Optimal Temporary Vaccination Strategies for Epidemic Outbreaks

K. Muqbel, A. Dénes, and G. Röst

1 Introduction

Mathematical models of the transmission dynamics of infectious diseases are useful in gaining insights into the mechanisms of disease spread, in estimating key epidemiological parameters, in making predictions about the expected outcomes, and also in devising, evaluating, and comparing intervention strategies. Vaccination is the most successful and cost-effective preventive measure against many infectious diseases [2]. However, for some emerging diseases, the delay in identification of the pathogen (such as the particular strain), the time needed to develop novel vaccinations, and the limited capacity in production, distribution, and administration of vaccines may lead to a situation where vaccination programs run parallel in time with the disease outbreak. During the recent West African Ebola virus epidemic (2013–2016), at the beginning no licensed vaccines for the disease were available. The rVSV-ZEBOV vaccine was developed during the course of the epidemic [5]. Until the vaccine became available, other coordinated public health measures have been implemented [1]. A similar situation occurred also in many developed countries during the 2009 influenza H1N1 outbreak [4]. For instance, in Canada, due to the limited availability of the vaccine at the outset of the outbreak, and the inability to vaccinate the entire population simultaneously, a sequencing strategy has been developed that identified groups of different levels of priority [3]. In some countries a significant portion of the influenza vaccines were administered in the later phase of the epidemics [4], when the number of prevented cases per a unit of

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administered vaccine drops sharply. This raises the question of cost-effectiveness, and also suggests that the vaccination program should stop at some well defined point of the epidemics.

Motivated by this problem, in this study we propose a family of temporary vaccination strategies. For the sake of simplicity, we work in the basic SIR-framework. An intervention strategy will be defined by two parameters which determine the time interval it is applied as well as the intensity of vaccine administration. Our goal is to find out which strategy is the most cost-efficient, where costs are assigned to cases of infections and units of administered vaccines.

2 Specification of the *VUHIA* Strategy and Its Total Cost

We consider a constant population divided into susceptible ($S(t)$), infected ($I(t)$), and removed ($R(t)$) compartments. New infections occur with transmission coefficient β and infected individuals recover with rate α. Upon recovery, full immunity is assumed. Vaccination of susceptibles is included in the model with time dependent vaccination rate $v(t)$, to be specified later. Vaccination is assumed to be fully protective, thus vaccinated individuals are placed in the R-compartment as well. Hence, we consider the following system of differential equations:

$$\begin{aligned} S'(t) &= -\beta S(t) I(t) - v(t) S(t), \\ I'(t) &= \beta S(t) I(t) - \alpha I(t), \\ R'(t) &= \alpha I(t) + v(t) S(t). \end{aligned} \tag{1}$$

We are interested in the situation when a small number of infected hosts are introduced into a fully susceptible population, hence we consider initial data $S(0) = S_0$, $I(0) = I_0$, $R(0) = 0$, where I_0 is relatively small compared to the total population size $N = S + I + R$. The basic reproduction number is given by

$$\mathcal{R}_0 = \frac{\beta S_0}{\alpha},$$

however by normalizing the population size at $N = 1$ and with $I_0 << 1$, we have $S_0 \approx 1$ hence the reproduction number simplifies to $\mathcal{R}_0 = \frac{\beta}{\alpha}$. Epidemic outbreak occurs when $\mathcal{R}_0 > 1$.

The total cost (TC) of an outbreak will be assessed by considering two components, the disease burden and the cost of vaccination. Disease burden is calculated as the total number of infections during the course of the outbreak (denoted by $\tilde{I}$) multiplied by the cost C_1 of a single infection. Vaccination cost is calculated as the total number of administered vaccines (denoted by $\tilde{V}$) multiplied by the cost C_2 of a single vaccination. This way, for the total cost we have

$$TC \coloneqq C_1 \tilde{I} + C_2 \tilde{V}, \tag{2}$$

where

$$\tilde{I} \coloneqq \int_0^\infty \beta S(t) I(t) dt = \alpha \int_0^\infty I(t) dt, \tag{3}$$

