Preparing for a smallpox bioterrorist attack: pulse vaccination as an optimal strategy

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Events of recent years have significantly increased our awareness of the potential threat of a bioterrorist attack, and the smallpox variola virus has been identified as an "eligible candidate" for a biological warfare agent. Epidemiological mathematical modeling has long been recognized as a crucial tool for assessing the repercussions of such a viral outbreak, as well as for comparing possible response strategies. Several studies have applied mathematical models with the hope of identifying an optimal vaccination strategy in case of an attack [1–4]. However, these particular studies do not produce clear-cut recommendations, upon which authorities can rely when formulating policies. In fact, conclusions of certain studies contradict those of others.

This inconsistency may stem from simulation results' extreme sensitivity to the value assumed for the disease's basic reproduction rate (R_0) [5], i.e. the number of secondary infections that an infectious individual is expected to produce if introduced into an entirely susceptible population. Because smallpox was eradicated in 1979, there is a lack of current epidemiological data on the disease, and R_0 must be estimated. However, as this value is dependent both on biological factors and on population

dynamics, it is extremely difficult to assess prior to an actual epidemic. Each of the above-mentioned studies assumes a different value for R_0, which may account for their contradictory results: a response strategy found to be effective in the case of a low disease transmission rate may fall short when faced with a higher transmission rate.

Furthermore, there is a fundamental limitation that compromises the practical value of theoretical smallpox studies to date: they examine response strategies that address only an initial epidemic, without considering long-term effects of the introduction of the disease into a contemporary population. Theory indicates that smallpox, like many other contagious diseases, is characterized by decaying oscillatory dynamics, i.e. periodic epidemics of decreasing magnitude [6]. Thus, while a given vaccination strategy may succeed in curbing an outbreak immediately following the release of the virus, it may not be able to prevent additional epidemics several years down the line (see Figure 1). Clearly, an efficient follow-up strategy is no less important than initial crisis aversion. Nevertheless, most smallpox studies either fail to mention such a strategy, or simply assume that the entire population will continue to be vaccinated in the years following the outbreak. This type of continuous vaccination policy would be far from optimal, as vaccinia, the smallpox vaccine, is known to cause serious, and even fatal, side effects. Additionally, the vaccine carries quite a few contra-indications: for example, it is not recommended to administer it to young children [6]. Due to these significant constraints, it becomes evident that a general idea for a long term vaccination strategy is insufficient; this strategy must be rigorously defined. Theory implies that efficient control of phenomena such as smallpox transmission, which display clear periodicity, should involve a **periodic** strategy with a period different from that of the phenomenon being counteracted [7, 8].

Based on these guidelines, we examine a vaccination strategy that has not yet been considered in the context of response to a smallpox bioterrorist attack: *pulse*

vaccination, i. e. periodic vaccination of certain percentages of the susceptible population following attack. The *pulse* strategy has previously been proposed as an efficient method for measles eradication [9, 10]. In addition to its theoretically proven efficacy, this strategy also enables flexibility: the number of people vaccinated and the duration of time between vaccination campaigns (inter-vaccination interval) can be varied according to arising circumstances. This flexibility is crucial when dealing with a situation as sensitive as a smallpox bioterrorist attack, with so many unknown and unpredictable factors, e.g. the disease's actual basic reproduction rate, the population's response to an outbreak and willingness to comply with vaccination campaigns, available vaccine stockpile, vaccine efficacy, etc.

In this study, we compare the *pulse vaccination* strategy to two known smallpox response strategies: (i) *preliminary vaccination*, i.e. vaccination of a certain percentage of the population prior to the attack; (ii) *one-time mass vaccination*, in which most of the population is vaccinated immediately following the attack. Additional vaccination strategies that have been considered for smallpox protection are *trace* and *ring vaccination,* in which vaccination is limited to close contacts of infected individuals. Though these approaches are potentially effective in large countries [11], they are not considered feasible in small countries with high population density such as Israel, and therefore we did not include them in our study.

