can see from figure 5, the more people we reach with the press release, the more people can be saved. Note that at the 40 hour mark, antibiotics cannot stop the course of illness. Thus if a larger 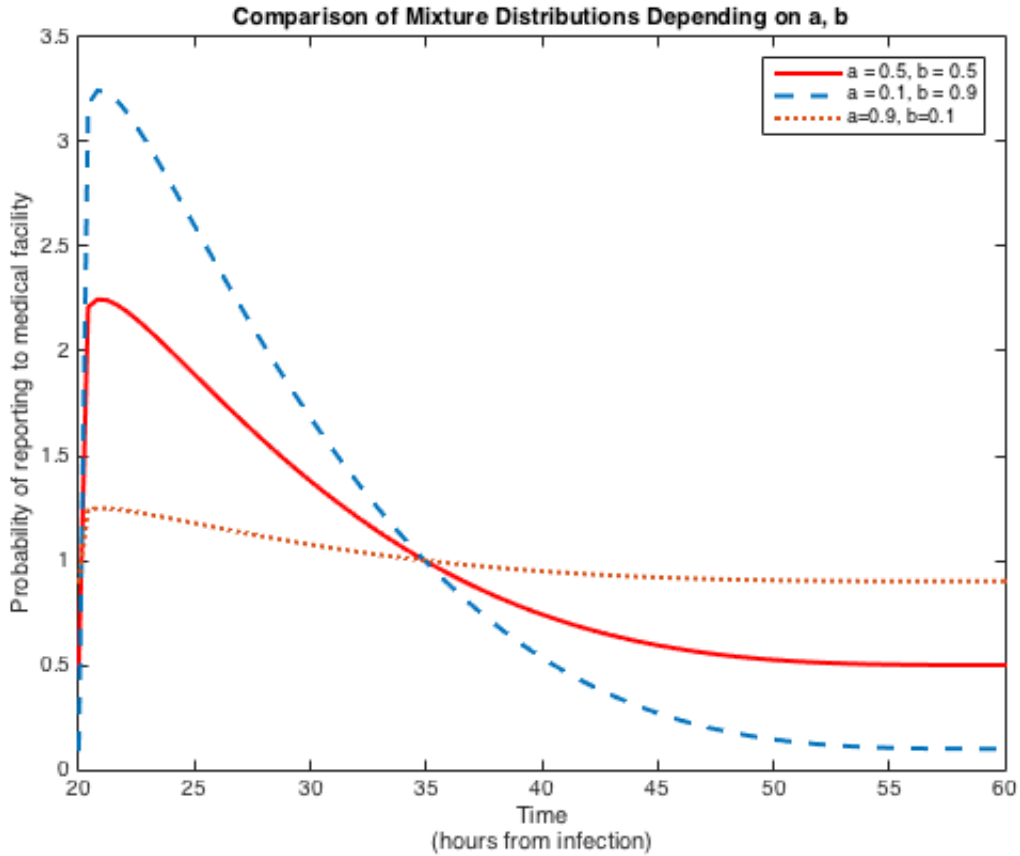proportion of patients could report in time, most of them would only require one dose of the antibiotic, and the fraction of terminal patients would decrease.

We would like to note here that under normal circumstances, the proportion of the population with flu-like symptoms that seeks medical help within the given time period is 13% at maximum [2]. As the disease awareness spreads among the public, the contribution from the uniform distribution will decrease, a will decrease, and b will increase.

For future estimates, we assume $a = 0.1$ and $b = 0.9$. We suppose that we can reliably transmit the press release to most of the population. These parameters can be adjusted based on the state of the communication infrastructure in the affected region. We estimate that the number of people who will seek medical attention after 40 hours or more of being infected with the Hantavirus is at maximum 4.2%. The exact fraction of the people who could be cured but will not be administered treatment will vary depending on the precise supply and demand of the antibiotics in the affected region.

5.5   Supply

An immediate and pressing question is how many doses of antibiotic to equip a field unit with in order to ensure that they will most likely have enough doses to handle potential incoming cases of Hantavirus appropriately.

In Four Corners, there were 31 suspected cases of Hantavirus, of which 18 were confirmed, over a two month period [1].

