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The impact of current infection levels on the cost-benefit of vaccination

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Abstract

When considering a new vaccine program or modifying an existing one, economic cost-benefit analysis, underpinned by predictive epidemiological modelling, is a key component. This analysis is intimately linked to the willingness to pay for additional QALYs (quality-adjusted life-years) gained; currently in England and Wales a health program is economically viable if the cost per QALY gained is less than £20,000, and models are often used to assess if a vaccine program is likely to fall below this threshold cost. Before a program begins, infection levels are generally high and therefore vaccination may be expected to have substantial effects and therefore will often be economically viable. However, once a program is established, and infection rates are lower, it might be expected that a re-evaluation of the program (using current incidence information) will show it to be less cost-effective. This is the scenario we examine here with analytical tools and simple ODE models. Surprisingly we show that in most cases the benefits from maintaining an existing vaccination program are at least equal to those of starting the program initially, and in the majority of scenarios the differences between the two are minimal. In practical terms, this is an extremely helpful finding, allowing us to assert that the action of immunising individuals does not de-value the vaccination program.

Introduction

Mathematical modelling has become an important tool in the study of infectious diseases and their control. Models have been used for both scenario planning (Anderson and May, 1983; McLean and Anderson, 1988; Ferguson et al., 2003) and real-time challenges (Baguelin et al., 2010), and enable policy makers to gain predictions associated with different courses of action. By far the most developed area of epidemiological modelling comes from the cost-effectiveness evaluations associated with vaccination (Williams et al., 1996; Trotter and Edmunds, 2002; Melegaro and Edmunds, 2004; Jit et al., 2008; Baguelin et al., 2010; van Hoek et al., 2011). Such model-based input is seen as vital in ensuring that health resources budgets are used most effectively.

In England and Wales, advice on vaccination programmes is provided by the JCVI

(Joint Committee on Vaccination and Immunisation) as an an independent Departmental Expert Committee and a statutory body. JCVI has strict criteria which determine if a vaccination programme can be recommended (JCVI, 2013): in addition to the vaccine being safe and effective, it must also be cost-effective. This is determined as a trade-off between vaccine costs and health benefits. Health benefits are measured in quality adjusted life years or QALYs (Mehrez, 1989); to be deemed cost-effective in England and Wales there needs to be at least 1 QALY gained for each £20,000 spent (where savings in medical costs can be offset against the costs of the vaccine and its administration). This relationship between health benefits and costs can then be translated into a threshold price (willingness to pay) for the vaccine, below which the vaccine will be considered cost-effective.

In practise this is a difficult calculation, where the QALY loss due to infection and the associated medical costs need to be calculated based on available health data and health-risks within the population (Richardson and Manca, 2004). However, in the context of this paper it is sufficient for us to assume that QALYs will be directly proportional to cases, and that the threshold willingness to pay will be proportional to the QALYs gained per vaccine delivered. Our two fundamental measures are therefore the amount of vaccine deployed and the total reduction in cases due to vaccination. In this way we remove much of the medical heterogeneity and instead concentrate on the relationship between vaccination and reduction in cases.

One fundamental aspect of health-economic theory is the concept of discounting – that future costs and benefits are worth less than current ones. This can either be viewed as providing some account of future uncertainties (it is difficult to estimate the impact of infection in 50-years times) or can be related to inflation and alternative ways of investing the health budget. In the UK a discounting rate of δ =3.5% per year is generally applied; this has the mathematical and conceptual advantage that all long-term integrals are finite, and accounts for the natural inclination that it is better to save one life now than one life in the future (all other things being equal). Therefore, when we talk about total future costs

and benefits, this discounting is naturally applied:

$$\text{Total Costs} = \int_0^\infty \text{Costs}(t)\, e^{-\delta t}\, dt \qquad \text{Total Benefits} = \int_0^\infty \text{Benefits}(t)\, e^{-\delta t}\, dt$$

Throughout this work we make a number of simplifying assumptions about the infection biology which allow us to analytically predict the impact of vaccination with a range of models. We generally assume SIR (susceptible-infectious-recovered) dynamics with life-long immunity, thus ignoring the delays caused by a non-infectious latent (or exposed) class (Anderson and May, 1992; Keeling and Rohani, 2008). We also assume a homogeneous population where the risk of infection is independent of risk of disease, such that we can assume that the health costs are directly proportional to the number of infected cases. Finally, we make the simplifying assumption that individuals are vaccinated at birth and that the vaccine provides 100% protection for life; although other levels of protection could be readily included although this would introduce an extra scaling factor. In the following section we build-up from simple ODE models, where some analytical traction is possible, to more complex age-structured models which have greater realism.

