Sensitivity analysis for parameters important for smallpox transmission

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Mathematical modeling provides a very cost effective means of studying epidemics by providing a means to understanding the particular disease without necessarily having to conduct the experiment physically. It serves as a primary source and can help guide experimental designs and even on an expanded scope; models can help us visualize aspects of an experiment that we may otherwise be unable to observe. It is a very useful technique in all academic fields employs it in different means. Not only epidemics but numerical methods can also be used to estimate impact of biological attacks and in designing appropriate response strategies (4). Here we developed a model for smallpox in order to determine the parameter sensitivity of smallpox transmission.

Smallpox is an infectious disease unique to humans and even though commonly agreed to have been eradicated in 1979 it still presents a threat as a potential biological weapon. Release of smallpox back into the population could constitute a significant public health problem (1). Upon infection with smallpox, the disease progresses through several distinct stages. Immediately following infection there is an incubation phase of the virus during which the infected individual shows no symptoms and is also not contagious. This phase lasts up to about 2 weeks upon which the individual starts displaying early symptoms. In this prodrome phase the patient experiences fever and body ache and even though contagious the infectivity is often negligible (3). This phase lasts about 4 days and then transitions to the last phase where the late symptoms of smallpox infection are apparent. The fulminant phase begins with the onset of rash which spreads to cover the entire body within 24 hours (4). At this stage the person is extremely contagious and will stay so for about 10 days after the rash appears. If the person recovers the scabs from the rash, which retain their infectivity somewhat longer, fall off after about 3 weeks. Therefore within an individual, the full cycle of the disease from infection to recovery takes about 7 weeks time.

The SIR model is widely used to describe the spread of a disease through a population and is an excellent model for smallpox whose transmission usually require direct personal contact with an infected individual (4). In this simplified model the population is broken into three categories. The Susceptive population is open to infection by the virus and those who are infected move to the Infected group forming the second category. Following successful recovery from the disease after infection the individual is assumed to acquire lifetime immunity against the virus and joins the third catergory, Recovered population. Another simplifying assumption is that each individual in the population being studied has to belong to one of these categories. This is often a reasonable assumption since the cycle of the disease being modeled is often much shorter than the natural life expectancy and as such the natural increase or decrease in the

population due to new births or deaths can be neglected. Of course, when looking at epidemics such as s HIV with longer cycles the model has to be adjusted appropriately in order to more closely simulate the epidemic.

For our simulation, in order to better model the transmission of smallpox we used a modified SIR that accounted for the specific stages that arise during the progress of the disease. Since the disease evolves over a period of a about 7 weeks we made the assumption that changes in the total population were negligible. The entire population was then divided into seven distinct categories. The first category is the Susceptible population who are not yet infected but can be under the appropriate conditions. Once infected the second category refers to the Incubation phase of the virus when the individual is not yet contagious. The third is the Prodrome who are infected and showing early symptoms of infection. Even though they can infect the susceptible population their infectivity is negligible. After this phase the individual starts displaying more specific symptoms and enters the fourth category who are highly Contagious. These are the most infectious group of the population. Based on previous responses to epidemic outbreaks the individual is often quarantined after getting to the contagious phase and this Quarantined population forms the fifth category of our model. Since they have been isolated from the general population we assume that they are no longer able to infect the susceptible population. Subsequently the quarantined population is then faced with either of two fates, Death or Recovery, which form the last two categories of our model for smallpox.

For this model we assume that all the infected individuals go through the quarantine phase and this can be used to simulate isolation response strategies (4). The transition probabilities β, α, γ, σ, ν and λ determine the rates that the population in each phase shifts from one to the next. With these variables and parameters the representation of our model in picture format as well as the equations we used to simulate it are shown below.

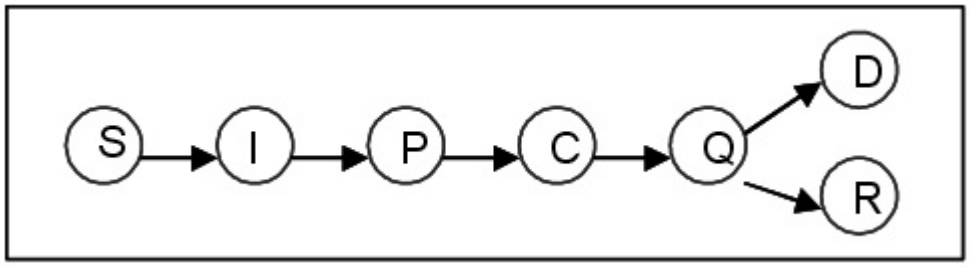

Figure 1. An illustration of disease transmission process (4).

$$\frac{dS}{dt} = -\beta SC$$

$$\frac{dI}{dt} = \beta SC - \sigma I$$

$$\frac{dP}{dt} = \sigma I - \alpha P$$

$$\frac{dC}{dt} = \alpha P - \gamma C$$

$$\frac{dQ}{dt} = \gamma C - \nu Q$$

$$\frac{dD}{dt} = \lambda \nu Q$$

$$\frac{dR}{dt} = (1 - \lambda)\nu Q$$

Figure 2. A system of equations used to model smallpox transmission

Our simulation was designed to test the sensitivity of each of the parameters to the different variables. In order to test this we started with a fixed population having 90% susceptible individuals with the rest infected with smallpox. All of the parameters were fixed at a value of 0.1 while varying only the one being tested incrementally from 0 to 1. For instance, in order to test the sensitivity of the susceptible population to changes in the probability of transmission, β, we set all other parameters to 0.1 while varying β over a range of 0 to 1 in 0.1 increments. We then ran the simulation and observed how this changed the composition of the susceptible population. This particular simulation yielded the plot displayed below.

