Sensitivity analysis for parameters important for smallpox transmission

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Abstract

In order to determine the relative importance of model parameters to disease transmission, we perform sensitivity analyses on a mathematical model for smallpox. Using matlab® we compute sensitivity indices for the parameters important for smallpox transmission. We find that disease transmission is most sensitive to the parameter R_0, which is proportional to the rate at which infected individuals transition from the incubation stage to subsequent stages of smallpox pathogenesis. This suggests that optimal efficacy of efforts to stop the spread of the disease and reduce its fatality should focus on affecting this stage of the infection process.

Introduction

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 requires 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 category, 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 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 that is 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.

There are several parameters involved in determining the transmission of smallpox. Since the spread requires physical contact with an infected individual controlling the disease is feasible by quarantine (4). The quarantine protocols though have to be set for optimal results and this can be achieved by targeting the parameters most sensitive for transmission process. An evaluation of the sensitivity indices of such parameters allows us to determine their relative significance in the process of smallpox transmission which is necessary in order to reduce the mortality. The proportion of infectious individuals within a population is important because it directly relates to the death rate and is also the condition most affected by quarantine procedures. Here we calculate the sensitivity indices of the parameters in the model simulating smallpox transmission. These indices tell us how crucial each parameter is to the transmission of smallpox and allows for suggestions as to what parameters should be the target of disease control strategies.

Methods

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, σ, α, γ, ν and λ determine the rates that the population in each phase shifts from one to the next starting with the susceptible, incubating, prodrome, contagious and quarantined respectively. Shown below are these variables and parameters representing of our model, in both picture format as well as the equations we used to do the simulation.

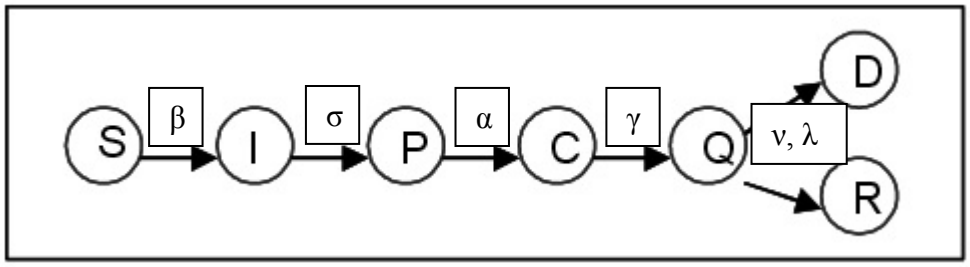

Figure 1. An illustration of disease transmission process, including the parameters affecting transition between the different stages of infection (4)

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

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

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

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

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

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

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

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

We performed both continuous and discrete analysis of our system using matlab®. For the discreet analysis we fixed the values of the parameters and observed how the entire system is affected by incrementally changing only one of the parameters. This analysis yields an estimate for the parameters that will affect the system and are therefore their sensitivity but in order to quantify this analysis we calculated the sensitivity indices of these parameters.

In order to calculate the sensitivity indices we first determined the Jacobian for our system of equations. We then determined the partial derivatives of the system of equations with respect to the parameters. We coded the matrix in matlab® and using the partial derivative of the nondimesionalized parameters determined the solutions to the linear systems. Solving the linear systems gives the partial derivative of each variable

with respect to the parameter and multiplying this by the reciprocal of the undifferentiated values give the sensitivity index. The sensitivity index quantifies the sensitivity of each variable to the given parameter.

Results

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 other 10% infected with smallpox. For the first trial, 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.