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Occurrence of Hantavirus is a rare event in the literature, with only a handful of confirmed cases even during an outbreak. We also recognize that the antibiotics and other relevant corequisite medical supplies required to treat potential cases of' Hantavirus may be limited by cost of production, logistics of transport, etc. As a result, the following section will discuss numerous tradeoffs and treatment schemes that can be selected between, depending on the availability of the Antibiotic.

A core principle in selecting between treatments is the fact that most patients who present with a case of Hantavirus that is curable with a finite number of doses of antibiotic will be cured by up to 3 doses. If, after 3 doses they are not cured, they are very likely to either have the flu or to be in a stage where they are not treatable, as opposed to being in the later stages of being treatable.

To be more precise, we recall that based on the available case study of outbreaks in Four Corners, Texas, roughly 50 percent of cases will have the flu, versus 2.5 percent of people who will require more than 3 doses to recover from the virus. Therefore a person that is not responding to treatment after a small number of doses is 20 times more likely to have the flu than to be both infected with Hantavirus and still curable. We leverage this fact to choose regimes that maximize the effectiveness of a small supply of antibiotics at saving the most number of lives.

We also recognize that it may be necessary to switch between regimes, since cases arrive in an on-line manner - the rate at which cases arrive will not remain constant over the time period a medical unit is deployed. We discuss an optimal strategy for deciding when to switch over.

5.5.1   Sufficient Supply - Antibiotic Availability not a Factor

In this case, all asymptomatic people will be asked to wait until they present with symptoms. At this point, a single dose of the relevant antibiotic will be administered to them, and if they were infected with the Hantavirus, they will be cured. As a result, they will be placed on observation for a few more hours to see if the condition worsens - if so, they were not infected with Hantavirus, and care can be managed as though they had the flu or other related illness.

All symptomatic people will be given regular doses of antibiotic every hour until either their symptoms subside, or they have received 52 doses of antibiotics. If their symptoms subside, they will be given one more dose so that we are sure we have killed the virus. This strategy guarantees that out of all incoming patients, everyone who can be cured, will be.

If the antibiotic is administered liberally, the expected value of doses per person is approximately 27.85.

5.5.2   Sufficient Supply - Antibiotic Availability a Small Factor

All people who present with symptoms which they report as having started that day or the previous day will be given a dose of antibiotics. Of these, we expect the individuals who have had the disease for 15 hours or less to be cured. Individuals whose symptoms subside after this first dose will be kept around for observation for 20 hours - if symptoms return, then they will be given a second dose of antibiotic.

Individuals whose symptoms do not subside will be given antibiotics until a total of 8 doses, at which case we halt treatment. Similar to the first case, if symptoms subside they will be kept around for observation for a further 20 hours: if symptoms return, we will give them another dose, guaranteeing that they are cured.

If there is insufficient space to accommodate keeping patients around for observation, then because the risk of person-to-person transmission is negligible we can allow patients to return home, and ask them to return immediately if symptoms recur.

In this case, the expected value of doses per person is approximately 4.78. In this scenario, we expect to lose 1.2% of all the people we could have saved.

5.5.3 Sufficient Supply - Antibiotic Availability a Large Factor

All people who present with symptoms which they report as having started that day or the previous day will be given a dose of antibiotics. Of these, we expect the individuals who have had the disease for 15 hours or less to be cured. Individuals whose symptoms subside after this first dose will be kept around for observation for 20 hours - if symptoms return, then they will be given a second dose of antibiotic.

Individuals whose symptoms do not subside will be given antibiotics until a total of 3 doses, at which case we halt treatment. Similar to the first case, if symptoms subside they will be kept around for observation for a further 20 hours: if symptoms return, we will give them another dose, guaranteeing that they are cured.

If there is insufficient space to accommodate keeping patients around for observation, then because the risk of person-to-person transmission is negligible we can allow patients to return home, and ask them to return immediately if symptoms recur.

In this case, the expected value of doses per person is approximately 2.10. In this scenario, we expect to lose 7% of all the people we could have saved.

