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What is the best control strategy for multiple infectious disease outbreaks?

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Effective control of infectious disease outbreaks is an important public health goal. In a number of recent studies, it has been shown how different intervention measures like travel restrictions, school closures, treatment and prophylaxis might allow us to control outbreaks of diseases, such as SARS, pandemic influenza and others. In these studies, control of a single outbreak is considered. It is, however, not clear how one should handle a situation where multiple outbreaks are likely to occur. Here, we identify the best control strategy for such a situation. We further discuss ways in which such a strategy can be implemented to achieve additional public health objectives.

Keywords: infectious disease outbreak; SARS; influenza; epidemic control; mathematical model

1. INTRODUCTION

Despite all medical advances, infectious disease outbreaks still pose a significant threat to the health and economics of our society. Two examples that immediately come to mind are the relatively recent SARS outbreak—which was fortunately contained but nevertheless caused loss of life and significant economic damage (Peiris *et al.* 2004; Skowronski *et al.* 2005)—and the looming possibility of an influenza pandemic caused by a human-to-human transmissible H5N1 virus (Beigel *et al.* 2005; Ungchusak *et al.* 2005).

Since future infectious disease outbreaks—caused either by naturally emerging or deliberately introduced pathogens—are virtually certain to occur, it is of utmost importance to investigate effective control strategies that can minimize the impact of such outbreaks. Arguably, the best control strategy is early containment. This approach was successfully implemented for the case of SARS (Ho & Su 2004; Svoboda *et al.* 2004), and it has also been suggested as the optimal strategy against an avian influenza outbreak (Ferguson *et al.* 2005; Longini *et al.* 2005). However, containment might not always be possible. Both the SARS and influenza viruses are endemic in animals (Webster 2004) and therefore the occurrence of multiple outbreaks within a short time span is a possibility (Mills *et al.* 2006). Multiple outbreaks, as well as a situation where an outbreak occurs in a region with poor public health infrastructure, might lead to containment failure.

If outbreak prevention is not possible, then reducing its severity is the next goal. The impact of a variety of intervention measures has been studied for SARS (Lipsitch *et al.* 2003; Pourbohloul *et al.* 2005), and more recently for a potential pandemic influenza outbreak (Ferguson *et al.* 2006; Germann *et al.* 2006). Such studies provide vital information for public health officials. However, there is one important caveat to the results obtained from these studies. Namely, it is most often assumed that the outbreak occurs in a closed population, i.e. no new infecteds enter the population and no secondary outbreaks are considered. Under such a scenario, more severe intervention measures lead to less infections and accompanying mortality. Therefore, from a viewpoint of reducing the number of infecteds, the best control strategy is one that is as stringent as can possibly be implemented. However, this is not necessarily true anymore if one considers the case of multiple outbreaks. We will explain here how the best control strategy should look like for such a situation.

2. THE MODEL

To illustrate our ideas, we use a simple compartmental SIR model (Anderson & May 1991; Hethcote 2000). To keep the model as simple as possible, we ignore natural births and deaths as well as disease-induced mortality. We consider the dynamics of susceptibles S, infecteds I and recovereds R. The equations are given by $\dot{S} = -(1-f)\beta IS/N$, $\dot{I} = (1-f)\beta IS/N - I/D$ and $\dot{R} = I/D$. For our illustrative figures, we (arbitrarily) set the population size as $N = 10\,000$ and the duration of infection as $D = 4$. The parameter f describes the reduction in transmission due to intervention strategies. The transmission parameter β is specified through the basic reproductive number R_0, which for our model is given by $R_0 = (1-f)\beta D$.

The figures are created as follows. For figure 1, we choose $R_0 = 2$ (corresponding to $\beta = 0.5$) and $f = 0$. For figure 2, the weak, optimal and strong control scenarios correspond to $f = 0.2$, 0.3 and 0.4, respectively. For figure 3, R_0 is varied from 1.05 to 7 by changing β accordingly, f is set to 0 for no control and 0.3 for optimal control. For figure 4, the light grey curve is produced by setting $f = 0.3$. The dark grey curve is produced by setting $f = 1$ at time $t = 27$. The black curve is produced by changing f, in a way that R_0 stays at $R_0 \approx 1.01$.