$$\tilde{V} \coloneqq \int_0^\infty v(t) S(t) dt. \tag{4}$$

There has been a number of studies using optimal control theory to find the control function $v(t)$ that minimizes some (typically quadratic) cost function (see [7] for an example). However, a continuously changing $v(t)$, which is the common output from that approach, is not feasible to be realized as a public health policy. Hence, we aim to define a strategy $v(t)$ in a simpler way, and we assume that $v(t)$ is a piecewise constant function, taking values of either 0 (control is off), or some $p > 0$ (control is on). This means that we propose to apply vaccination with a given rate on some time interval. It remained to determine when to start and when to finish the intervention. We cannot expect in general that the intervention can start immediately, as the epidemic may not have been detected or the resources are not in place at the beginning of the outbreak. A reasonable assumption is that the starting point of interventions is when the number of infected individuals reaches a threshold value k, as it has been in [6]. However, in outbreak models using the same threshold to define the end of intervention may not be adequate, given that if k is too large then we finish vaccination too early, while when k is too small then vaccination may go on even when it does not have any significant impact on the epidemic any more. Instead, we propose to stop the vaccination when the number of infections starts decreasing, which is the same point when the number of susceptibles becomes so low that herd immunity has reached in the population. We call such an intervention a *VUHIA*-strategy of (k, p)-type, referring to *vaccinate until herd immunity achieved* with parameters (k, p).

In mathematical terms, the *VUHIA*-strategy of (k, p)-type is defined as follows. Let

$$v(t) = \begin{cases} 0, & t \notin J, \\ p, & t \in J, \end{cases}$$

where J is the intervention interval $J = [T_{\text{start}}, T_{\text{end}}]$ with

$$T_{\text{start}} = \min\{t \geq 0 : I(t) \geq k\}$$

and

$$T_{\text{end}} = \min\{t \geq 0 : \beta S(t) - \alpha \leq 0\}.$$

The time T_{start} is well defined as long as $k \in [I_0, I_{\max}]$, where $I_{\max}$ denotes the peak of the SIR-epidemic in the absence of any intervention. It is well known for the SIR model (with $N = 1$) that

$$I_{\max} = 1 - \mathcal{R}_0^{-1}(1 + \ln \mathcal{R}_0).$$

Clearly we have $I'(t_*) = 0$ when $S(t_*) = \alpha/\beta$, and $I'(t) < 0$ for any $t > t_*$ regardless we vaccinate or not at some $t > t_*$. Since the epidemic eventually always dies out, T_{end} is well defined, and (4) becomes

$$\tilde{V} := p \int_{T_{\text{start}}}^{T_{\text{end}}} S(t)dt. \tag{5}$$

Figure 1 depicts how the epidemic plays out with two different strategies. In one, we start vaccinating early with a low rate; in the other we start vaccinate later but with a higher rate. As Fig. 1 shows, it is unclear which of these two strategies is better, hence we will systematically explore this in the forthcoming sections by computer simulations.

3 The Relation Between the Total Cost and the Vaccination Rate

To see how the total cost depends on the vaccination rate, we shall consider various fixed k-s and vary p. The change in the total cost then depends on

$$\frac{d}{dp}TC(p,k) = C_1\frac{d}{dp}\tilde{I} + C_2\frac{d}{dp}\tilde{V}.$$

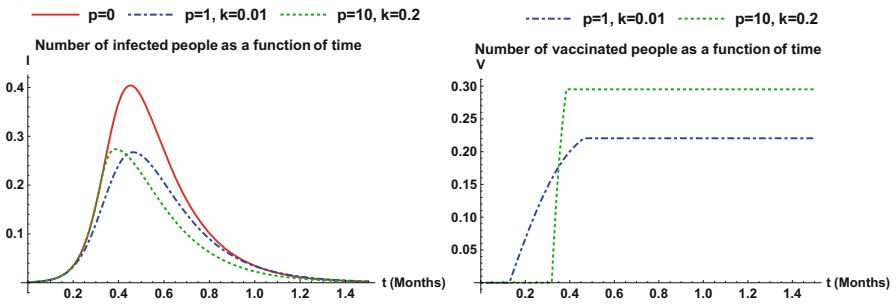

Fig. 1 The total number of infected (left) and vaccinated (right) people during the epidemic for different strategies. The epidemic parameters are $\mathcal{R}_0 = 4$, $\alpha = 6$, $\beta = 24$. On the left, the red curve is the epidemic curve in the absence of intervention. On the right, we can clearly see when the vaccination starts and stops