5.5.4 Insufficient Supply of Antibiotics

All asymptomatic people will be asked to wait until they present with symptoms. After they present with symptoms, we will keep them around for observation for a further 14 hours, after which they will be administered a single dose of antibiotic. If too many people requiring antibiotics appear at a time, they will be given doses on a first-come first serve basis, with the exception of if one of the affected individuals is a young child, in which case a dose for them will be set aside and removed from the general pool.

This 14 hour delay from the onset of symptoms prevents false positives of administration of the antibiotic to cases which were not truly caused by Hantavirus - if the symptoms subside after treatment with conventional methods designed to reduce fever and myalgia, then we do not need to administer a dose of the antibiotic. It is critical, however, that antibiotic be administered 14 hours after onset of symptoms, since after the 15 hour mark it will require more doses to cure an affected individual.

People who present with symptoms that may be the result of Hantavirus will be triaged first according to age group (child, adult), then according to order of arrival, with young children taking precedence. One dose of antibiotic will be administered to every affected individual while supplies last. These treated individuals will then be placed under observation for the next 2 days, and those who recover fully can be discharged.

5.6 Choosing a Regime

How many people get the flu per month will depend on the population density of the affected region and overall infrastructure of the country. Each month, some people will report to the hospital with flu-like symptoms. Some of these people will have the flu; some will have the Huntavirus. Assuming that the two diseases are initially indistinguishable, the course of action to prevent deaths is to administer antibiotics to every patient with flu-like symptoms. However, antibiotics have been shown to weaken the immune system [5], and therefore we should not administer the cure liberally. Instead, depending on the initial tuning of the system and the average number of people who get the flu each year, we should choose an appropriate regime.

We recommend starting at the 8 dose maximum regime, as the drop in expected doses per person is sharp and the proportion of patient who are not cured is relatively small.

5.7 Switching Regimes

Let us assume that the medical unit is deployed for some set amount of time t. Over this time, they will be given an amount of antibiotic that sufficient to treat the number of cases they are expected

to receive - without loss of generality, let us assume that resources are abundant and we are able to supply them with the recommended number of 28 doses per person they are expected to see, thus allowing them to cure everyone that we are capable of saving.

The question is when this medical unit should switch to an alternate scheme of administering doses of the antibiotic, as a response to unexpected increased demand. We do not want to arbitrarily restrict access to the antibiotic until it is necessary, since we may have been able to save more people if demand suddenly sharply drops after a spike. Likewise, we do not want to exhaust our supply of antibiotics early, since a large proportion of people only require 1 dose to be cured.

We have defined regimes where we expect to allocate 28 doses per person, 5 doses per person, and 2 doses per person, and propose the following strategy for deciding when to switch between them.

We can calculate how many people we expect to see in the remaining time, and as a result calculate the expected number of doses we can administer per person. If the number of remaining doses per person decreases to the amount rationed by a stricter regime, we should switch regimes. We can also relax regimes if we experience a period where fewer people present with symptoms.

5.8   Handling Remains and the Terminally Ill

Due to the rapid onset of this virus, it is likely that some patients will arrive for medical attention with 1 billion or more copies of the virus already present, in which case we cannot help them. In this scenario, it will be necessary for us to collaborate with local hospitals or mortuaries for final palliative care and disposal of dead bodies according to the wishes of the community. For this disease in particular, the major issue is not one of sanitation - as we assume the virus does not spread through person-to-person contact and in general "bodies are quite unlikely to cause outbreaks of diseases such as typhoid fever, cholera, or plague" [6] according to the WHO - but of the mental health of the community. Thus, in order to minimize panic about the viral outbreak and respect the cultural or religious practises for death, we should allow local hospitals to care for the terminally ill and dispose of the bodies rather than attempting to do so ourselves.

6   Model Analysis

6.1   Advantages

Firstly, we analyzed the worst case scenario: influenza and the Hantavirus are indistinguishable. Our results will only improve if a more precise diagnosis is possible. Based on the course of the virus outlined in the problem statement, we have a deterministic and fairly simple to compute model for the progression of the disease in a person. Using this model, assessment of symptoms and appropriate actions to take can be determined by any health care professional without requiring additional training.

Our model features a large number of parameters that can be adjusted to reflect the idiosyncrasies of the affected region.