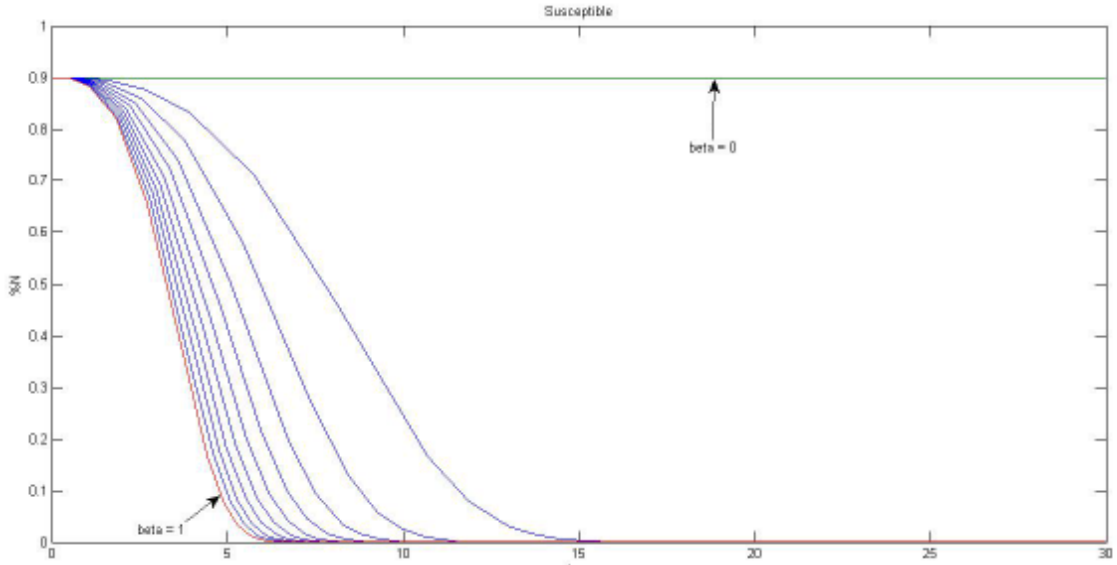

Figure 3. S as a function of time for different values of β

The top (green) line represents the susceptible population when β=0 while the bottom (red) line shows the susceptible population when β=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 them affected the system.

This initial trial gave as a suggestion as to which parameters were sensitive to the system but did not give a quantifiable result to determine the relative sensitivity of each of the parameters. Therefore on a subsequent trial we calculated the sensitivity indices of our parameters in order to allow this comparison. Rather than using fixed values for the parameters, in this trial we derived realistically feasible values for the parameters as obtained from previous studies on the infection of smallpox. Following natural infection these values are β=0.02, σ=0.09, α=0.4, γ=0.5, ν=0.06 and λ=0.3 (4). Using these values we calculated and obtained the relative sensitivities of the system to changes in each of these parameters. The values from this analysis are shown below.

	R_0 (σ / β)	R_1 (α / β)	R_2 (γ / β)	R_3 (ν / β)	λ
Susceptible	-1.1104	-0.3978	1.5911	__	__
Incubation	-1.7429	0.3199	-0.8148	__	__
Prodrome	1.0839	-1.1469	-0.7684	__	__
Quarantine	1.159	0.468	-1.6656	__	__
Contagious	1.0961	0.4444	-0.6916	-0.9844	__
Dead	0.851	0.3565	-0.412	0.1215	1
Recovered	0.851	0.3565	-0.412	0.1215	-0.4286

Table 1. Sensitivity indices of Parameters for smallpox model shown relative to the stages in the process of smallpox transition

Discussion

From the simulation results we arrived at several interesting conclusions about our model. Variation of β showed most fluctuation in the susceptible and incubating populations as may be expected from analysis of 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 system of differential equations. As σ increases the population transitions faster between the incubating and prodrome stages. This pattern also holds for α –the frequency of prodrome – where 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 can be 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.

From these observations of the discrete analysis of the parameters in the system one may estimate the relative sensitivity of each of these parameters by how much the system is perturbed when their values are changed. By calculating the sensitivity indices of the parameters though we were able to obtain more conclusive results. From these indices we observe that the normalized parameter R_0 shows the most sensitivity in all stages of smallpox infection. This parameter, proportional to the frequency of incubation, suggest that on a natural smallpox outbreak the rate at which individuals transition from incubation phase to subsequent phase of infection determine the transmission of the disease. During the incubation phase since the individual is not yet infectious, if the disease can be detected in this stage and the patient quarantined, then the spread can most effectively be contained. Since the disease is asymptomatic in this stage, detection of

such individuals is difficult and may explain why current quarantine protocols are delayed to the contagious phase. Though showing less sensitivity than R_0 to the other variables in the system, the parameter R_2, proportional to the rate of quarantine, has the most impact on the susceptible population. An increase in the rate of quarantine thus prevents the spread of smallpox by limiting the infection of susceptible individuals.

Using our model simulations we were able to determine the relative sensitivity of various parameters to the transmission of smallpox. In the discrete analysis of the parameters all the variables tested showed some sensitivity to the parameters β, α, γ, and σ even though their magnitudes were different. 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. These results are consistent with those obtained by continuous analysis of the system in which the sensitivity of the parameter are determined on the system as a whole. The parameter R_0 shows the most sensitivity in terms of the overall transmission of the disease and R_2 has the most effect on the susceptible and quarantined population. Interestingly the sensitivity of the parameter R_2 is only observed for higher valuses and when it is low the the system is not strongly affected. These results lead to some important factors to consider in case of a smallpox outbreak. Control strategies should be focused on early detection of infected individuals and their immediate quarantine.

References

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