From Fig. 2 we can see that $\tilde{I}$ decreasing while $\tilde{V}$ decreasing in p, thus the sign of the rate of change of the total cost is determined by the ratio of C_1 and C_2 relative to the rates of change in $\tilde{I}$ and $\tilde{V}$. In the sequel we always normalize the cost of disease burden $C_1 = 100$, and we will vary C_2 to compare different scenarios. What we can see in Fig. 3 is that when $C_2 \ll C_1$, the total cost is decreasing in p, meaning that when vaccination is relatively cheap, we should vaccinate as high rate as possible. On the other hand, when $C_2 \gg C_1$, the total is increasing in p, meaning that when vaccination is very expensive relative to the disease burden, the strategy that give minimal cost is to not vaccinate at all. We can also see that the total cost is more sensitive to p when the vaccination rate is small. These results are what one would expect; however, there is a curious situation when C_1 and C_2 are of similar magnitudes: there is a possibility that the total cost is not monotone in p. This scenario is highlighted in Fig. 3, right. In this case, vaccination with a small rate yields a higher cost than no vaccination (see the red line); however, vaccination with a high rate yields a smaller cost. Let p_* be the value where the cost curve intersects the straight red line corresponding to cost of no vaccination. This means that if we are capable to vaccinate with a sufficiently high rate $p > p_*$, then we should do it, but if with our capacities and resources only a smaller rate $p < p_*$ can be achieved, it is better to not vaccinate at all.

4 The Relation Between the Total Cost and the Threshold Level

Next we consider how the total cost changes when we vary k for fixed values of p. Figure 4 shows that by increasing k, that is we start vaccinating later, the total number of infections increases while the total number of vaccinations decreases. Again, the change in total depends on how $C_1{:}C_2$ relates to $\frac{d\tilde{I}}{dk}{:}\frac{d\tilde{V}}{dk}$. This is depicted in Fig. 5 (left) for various values of C_2. Similarly as before, we see that if vaccination

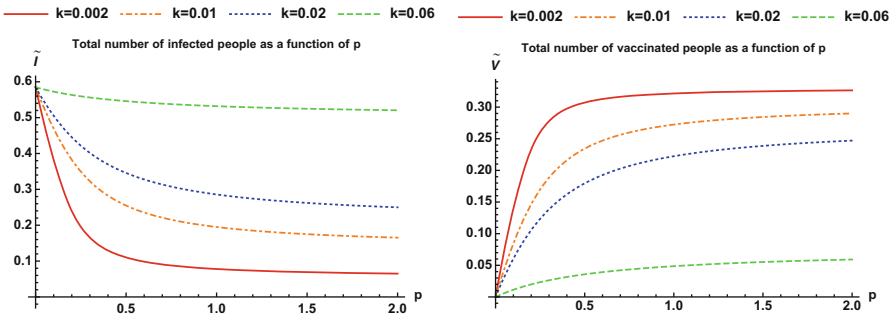

Fig. 2 The total number of infected (left), and vaccinated (right) people during the epidemic as a function of vaccination rate p. Parameters are $\mathcal{R}_0 = 1.5$, $\alpha = 6$, $\beta = 9$

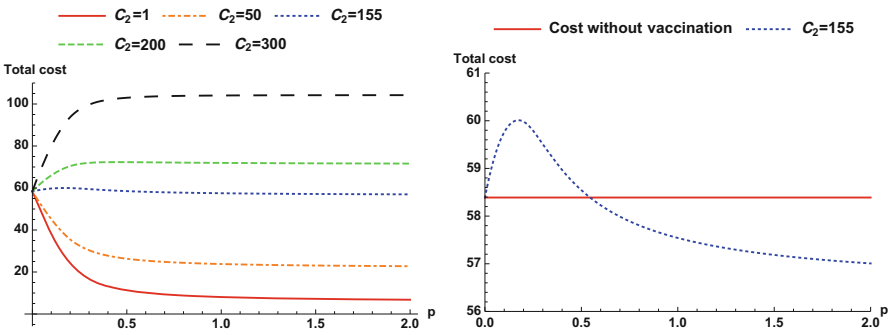

Fig. 3 The total cost as a function of p, for five different vaccination costs (left). In the right, the case $C_2 = 155$ is highlighted by zooming in. Parameters are $\mathcal{R}_0 = 1.5$, $\alpha = 6$, $\beta = 9$, $k = 0.002$