To compare the performance of the different vaccination strategies under a wide range of conditions, we adapted the SEIR epidemiological model [6] to describe the effects of a smallpox bioterrorist attack on the Israeli population over a period of ten years. We simulate and compare the different vaccination strategies under the constraints of low compliance, insufficient vaccine stockpile, contra-indications, side-effects, cost of vaccination, etc. In order to obtain robust conclusions, we evaluate the

performance of each studied vaccination strategy over a wide range of potential basic reproduction rate (R_0) values ($1.5 \leq R_0 \leq 30$).

It is important to note that though these simulations were carried out with smallpox in mind, the results are applicable to almost any infectious disease.

Mathematical Modeling

We adapted a classic SEIR model for the transmission of an infectious disease in a spatially heterogeneous population [6]. We assume that the smallpox virus is introduced into the Israeli population by one infective carrier. The model takes into account three stages of infection [12], assuming that each stage has a constant duration (d_1, d_2 and d_3 in Table 1 respectively): (1) infected, noninfective and vaccine sensitive; (2) infected, noninfective, vaccine-insensitive; (3) infected and infective. We define the basic transmission rate as: $\beta = \frac{R_0}{Nd_3}$, where N is the initial population size. A certain fraction of infective cases die of the disease, and the remaining fraction eventually recovers, becoming immune to reinfection. The model does not consider loss of immunity following vaccination or recovery from the disease [13].

We examine three vaccination policies as follows: (i) *Preliminary vaccination*: Different percentages of the population are vaccinated prior to attack, from 0 to 100% in increments of 5%; (ii) *One-time mass vaccination*: We define a “maximum vaccination capacity”, i.e. the maximum number of people that can be vaccinated per day (see Table 1). The percentage of capacity utilized (PCU) is varied between 0 and 100% in increments of 5%, and the duration of the vaccination campaign is varied between 1 and 15 days in increments of 1 day; (iii) *Pulse vaccination*: PCU is varied from 0 to 100% in increments of 5%, and the interval between cycles is varied from 50 to 2000 days in

increments of 50 days. Due to computational considerations, the duration of periodic vaccination campaigns is set as constant (3 days).

When applying *one-time mass vaccination* or *pulse vaccination* strategies, priority is given to individuals who have been exposed to the disease but can still be effectively vaccinated.

Strategy assessment: the "cost" of an outbreak

Theoretically, continuous vaccination of the entire population would be a foolproof means of preventing disease outbreak. However, as previously mentioned, this would not be the optimal strategy, due to the constraints imposed by the vaccinia vaccine [12]. In addition, it would probably not be reasonable to expect full compliance, especially over a long period of time after the initial outbreak. Therefore, an optimal strategy should not only prevent disease outbreak, but should allow as few individuals as possible to be vaccinated.

Vaccinating fewer individuals will not only prevent side effects, but will be less disruptive to routine. Thus, in order to assess the efficacy of a particular strategy, we determine a "cost" which takes into account the following factors: (i) number of deaths by infection (D_{inf}); (ii) number of infections (I); (iii) number of people vaccinated (N_{vac}); (iv) number of deaths resulting from vaccination ($Dvac$); (v) non-fatal side effects of vaccination (E); (vi) a "stress factor": number of post-attack vaccinations performed per day (S).

Each factor is attributed a "weight", and the cost C is calculated as follows:

$$C = (WD_{\inf} + \frac{W}{2} I + N_{vac} + \frac{W}{10} E + 2WD_{vac})(1 + Se^{-7}).$$

Where W is an "anchor weight" which represents the ratio between the weight of death by infection and the number of vaccinees. This value can be interpreted as the number of individuals a country is willing to vaccinate in order to save one life. Clearly, the resulting cost is closely dependent on the value of these weights. Therefore, to obtain robust results, we run simulations over a wide range of "anchor weights" (range: 1-10,000).

Model parameters are presented in Table 1, where demographic parameters apply to the Israeli population. Additional parameter values such as disease phase duration, etc. are taken from classic references. Clearly, disease and vaccine fatality rates are extremely influential when determining the tradeoff between the number of vaccinees and the number of deaths by disease. The model's possible sensitivity to these parameters is accounted for by varying the "anchor weight" applied when computing the cost (see above). As previously mentioned, a crucial parameter for assessing the effects of an outbreak is R_0. However, this parameter is also extremely difficult to estimate, as it is dependent on dynamic factors such as socioeconomic conditions [6, 12]. The basic transmission rate of smallpox has been estimated between 3 and 10 [14, 15], and values implemented in studies vary between 1.5 and 15 (e.g. [2, 3]). Instead of assuming a single value for R_0, we run simulations over a wide range of values, which vary between 1.5 and 30.