3. THE UNCONTROLLED SITUATION

Figure 1 shows the number of susceptibles and infecteds during an outbreak. The initial growth phase of the epidemic is characterized by an approximately exponential

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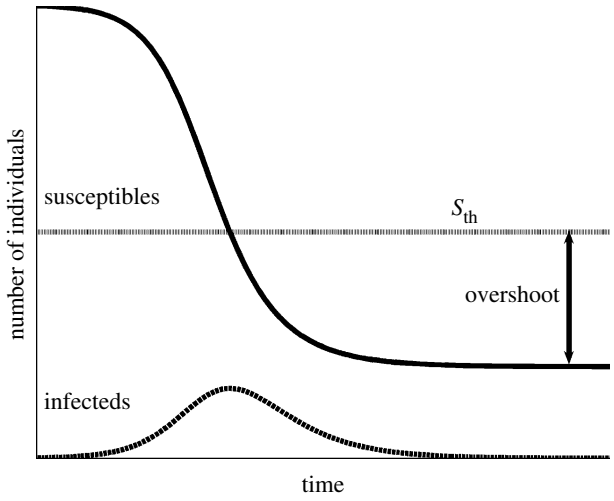

Figure 1. Susceptibles and infecteds for an uncontrolled epidemic. The dotted horizontal line indicates the threshold level of susceptibles S_{th} below which population immunity prevents further outbreaks. The arrow indicates the difference between the number of susceptibles at the end of the outbreak and S_{th}. We term this difference the overshoot. (Equations and parameters used to produce all the figures are given in §2.)

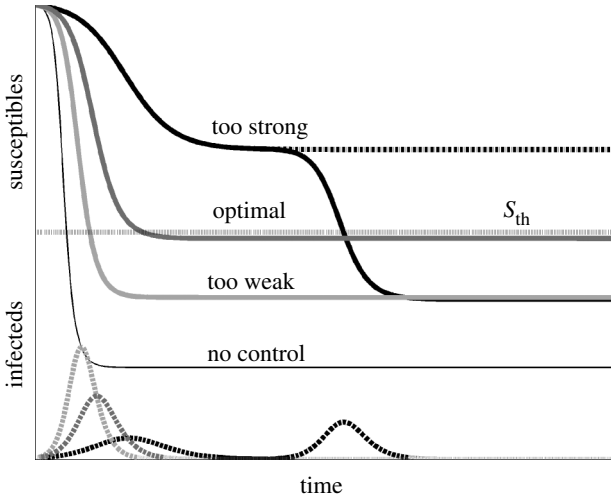

Figure 2. Control strategies of different strength. Susceptibles and infecteds for intervention measures that are too weak (light grey), too strong (black) and optimal (dark grey). Also shown are the susceptibles for the uncontrolled case (thin solid curve) and for the case of strong control in a closed (single outbreak) population (dash-dotted line). (For better illustration purposes, number of infecteds are not drawn to scale.)

increase in the number of infecteds, accompanied by a decline of susceptibles. Once the number of susceptibles crosses a threshold level S_{th}, the average number of new infections caused by an infected person falls below 1 and the epidemic wanes. If the final number of susceptibles is below S_{th}, further outbreaks cannot occur due to population immunity. The concept of population immunity has been widely used in the implementation of vaccination programmes (Anderson & May 1991; Scherer & McLean 2002; Hill & Longini 2003), and it has recently been studied for the spread of multiple pathogens through networks (Newman 2005). If a vaccination campaign can drive the number of susceptibles below S_{th} (drive the basic reproductive number R_0 below 1), then the disease can be eliminated. As figure 1 illustrates, in an uncontrolled epidemic, the number of susceptibles can fall well below S_{th}. We refer to this additional depletion of susceptibles as overshoot.