Methods

We begin by defining the simple SIR (Susceptible - Infectious - Recovered) ODE model, and consider the equilibrium points and their stability with and without vaccination. The basic ODE model with vaccination is given by:

$$\begin{aligned} \frac{dS}{dt} &= B(1-v) - \beta S I - dS \\ \frac{dI}{dt} &= \beta S I - \gamma I - dI \\ \frac{dR}{dt} &= \gamma I - dR \\ \frac{dV}{dt} &= Bv - dV \end{aligned} \tag{1}$$

where we assume that S, I, R and V are the proportions of the population that are susceptible, infectious, recovered and successfully vaccinated and immunised respectively (Anderson and May, 1979; May and Anderson, 1979; Anderson and May, 1992; Keeling and Rohani, 2008). Other parameters are: B the population-level birth rate, d the natural death rate, β the transmission rate of the pathogen from infectious to susceptible individuals, γ the recovery rate and v is the proportion of new-borns that are protected by vaccination. In what follows, we make the simplifying assumption of constant population size ($B = d$, $S + I + R + V = 1$), and because we are assuming that both infection and vaccination confer complete life-long immunity, it is appropriate to amalgamate the R and V classes and simply concentrate on the 2-dimensional system given by S and I.

For this model, the basic reproductive ratio R_0 is a crucial parameter (Anderson and May, 1979; May and Anderson, 1979; Anderson and May, 1992; Keeling and Rohani, 2008): when $R_0 > 1$ the infection can invade and spread in the absence of vaccination; whereas when $R_0 < 1$ any invasion is doomed to deterministic failure. For this simple, the basic reproductive ratio is defined as:

$$R_0 = \frac{\beta}{\gamma + d} \tag{2}$$

Throughout we will make the obvious assumption that we are only concerned with controlling infectious diseases with $R_0 > 1$.

One equilibrium point of the system of SIR equations is the disease-free state ($S^* = (1-v)$, $I^* = 0$), which is only stable if $v > 1-(\gamma+d)/\beta$. This threshold ($v_c = 1-(\gamma+d)/\beta = 1 - 1/R_0$) defines the point at which the amount of on-going vaccination is sufficient to eradicate the infection. The alternative endemic fixed point (which is stable if $v < v_c$) is given by:

$$\begin{aligned} S^* &= \frac{1}{R_0} = \frac{\gamma + d}{\beta} \\ I^* &= \frac{d(1-v)}{\gamma + d} - \frac{d}{\beta} = \frac{d}{\beta}((1-v)R_0 - 1) \end{aligned} \tag{3}$$

For clarity in what follows we use I_0^* and I_v^* to refer to the endemic level of infection with and without vaccination.

We next consider the stability of the endemic equilibria (I_v^*); this is given by the Jacobian at the fixed point:

$$J = \begin{pmatrix} -\beta I_v^* - d & -\beta S_v^* \\ \beta I_v^* & \beta S_v^* - \gamma - d \end{pmatrix} = \begin{pmatrix} -(1-v)R_0 d & -(\gamma + d) \\ ((1-v)R_0 - 1)d & 0 \end{pmatrix}$$

Hence the eigenvalues Λ obey:

$$\Lambda^2 + \Lambda(1-v)R_0 d + (\gamma + d)((1-v)R_0 - 1)d = 0$$

and the solutions are:

$$\Lambda_v = -\frac{(1-v)R_0 d}{2} \pm \frac{\sqrt{(1-v)^2 R_0^2 d^2 - 4(\gamma + d)((1-v)R_0 - 1)d}}{2} \tag{4}$$

Making the standard assumption that the birth and death rates are low compared to other parameters ($B = d \ll 1$) (Anderson and May, 1979; May and Anderson, 1979) and that the vaccination rate is significantly below the critical level for eradication ($v < v_c$), the eigenvector is complex and hence the dynamics close to equilibrium are damped oscillatory cycles (Figure 1).

Another interesting case to be considered is the limit when v approaches the critical value for eradication v_c; in this limit $I_v^* \to 0$ and $\Lambda_v \to -d$ and 0. In this limit the dynamics are no-longer oscillatory and the fixed point is neutrally stable. Finally these two regions (where the approach to the fixed point is oscillatory and non-oscillatory) are separated by the point v_{max} which is when the square-root in equation (4) is zero.