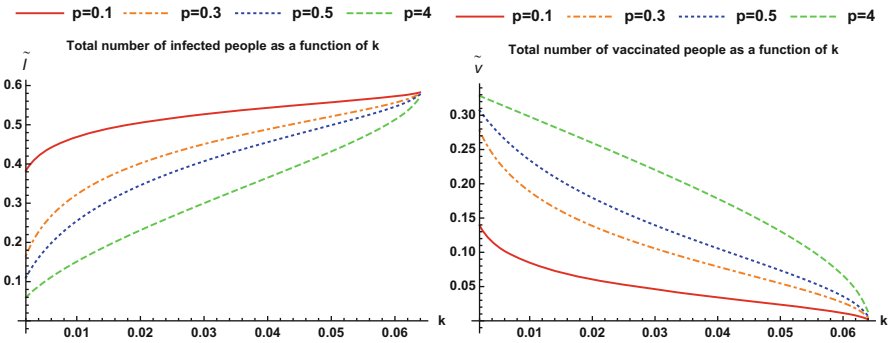

Fig. 4 The total number of infected (left) and vaccinated (right) people during the epidemic as a function of k. Parameters are $\mathcal{R}_0 = 1.5$, $\alpha = 6$, $\beta = 9$

is relatively cheap, it is better to start early, and when it is very expensive, it is better not to start at all. The graphs of all five curves meet at the right when $k \to I_{\max}$. When similar costs are assigned to disease burden and vaccination, we can see a non-monotone behavior, which is highlighted in the right of Fig. 5. The interpretation of this figure is that in the scenario of the blue dotted curve there is a k_*, such that if we are capable to start the intervention earlier that k_*, then we should as soon as possible. But, if for any reason we could not start the intervention before $I(t)$ reached k_*, then it is better not to vaccinate at all. This k_* is given by the intersection of the blue dotted curve with the horizontal red line.

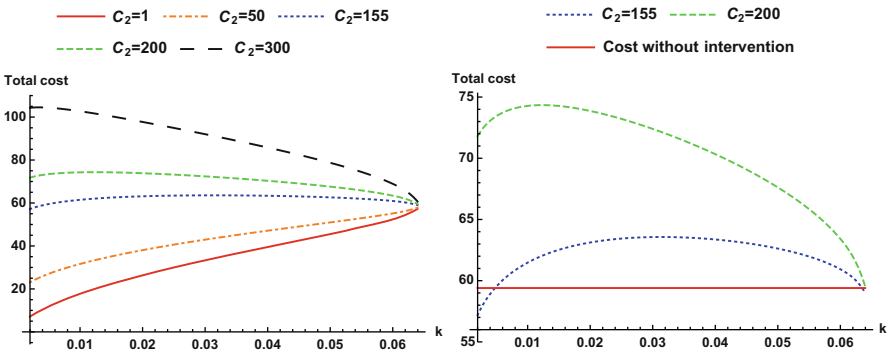

Fig. 5 The total cost as a function of k for five different vaccination costs (left). The cases $C_2 = 155$ and $C_2 = 200$ are highlighted by zooming in (right). Parameters are $\mathcal{R}_0 = 1.5$, $\alpha = 6$, $\beta = 9$, $p = 1.5$

5 Conclusions and Summary

We have proposed a family of temporary vaccination strategies in the framework of the SIR model. These strategies are characterized by parameters (k, p), where vaccination starts when the number of infected hosts reaches the threshold value k, and with rate p we continue vaccination until herd immunity is achieved (*VUHIA*). The advantages of the *VUHIA*-strategy are the following. First, it has a clear and meaningful definition: we start the vaccination with rate p when a threshold k is reached in the level of infection, and we stop the vaccination when the number of susceptibles drops below $\mathcal{R}_0^{-1}$, that is herd immunity achieved the number of infected will decrease anyway. Second, it is determined only by the parameters (k, p), hence all strategies from this family can be explored in a two dimensional parameter space.