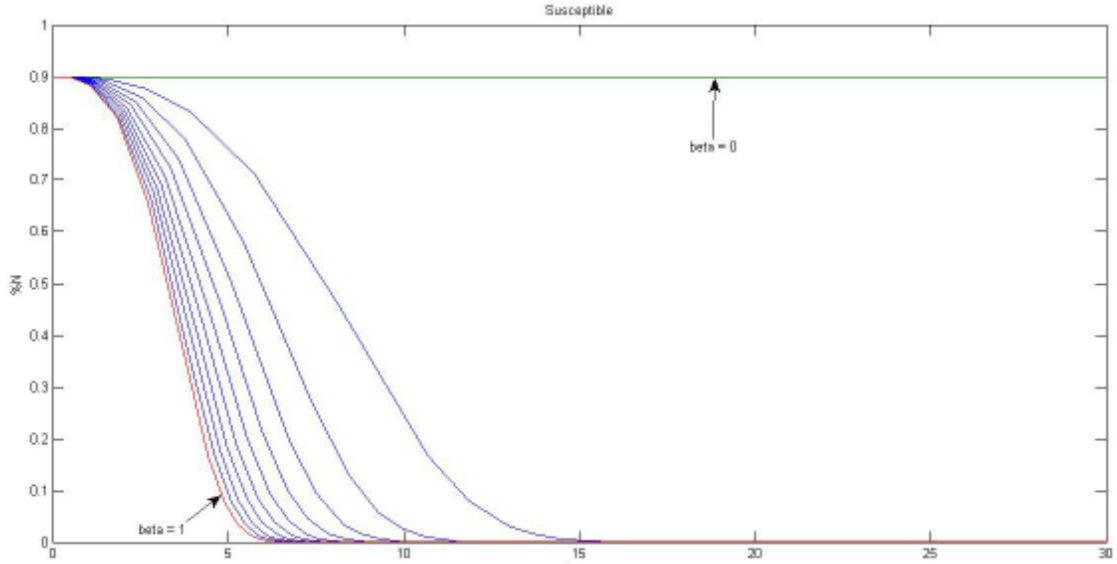

Figure 3. S as a function of time for different values of β

The top (green) line represents the susceptible population when $\beta=0$ while the bottom (red) line shows the susceptible population when $\beta=1$. The intermediate blue lines show how the susceptible population changes with β. We did similar simulations for all of the other variables with each of the parameters in order to determine each of their sensitivities to the system.

From the simulation results we arrived at several interesting conclusions about our model. Variation of β showed most sensitivity in the susceptible and incubating populations as may be expected from the system of differential equations used for the model. Since β determines the rate of transmission it is inversely related to the susceptible population but directly related to the incubating population. Thus as β increases we observed that the susceptible population decreases faster while the incubating population increases. Similarly, varying σ - the frequency of incubation- mostly affects the incubating and prodrome population to which it is directly linked by the differential equations. As σ increases the population moves faster between the incubating and prodrome stages. This pattern also holds for α –the frequency of prodrome. As α increase we observe the population transitioning faster to the contagious state.

An interesting situation occurs in the case of γ – the rate of quarantine. Once quarantined the individual is assumed to no longer be able to transmit the disease to the susceptible population so we notice sensitivity in both the contagious, incubating and susceptible populations. As we increase the value of γ above zero the population is transitioning faster from the contagious to the quarantined state. We observe the fast decline in the contagious population as γ is increased. If most of the population is quarantined there are less individuals who are susceptible that are infected. Accordingly we observe a steady decline in the incubating population. Lastly, for ν – the frequency of disease- sensitivity is only observed in the quarantined population as may be expected from observing the system of equations. This result is similar to that obtained for λ – the death rate- which of course only affects the ratio of the Dead and Recovered populations, without showing any sensitivity in the other variables.

Using our model simulations we were able to determine the sensitivity of various parameters to the transmission of smallpox. All the variables tested showed some sensitivity to the parameters β, α, γ, and σ even though the magnitude of this sensitivity differed between the different variables. ν and λ only showed sensitivity to the variable they were directly linked by the differential equations and are thus the least sensitive of the parameters tested. We are still pursuing other avenues of sensitivity analysis, specifically encoding the Jacobian matrix for our set of variables and parameters, in order to determine the most sensitive of these parameters to the transmission of smallpox.

References

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