Results

As previously described, we simulated and compared various applications of *preliminary*, *one-time mass vaccination* and *pulse vaccination* strategies. Each simulated strategy design produced a final cost, a low cost signifying an efficient strategy, and a relatively high cost signifying an inefficient strategy. Figure 2 presents the distribution of

costs attained by each strategy simulated, for several values of R_0. Different costs for the same strategy are achieved by varying strategy design (e.g. a *preliminary vaccination* strategy in which 75% of the population is vaccinated may produce a lower cost than a *preliminary* strategy in which only 20% of the population is vaccinated). Figure 2 indicates that for $R_0 \leq 1.5$, all three vaccination strategies tested can potentially be efficient: if properly designed, they can reduce "cost" to 0. However, for $R_0 > 1.5$, *pulse vaccination* is the only strategy that succeeds in minimizing cost. This result holds true even for $R_0 > 10$, i.e. beyond the range of values that have been estimated. The same qualitative results are obtained even when the "anchor weight" is varied, provided that the weight chosen indicates vaccination to be preferable over non-vaccination (Figure 3).

Pulse Vaccination: finding the optimal design

Though *pulse vaccination* can potentially be an effective strategy, inappropriate strategy design is likely to produce high costs (see Figure 2). Therefore it is crucial to identify the optimal strategy design, in terms of PCU and the interval between "pulses". Figure 4 presents graphs of cost as a function of PCU and interval between pulses for several values of R_0.

As is evident from these graphs, for each R_0 value there is a "zone" (shaded areas) in which costs are low, and outside of which costs rise suddenly. This zone is defined by a diagonal contour, which means that there is a critical ratio of PCU to interval between pulses above which the *pulse* strategy will effectively reduce costs, and below which the strategy is inefficient. This critical ratio increases in direct relation to R_0 (Figure 5).

Discussion

Our study suggests that compared to *one-time mass vaccination* and *preliminary vaccination*, *pulse vaccination,* i.e. multiple vaccination campaigns with precisely calculated inter-vaccination intervals, is by far the most promising strategy for ensuring long-term population protection against smallpox. Simulations show that while *one-time mass vaccination* and *preliminary vaccination* may be effective vaccination strategies for a virus with a low basic reproduction rate ($R_0 \leq 1.5$), a *pulse vaccination* strategy can be designed so as to prevent disease outbreak for a broad range of R_0 values, and over a long period of time. We analyzed the effect of the two crucial *pulse* strategy parameters - namely the coverage level and the inter-vaccination intervals - on the final "cost" of the outbreak, and reached the conclusion that there exists a critical ratio between the percent of vaccination capacity utilized and the interval between vaccination campaigns above which the strategy will be effective, and below which the "cost" of attack will rise suddenly.

These results may carry significant implications for countries planning a response to a smallpox bioterrorist attack, or to an outbreak of any disease for which a vaccine exists, but about which little else is known. They indicate that given the realistic range of the disease's basic reproduction rate and the estimated compliance level, authorities can design a detailed, optimal vaccination plan for years to come. This plan would be extremely flexible and robust: if unexpected circumstances should arise, e.g. insufficient stockpiles or low compliance, maximum protection could still be ensured by modifying the interval between vaccination campaigns, or the number of people vaccinated at each campaign. Additionally, the pulse strategy would enable authorities to test their facilities, e.g. by initially vaccinating first responders, and only later the general public. This preparation would allow them to draw conclusions for further campaigns, increasing overall efficiency.

Clearly, for both bureaucratic and psychological reasons, the government of a country may prefer to provide a mass or preliminary vaccination policy. The pulse strategy would not have to replace either of these strategies. Rather, it could be used as a backup strategy, and as a long term policy, which would probably become increasingly necessary, as compliance may decrease after initial panic subsides. The critical ratio between the percent capacity utilized and the interval between pulses offers authorities quite a bit of leeway when deciding upon the timing and the magnitude of these campaigns.