We have assigned a total cost to each strategy composed of cost of disease burden and cost of vaccination, and systematically investigated the dependence of the total cost on the parameters. Essentially, we have found three types of behaviors:

(i) *vaccination cost is very low compared to the cost associated to disease burden*: in this case increasing the vaccination rate and start vaccination earlier reduce the total cost;
(ii) *vaccination cost is very high compared to the cost associated to disease burden*: in this case the optimal strategy is to not vaccinate at all;
(iii) *vaccination cost and disease burden cost are of similar magnitudes*: there may be non-monotone relationships between the vaccination rate, the starting threshold and the total cost.

These three typical behaviors are plotted into a heatmap in Fig. 6. In case (iii), it may happen that a better strategy is to start earlier but only if we can start sufficiently early, or, it is better to increase vaccination rate but only if we can increase it to a

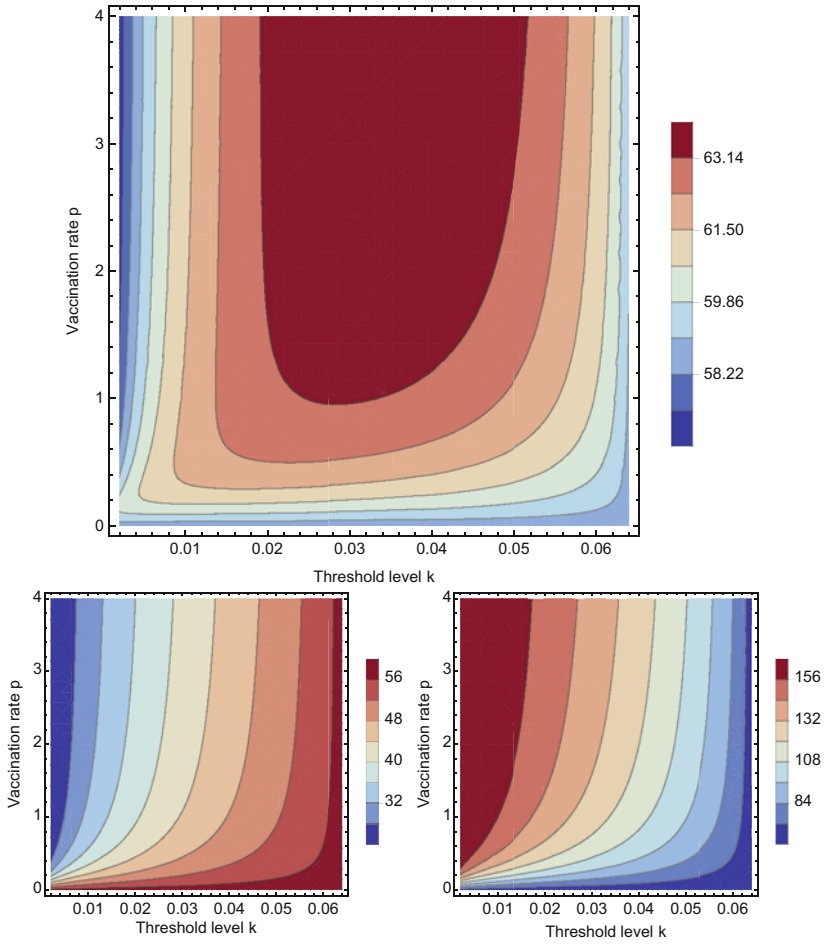

Fig. 6 Dependence of the total cost on (k, p) in three typical situations: $C_2 = 50 \ll C_1$ (bottom left), $C_2 = 500 \gg C_1$ (bottom right), and $C_2 = 155$ (top). Parameters are $\mathcal{R}_0 = 1.5$, $\alpha = 6$, $\beta = 9$, and $C_2 = 50{,}155{,}500$, respectively. The bottom plots show monotone cases, while in the top plot we can find non-monotonicity in both k and p

sufficiently high level. If we cannot meet those criteria, then the best decision is to not vaccinate. The top plot of Fig. 6 illustrates these intricate non-monotonicity properties.