4. THE BEST CONTROL STRATEGY

Figure 2 shows schematically the impact of (as yet unspecified) control strategies of differing strength. For weak intervention, the final number of susceptibles is above that of the uncontrolled epidemic but below S_{th}, thereby preventing consecutive outbreaks. Increasing the strength of interventions will decrease the number of infecteds and therefore increase the number of susceptibles that remain after the outbreak is over. The dash–dotted line shows a situation where strong intervention measures are applied. The final number of susceptibles is high. However, since the level of susceptibles at the end of the outbreak is above S_{th}, the possibility exists for a second outbreak to occur if the infection is reintroduced into the population. If control of the first outbreak depleted resources—such as drug stockpiles or 'goodwill' among the population to follow quarantine measures—the second outbreak will be largely uncontrolled, producing a significant overshoot and potentially reducing the number of susceptibles well below S_{th}. The solid black curve shows such a situation. Therefore, if multiple outbreaks are possible, intervention measures that are too strong can result in an outcome that is as suboptimal as a situation with weak intervention measures. The best control strategy is one that leads to a final number of susceptibles at S_{th}, since this is the maximum number of susceptibles that can be present without risking a consecutive outbreak. This corresponds to a control strategy that minimizes the overshoot. Figure 3 shows the potential reduction in the number of infecteds for such an optimal strategy. For the simple SIR model we use here, the number of prevented infections is found to be highest for intermediate values of $R_0 \approx 1.5$–3. These values are in the range of those estimated for some infectious diseases, such as influenza (Mills *et al.* 2004) or SARS (Lipsitch *et al.* 2003).

5. IMPLEMENTING THE BEST CONTROL STRATEGY

Any control strategy that results in the number of infecteds approaching zero as the number of susceptibles approaches S_{th} minimizes the overshoot and therefore the number of infecteds. A number of intervention measures such as prophylaxis, treatment, quarantine, movement restrictions, etc. could be used to achieve this outcome. These intervention measures can be implemented in various ways, depending on additional goals or constraints. A strategy that might be relatively easy to implement is one that uses constant intervention for the duration of the epidemic at a level such that at the end of the outbreak, S_{th} susceptibles remain in the population. Such a strategy is illustrated by the light grey curves in figure 4. Another objective might be to avoid a sharp peak in the number of infecteds and to spread out the epidemic in time so as to reduce strain on the health system. This could be achieved through adaptive intervention measures that are adjusted to keep the effective reproductive number just above 1, resulting in a 'slow burn' of the epidemic, as shown by the black curves in figure 4. For a fast evolving pathogen, such as influenza, the potential emergence of drug resistance could pose a serious problem (Stilianakis *et al.* 1998; Regoes & Bonhoeffer

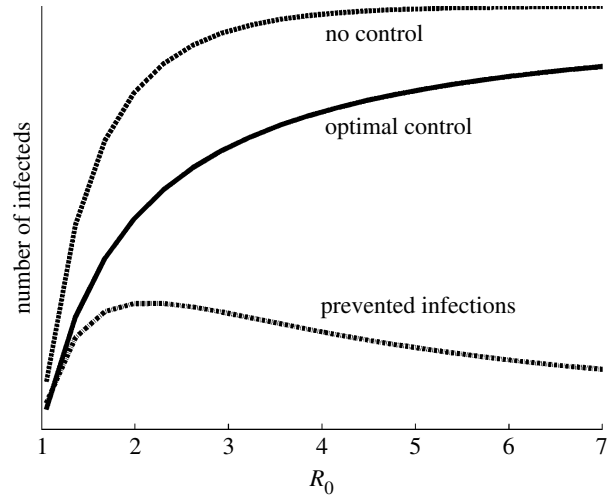

Figure 3. Prevented infections for the optimal control strategy as a function of the basic reproductive number. Also shown are the total number of infecteds for no and optimal control.