We manage to prescribe relatively few doses of antibiotic per person. However, our regimes allow to adapt to changing numbers of incoming patients rather than prescribing a deterministic solution.

6.2   Drawbacks

Some of our fundamental assumptions make the model not stable to noise. These assumptions include the possibility of transmission from human to human and instantaneous effectiveness of the antibiotic and the immune system. People might need additional doses when time is not discretized, as we modeled it.

The symptoms may not consistently start at exactly 20 hours after infection, or include fever and myalgia, which we have chosen as a fundamental metric.

We have no information about the region our unit is being sent to, and thus must make assumptions regarding the propogation of our press report as well as availability of local hospitals. In some parts of the world these assumptions may be incorrect, which would require re-evaluating several of our models.

Our approximations for the numbers of doses saved and the proportion of the population showing flu-like symptoms that actually carries the Hantavirus may have been limited by the small sample size in the case study [1]. The beta distribution only gives a crude approximation and does not necessarily reflect reality.

The ethical implications of cutting people off from the treatment are to be considered based on the severity of the situation. Ethics is a branch of macroeconomics.

6.3   Looking into the Future

If we had the time, we would build a classifier to determine whether someone's symptoms were the result of the virus or the flu. We could base this on data from previous Hantavirus outbreak studies as well as studies of general flu. Using a better metric to predict the probability of a patient's having the Hantavirus, we would be able to administer the antibiotic more precisely.

References

Scholarly articles

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[2]   AM Ross et al. "Presentation with influenza-like illness in general practice: implications for use of neuraminidase inhibitors". In: *Communicable Disease and Public Health* 3 (2000), pp. 256–260.

[3]   PJ Padula et al. "Hantavirus pulmonary syndrome outbreak in Argentina: molecular evidence for person-to-person transmission of Andes virus". In: *Virology* 241.2 (1998), pp. 323–330.

[4]   David M Engelthaler et al. "Climatic and environmental patterns associated with hantavirus pulmonary syndrome, Four Corners region, United States." In: *Emerging infectious diseases* 5.1 (1999), p. 87.

[5]   Takeshi Ichinohe et al. "Microbiota regulates immune defense against respiratory tract influenza A virus infection". In: *Proceedings of the National Academy of Sciences* 108.13 (2011), pp. 5354–5359.

[6]   J. Fisher. "Disposal of dead bodies in emergency conditions". In: *WHO Technical Note for Emergencies No. 8* (2008).

A MATLAB code

A.1 Virus Progression

```matlab
%%%%%%%%Problem: build up Vvec, a vector of numbers of virus copies at
%%%%%%%%each timestep
v0 = 1;
V = 1;
i = 0;
Vvec = [];
while V < 1e6
    V = 2*V;
    Vvec = [Vvec, V];
    i = i+1;
end
V
i


while(V < 1e9)
    V = 1.5*V - 200000;
    Vvec = [Vvec, V];
    i = i+1;
end
V
i


semilogy(linspace(1, i, i), Vvec)
title('Copies of virus present vs. time since infection in untreated patient')
xlabel('Time since infection with 1 virus, hours')
ylabel('Copies of the virus present')

%%%%%%%%Problem: graph initial number of virus copies vs. time to immune
%%%%%%%%response
figure
possStart = logspace(0, 6, 7);
is = []
for start = possStart
    v0 = start;
    V = v0;
    i = 0;
    sVvec = [];
    while V < 1e6
        V = 2*V;
        sVvec = [sVvec, V];
        i = i+1;
    end
    V
    i
    is = [is i];
end
semilogx(possStart, is);
title('Hours from infection to immune response vs. size of initial infection')
```

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```
xlabel('Copies_of_virus_at_initial_infection')
ylabel('Time_from_initial_infection_to_immune_response,_hours')

%%%%%%%%%Problem: at just under 1 billion, how long until the virus is
%%%%%%%%completely cured?
v0 = 1e9 - 1;
v = v0;
j = 0;
Vvec = [];
while(v > 0)
    v = (1.5*v) - 500000000;
    Vvec = [Vvec v];
    j = j+1;
end
plot(linspace(1,j,j), Vvec)
v
j