Depending on the available resources and public health capacities, there may be constraints on the parameters, such as $k \geq k_{\min}$ and $p \leq p_{\max}$. The optimal strategy with such constraints can be found even in these cases from the graphs in Figs. 3, 5, and 6. It is very easy when the total cost depends monotonically on the parameters, for example with an upper bound on p and in the situation of $C_2 = 50$ in Fig. 3, the optimal strategy is always $p = p_{\max}$. In contrast, for $C_2 = 155$ (see Fig. 3 right),

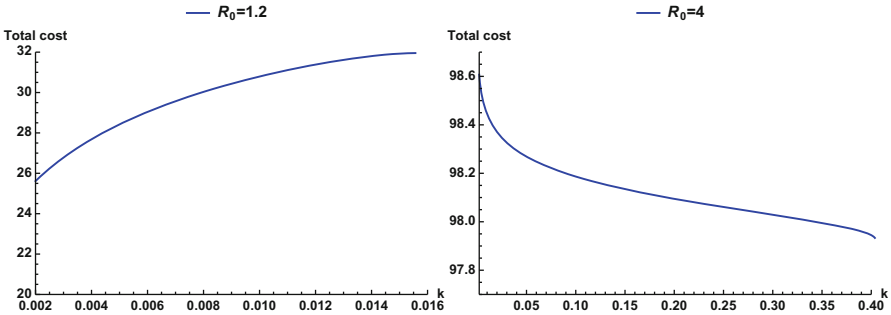

Fig. 7 Effect of $\mathcal{R}_0$ on the monotonicity of the cost curve. Parameters are $p = 0.25$, $C_2 = 115$, $\alpha = 6$ and $\beta = 7.2$, resp. $\beta = 24$. For $\mathcal{R}_0 = 1.2$, optimal strategy is achieved by vaccinating early, while for $\mathcal{R}_0 = 4$ it is better to not vaccinate at all

$p = p_{\max}$ is the optimal strategy only if $p_* < p_{\max}$, otherwise the optimal strategy is $p = 0$.

Another interesting phenomenon is depicted in Fig. 7, showing that for a fixed p, the monotonicity of the total cost in k can reverse varying the reproduction number. In that particular situation of Fig. 7, for a less contagious disease ($\mathcal{R}_0 = 1.2$), to minimize the cost vaccination should start as early as possible ($k \to 0$), while for a more contagious disease ($\mathcal{R}_0 = 4$) the lowest cost comes from not vaccinating at all ($k \to I_{\max}$).

Although this SIR vaccination model is certainly too simplistic to apply to any real outbreak, this simple epidemiological model already exhibits some surprising and counter-intuitive features, highlighting that in real applications with more complex models, a comprehensive mathematical investigation of the possible intervention strategies is really necessary.

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References

1. M.V. Barbarossa, A. Dénes, G. Kiss, Y. Nakata, G. Röst, Zs. Vizi, PLoS One **10**(7), 21 (2015). Paper e0131398
2. M. Drolet, É. Bénard, M. Jit, R. Hutubessy, M. Brisson, Value Health **21**, 1250–1258 (2018)
3. A. Durbin, A.N. Corallo, T.G. Wibisono, D.M. Aleman, B. Schwartz, P.C. Coyte, J. Infect. Dis. Immun. **3**(3), 40–49 (2011)
4. D. Knipl, G. Röst, Math. Biosci. Eng. **8**(1), 123–139 (2011)
5. S. Merler, M. Ajelli, L. Fumanelli, S. Parlamento, A. Pastore y Piontti, N.E. Dean, et al., PLoS Negl. Trop. Dis. **10**(11), e0005093 (2016)
6. Y. Xiao, X. Xu, S. Tang, Bull. Math. Biol. **74**(10), 2403–2422 (2012)
7. G. Zaman, Y.H. Kang, I.H. Jung, BioSystems **93**(3), 240–249 (2008)