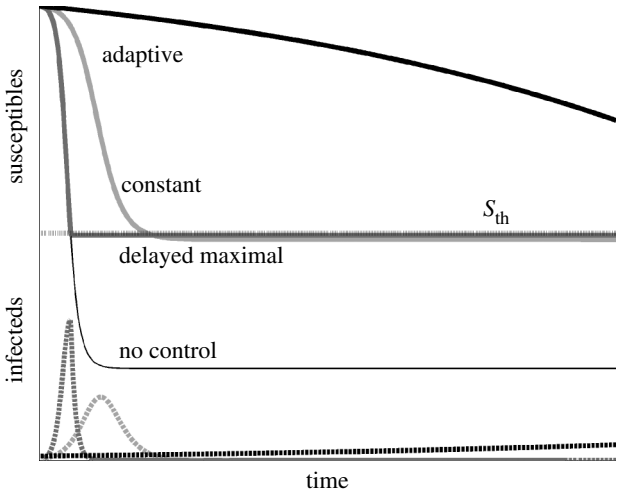

Figure 4. Examples of different control approaches. The light grey curve shows constant intervention. The black curve shows a scenario where intervention measures are constantly adapted such that the effective reproductive number is slightly above 1. The dark grey curve shows the number of susceptibles for the strategy best suited to prevent resistance emergence, namely no intervention until S reaches S_{th}, followed by maximal reduction of transmission. Also shown are the number of susceptibles without control. (For better illustration purposes, number of infecteds are not drawn to scale.)

2006; Lipsitch *et al.* in press). If we are concerned about drug resistance, the prolonged use of drugs should be avoided. In this case, the optimal control strategy could be implemented in such a way that no intervention is applied until the number of susceptibles is close to S_{th}, at which point control efforts should (for a short time) bring R_0 as close to zero as possible. The exact timing of the intervention is determined by the amount of reduction in transmission that can be achieved. This approach also minimizes the duration of the outbreak. The dark grey curves in figure 4 illustrate such a scenario.

6. DISCUSSION

Early containment of a potential infectious disease outbreak is the best possible scenario (Ferguson *et al.* 2005; Longini *et al.* 2005). If containment fails, strategies to reduce the outbreak severity are needed. Current control strategies focus on the reduction of infecteds for a single outbreak. This probably applies to outbreaks in places such as nursing homes, hospitals or isolated geographical regions. In contrast to that, pathogens such as a novel pandemic influenza strain will probably result in many local outbreaks that are unlikely to be synchronized, making continuous influx of new infecteds possible (Viboud *et al.* 2005). This means that at the end of an outbreak in one location, the infection could be reintroduced, potentially leading to a consecutive outbreak. Stringent control measures might lead to a significantly reduced primary outbreak with the final number of susceptibles well above S_{th}. However, if this strategy leads to the depletion of both drug stockpiles and goodwill among the population, then a second outbreak could occur in a largely uncontrolled fashion, producing a significant overshoot and reducing the number of susceptibles well below S_{th}. This is a potential problem for very strong intervention measures such as some of the most severe control strategies described for recent pandemic influenza control (Ferguson *et al.* 2006; Germann *et al.* 2006). In such a situation where multiple outbreaks are probable and resources are limited, the best strategy is to apply intervention measures in such a way that the number of susceptibles reaches exactly S_{th}.

We want to stress that such a control strategy should only be considered if other strategies are impossible. If enough resources are available to control multiple outbreaks, then one should use for each outbreak the control strategies that lead to the lowest number of infecteds. Further, if control can buy enough time to, for instance, produce and deploy vaccines—as might be possible for a novel influenza virus—then control should also be as stringent as possible until the vaccine is available. However, we might find ourselves in a situation where resources are limited and multiple outbreaks are probable. If such a scenario were to occur, the approach that leads to a level of susceptibles just below the level S_{th} required for population immunity is the best result obtainable and control strategies should be implemented towards such a goal. Since such a control approach might potentially involve the deliberate withholding of drugs from infected individuals that are not at high risk, ethical considerations need to be taken into account (Foster & Grundmann 2006).