Acknowledgments

This work was supported in part by the Chai Foundation, and in part by the Israeli Defense Forces.

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Table 1: Model Parameters

Parameter	**Value**	**Unit**	**Reference**
Initial susceptible population	6439200	individuals	
Initial infective population	1	individual	
Birth rate	$9e^{-4}$		
Death rate	$9e^{-4}$		
First stage disease duration (d_1)	4	days	[12]
Second stage disease duration ($d2$)	13	days	[12]
Third stage disease duration ($d3$)	21	days	[12]
Disease fatality rate	0.3		[12]
Vaccine fatality rate	10^{-6}		[12]
Rate of non-fatal vaccination side effects	0.001		[12]
Maximum daily vaccination capacity	$1.8e^{6}$	individuals	
Duration of pulse vaccination campaign	3	days	

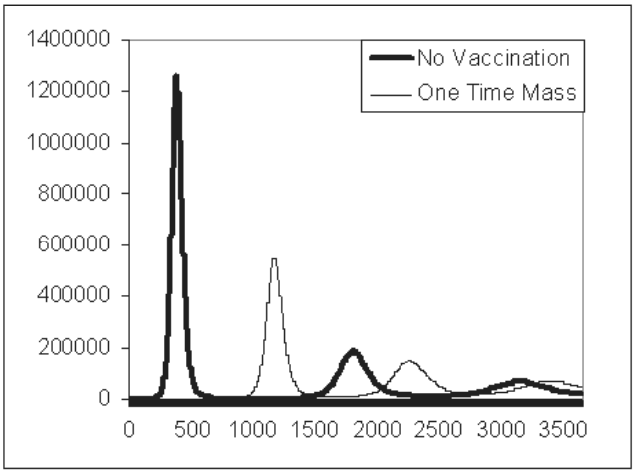

Figure 1: Simulation results of the adapted SEIR model: Number of infected individuals over time when disease is introduced into the Israeli population by one infective carrier. Thick line: natural disease dynamics (no vaccination strategy is implemented). Thin line: Disease dynamics after implementation of *one-time mass vaccination* strategy population is vaccinated at maximum capacity for three days following the attack).