%%%%%%%%%Problem: at just over 1 billion, how long until the patient is
%%%%%%%%%dead?
v0 = 1e9 + 1;
v = v0;
j = 0;
Vvec = [];
while(v < 1e12)
    v = (1.5*v) - 500000000;
    Vvec = [Vvec v];
    j = j+1;
end
plot(linspace(1,j,j), Vvec)
v
j

%%%%%%%%%Problem: graph cure time as a function of i
cureTimes = ones(1, i-1);
starts = linspace(1, i-1, i-1);
for t = starts
    %Starting at time t, we have Vvec(t) viruses
    V = Vvec(t);
    %Model until virus >= 0
    j = 0;
    while(V >= 0)
        V = (1.5*V) - 500000000;
        j = j+1;
    end
    cureTimes(t) = j;
end
plot(starts, cureTimes);
axis([1 40 0 10])
xlabel('Time_from_single_virus_infection_to_antibiotic_treatment,_hours')
ylabel('Quantity_of_antibiotics_necessary_for_complete_treatment,_hour-doses')
title('Total_hour-doses_of_antibiotics_required_vs._time_from_infection_to_start_of_treat
```

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A.2 Beta distribution

```
%find parameters for the beta distribution

sigma=1/40;
mu=8/40;
alpha=((1-mu)/sigma - (1/mu))*mu^2;
beta=alpha*((1/mu)-1);


x=linspace(20,60);
xprime=linspace(0,1);

pd1 = makedist('Uniform');

pdf1 = pdf(pd1,xprime);
pdf2= (betapdf(xprime, alpha, beta));

figure
plot(x, betapdf(xprime, alpha, beta));


hold on
plot(x,pdf1,'r','LineWidth',2);


hold off

xlabel({'Time','(hours_from_infection)'})
ylabel({'Probability_of_reporting_to_medical_facility'})
%possible distributions given how the public is informed
% a mixture of the two distributions
figure
plot(x,pdf1*0.5+0.5*betapdf(xprime, alpha, beta),'r','LineWidth',2);
hold on
plot(x,pdf1*0.1+0.9*betapdf(xprime, alpha, beta),'b','LineWidth',2);
plot(x,pdf1*0.9+0.1*betapdf(xprime, alpha, beta),'black','LineWidth',2);
hold off

legend({'a_=_0.5,_b_=_0.5','a_=_0.1,_b_=_0.9',...
    'a=0.9,_b=0.1'},'Location','NE');


xlabel({'Time','(hours_from_infection)'})
ylabel({'Probability_of_reporting_to_medical_facility'})


%integral of the curve
Z = trapz(xprime,pdf1*0.1+0.9*betapdf(xprime, alpha, beta)) ;
y=linspace(0.633333,1);
yprime=linspace(18/40,20/40);
```

B WHO Press Release on Swine Influenza

Swine influenza

Statement by WHO Director-General, Dr Margaret Chan

27 April 2009

The Emergency Committee, established in compliance with the International Health Regulations (2005), held its second meeting on 27 April 2009.

The Committee considered available data on confirmed outbreaks of A/H1N1 swine influenza in the United States of America, Mexico, and Canada. The Committee also considered reports of possible spread to additional countries.

On the advice of the Committee, the WHO Director-General decided on the following.

The Director-General has raised the level of influenza pandemic alert from the current phase 3 to phase 4.

The change to a higher phase of pandemic alert indicates that the likelihood of a pandemic has increased, but not that a pandemic is inevitable.

As further information becomes available, WHO may decide to either revert to phase 3 or raise the level of alert to another phase.

This decision was based primarily on epidemiological data demonstrating human-to-human transmission and the ability of the virus to cause community-level outbreaks.

Given the widespread presence of the virus, the Director-General considered that containment of the outbreak is not feasible. The current focus should be on mitigation measures.

The Director-General recommended not to close borders and not to restrict international travel. It was considered prudent for people who are ill to delay international travel and for people developing symptoms following international travel to seek medical attention.

The Director-General considered that production of seasonal influenza vaccine should continue at this time, subject to re-evaluation as the situation evolves. WHO will facilitate the process needed to develop a vaccine effective against A(H1N1) virus.

The Director-General stressed that all measures should conform with the purpose and scope of the International Health Regulations.