Obviously, the SIR model used here to illustrate our ideas is a very strong oversimplification of any real infectious disease outbreak. Real outbreaks take place on heterogeneous contact networks, involve stochasticity and uncertainty in parameter estimation and other complicating features. Nevertheless, the main ideas are still likely to hold, which are as follows:

(i) A critical level S_{th} exists below which population immunity prevents further outbreaks. This is true for any pathogen that induces immunity in a recovered person, which is the case for a significant number of infectious diseases. In a more detailed, heterogeneous epidemiological model, one might not have a single S_{th} but instead different threshold levels for certain subgroups, such as different age classes or localities (urban versus rural, for instance). Additionally, if the pathogen evolves between outbreaks, immunity created during a

previous outbreak might not be completely protective during a secondary outbreak. However, usually a significant amount of cross-immunity exists and therefore the concept of population immunity and S_{th} still applies. We therefore suggest that while the details might be complicated, the concept of a threshold S_{th} will hold true for realistic situations.

(ii) Uncontrolled epidemics produce an overshoot that leads to the drop in susceptibles below S_{th}. Detailed, agent-based epidemiological simulations show that the number of infecteds follows a time course closely resembling the one shown in figure 1 for the simple compartmental model. In general, the number of infecteds grows until the number of susceptibles has fallen to S_{th}. At this point, the average number of secondary infections created by an infected person drops below 1 and therefore the number of infecteds starts to decrease. However, right at this inflection point, the maximum number of infecteds is present. These infecteds will create on average less than 1, but still more than zero further infections, leading to additional depletion of susceptibles and therefore causing an overshoot. This is a generic feature of an infectious disease outbreak and not limited to the illustrative model used here.

(iii) If multiple outbreaks are likely and resources are limited the best control strategy is one that results in the final number of susceptibles reaching S_{th}. This follows from the preceding two points and the arguments we have presented in this work.

The practical implementation of our suggested control strategy relies on the same tools as those that have been and are being developed to study control for single outbreaks. First, once a novel pathogen causes an outbreak, it is necessary to rapidly determine the transmission characteristics of the pathogen (Wallinga & Teunis 2004; Cauchemez *et al.* 2006). This information can then be combined with recent detailed models (Ferguson *et al.* 2006; Germann *et al.* 2006) to simulate the outbreak and the impact of various control measures. This approach should be taken independent of the possibility of one or several outbreaks. If multiple outbreaks are likely to occur and resources are limited, control measures should then be implemented such that the number of susceptibles falls to S_{th}. As explained previously, there are many ways to achieve this. We showed three different examples in figure 4. These examples are meant to illustrate different ways in which control could be implemented. In the next step, one should specify exactly what kind of realistic control strategies are available and what additional objectives one would like to achieve, such as, for instance, minimizing the peak of the outbreak or the probability of drug resistance emergence. Once the intervention measures, constraints and possible additional outcome objectives have been specified, one can use sophisticated mathematical tools such as control theory to determine an optimal control schedule (Wickwire 1977; Greenhalgh 1986; Clancy 1999; Behncke 2000; Patel *et al.* 2005).

To summarize, we showed that when designing control strategies for infectious disease outbreaks, it is not enough to consider a single outbreak. Instead, any comprehensive emergency preparedness planning also needs to consider how certain control approaches perform under a scenario where multiple outbreaks are possible. We explained that if resources are limited and multiple outbreaks are probable, the best control strategy is one that drives the number of susceptibles to a threshold level S_{th} at which population immunity will prevent further outbreaks. We also illustrated several ways in which such a control strategy could be implemented. We suggest that comprehensive control strategies against large-scale infectious disease outbreaks should consider a wide range of strategies, such as containment at the source, optimal control of a single outbreak and optimal control of multiple outbreaks. We hope that the ideas presented here will stimulate further studies on how to best implement intervention measures that allow for an effective outbreak control for all possible scenarios.

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