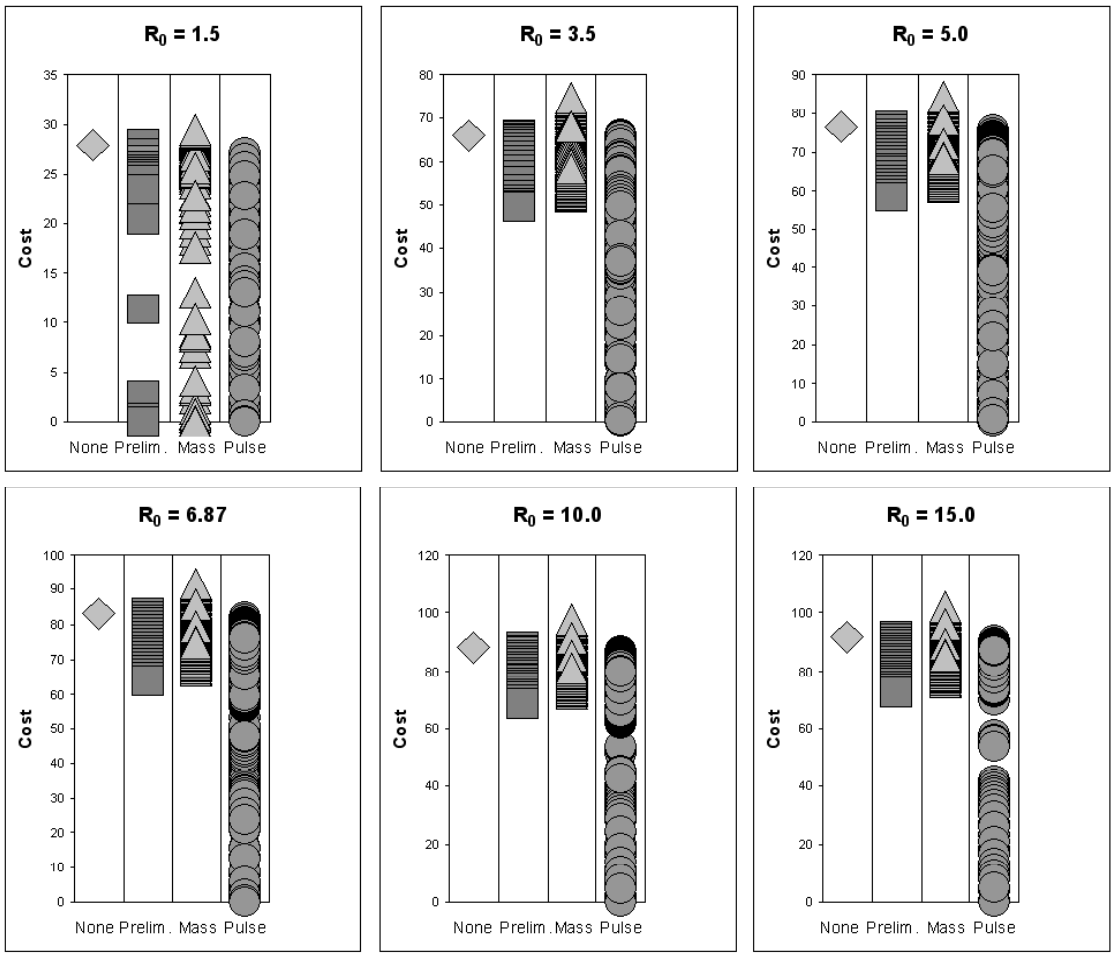

Figure 2: Costs produced by each simulated vaccination strategy for several values of R_0. Strategies tested: *preliminary vaccination* (squares), *one-time mass vaccination* (triangles) and *pulse vaccination* (circles). Different costs for the same strategy are obtained by varying strategy design.

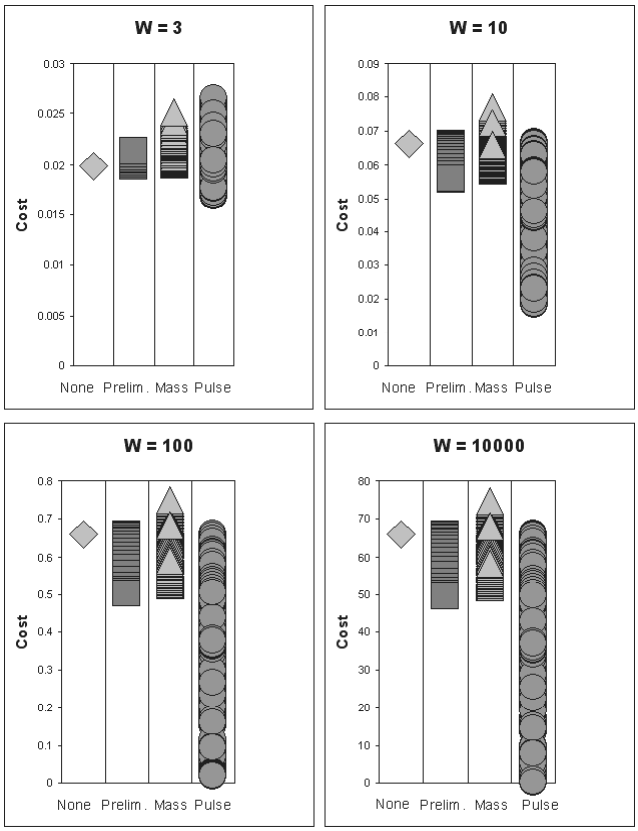

Figure 3: Costs produced by each simulated vaccination strategy for several values of the anchor weight (*W* = 3*;* 10*;* 100; R_0 is 3.5). As in Figure 2, strategies tested are *preliminary vaccination* (squares), *one-time mass vaccination* (triangles) and *pulse vaccination* (circles). Note that for *W* = 3, *pulse vaccination* is not more efficient than other strategies, but at the same time non-vaccination is as efficient as vaccination. For larger *W* values, *pulse vaccination* is more efficient.

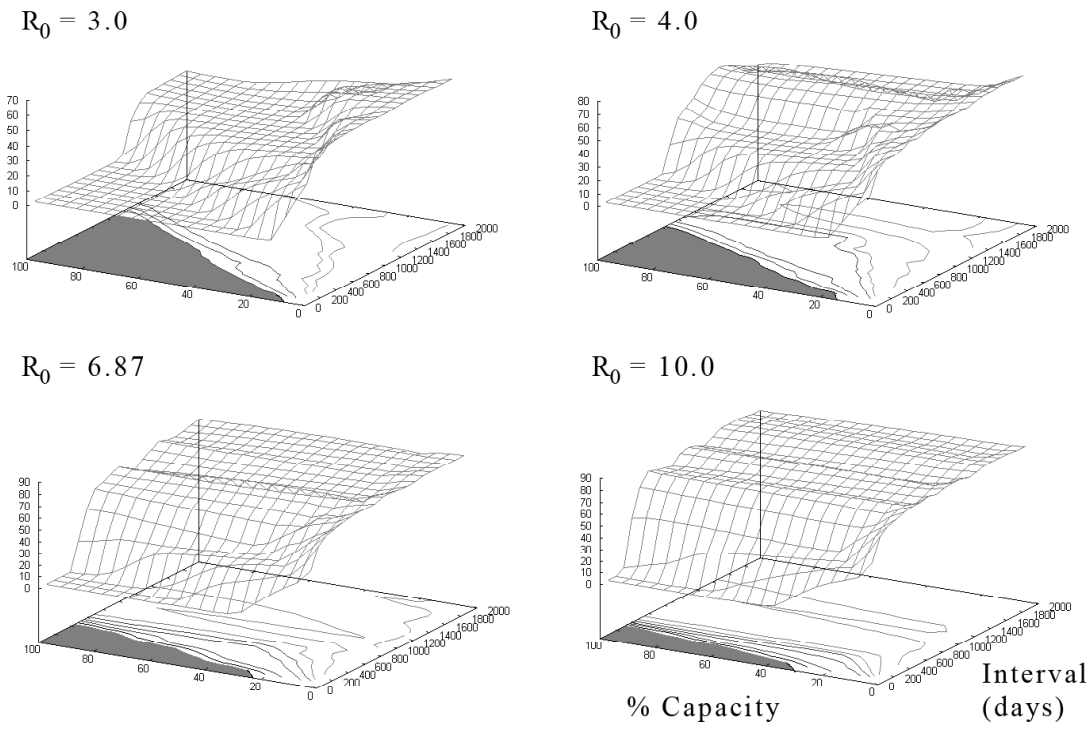

Figure 4: *Pulse vaccination*: cost as a function of percent vaccination capacity utilized and interval (in days) between pulses, for several R_0 values. There is a critical ratio (diagonal contour) between the two, above which the strategy will be effective (shaded area) and below which costs rise suddenly.

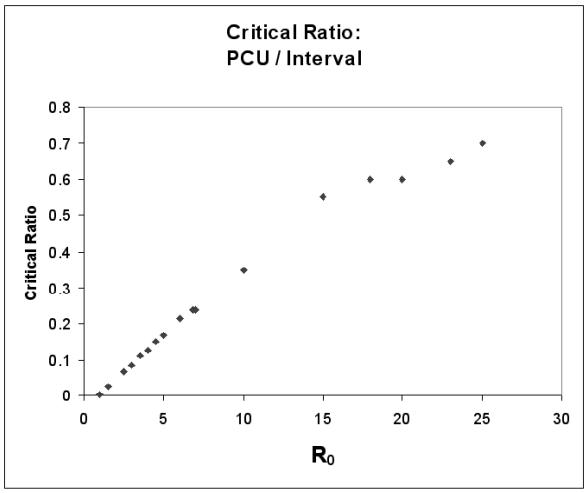

Figure 5: There is a critical ratio of percent vaccination capacity utilized to interval between pulses that must be exceeded in order for a *pulse* strategy to be effective. In graph: critical ratio as a function of R_0.