Economic Costs and Benefits

As stated above, the decision about where a vaccination programme is cost-effective is made by balancing the health benefits against the financial costs of vaccination. The health benefits of a vaccine program is measured as the reduction in the number of QALYs lost over time with a discounting factor (δ) applied. This discounting factor (generally set at 3.5% per year in England) ensures that the long-term costs and benefits remain finite, and account for the natural inclination that it is better to save one life now than one life in 50 years time (all other things being equal). For a simple homogeneous model the discounted QALY loss from infection is directly proportional to the discounted number of cases, which itself is proportion to the discounted proportion of infected individuals in the population, over all time. We therefore consider two important quantifies $I_v(t|S^0, I^0)$ and $I_0(t|S^0, I^0)$: the dynamics of infection with and without vaccination starting at the initial condition $S(0) = S^0$, $I(0) = I^0$. The main quantity of interest, the change in discounted QALYs over time with and without vaccination, is then proportional to the discounted change in cases with and without vaccination:

$$\Delta\text{QALY} \propto Z_v(S^0, I^0) = \int_0^\infty e^{-\delta t} I_0(t|S^0, I^0)dt - \int_0^\infty e^{-\delta t} I_v(t|S^0, I^0)dt$$

Figure 1a and 1b demonstrates this effect graphically: showing the dynamics of beginning at either the vaccinated or unvaccinated equilibrium, and the associated discounted saving (or gain) of cases. Here Figure 1a shows a prospective analysis of the number of cases averted at the cost of introducing vaccination, while Figure 1b shows a contemporary analysis of the number of additional cases caused by the cost-saving measure of stopping a successful vaccination programme. In this extreme example we have taken a high birth-rate, a low reproductive ratio and a high recovery rate to highlight the oscillatory infection dynamics.

The cost of any vaccination scheme, is a mixture of four factors integrated over all time: the total discounted cost of the vaccine; the total discounted cost of administering the vaccine; and any costs associated with adverse reactions to the vaccine (which should

be minimal); and any cost savings due to a lower number of cases and therefore less medical treatment. The first three of these are proportional to the amount of vaccine administered (v), while the latter is proportional to the change in cases Z_v. Therefore, all relevant quantities (such as costs per QALY gained, or threshold prices for the vaccine) are formulated in terms of simple relationship between v and Z_v.

Simple Analytics, below eradication threshold

Using the above formulae (equations 1, 3 and 4) with the assumption that the dynamics close to endemic equilibrium are oscillatory both with and without vaccination (that is, v is significantly below both v_{max} and v_c), we can calculate the expected benefit of any vaccination program. In particular, if we consider the eigenvalues to be of the form:

$$\Lambda_v \;=\; -A_v \pm i\omega_v$$

then the infection dynamics can be approximated as:

$$I_v(t|S^0, I^0) \;\approx\; I_v^* \;+\; (I^0 - I_v^*)\exp(-A_v t)\cos(\omega_v[t+\theta])$$

Here we can take $\theta = 0$, if we make the simplifying assumption that the dynamics begin from an equilibrium (steady-state) level of infection either with or without vaccination. In which case, we can drop the dependence on S^0 and our quantity of interest (which is proportional to the change in discounted QALYs due to a vaccination program) is approximated by:

$$\begin{aligned} Z_v(I^0) \;&\approx\; \int_0^\infty e^{-\delta t}\left[I_0^* \;+\; (I^0 - I_0^*)\exp(-A_0 t)\cos(\omega_0 t)\right]dt \\ &\qquad - \int_0^\infty e^{-\delta t}\left[I_v^* \;+\; (I^0 - I_v^*)\exp(-A_v t)\cos(\omega_v t)\right]dt \\ &\approx\; I_0^*\int_0^\infty e^{-\delta t}\left[1 - \exp(-A_0 t)\cos(\omega_0 t)\right]dt \;-\; I_v^*\int_0^\infty e^{-\delta t}\left[1 - \exp(-A_v t)\cos(\omega_v t)\right]dt \\ &\qquad + I^0\int_0^\infty e^{-\delta t}\left[\exp(-A_0 t)\cos(\omega_0 t) - \exp(-A_v t)\cos(\omega_v t)\right]dt \end{aligned} \tag{5}$$

We are now in a position to return to our original question: what is the impact of evaluating vaccination programs at different initial levels of infection? In particular we are interested in:

$$\Delta Z_v \;=\; Z_v(I_0^*) - Z_v(I_v^*)$$

the difference between evaluating a vaccination program before it has begun compared to once it has reached vaccinated equilibrium. From equation (5) it is clear that the dependency on the initial starting level of infection (I^0) can be readily separated:

$$\begin{aligned}\Delta Z_v &= [I_0^* - I_v^*]\int_0^\infty e^{-\delta t}\left[\exp(-A_0 t)\cos(\omega_0 t) - \exp(-A_v t)\cos(\omega_v t)\right]dt \\ &= [I_0^* - I_v^*]\left(\frac{A_0+\delta}{(A_0+\delta)^2+\omega_0^2} - \frac{A_v+\delta}{(A_v+\delta)^2+\omega_0^2}\right) \end{aligned} \tag{6}$$

Using the equilibrium values calculated in equation 3 and the real and imaginary eigenvalues calculated in equation 4, the first order terms in ΔZ_v can be found assuming that both d and δ are small compared to other terms:

$$\Delta Z_v = \frac{(d+\delta)v^2R_0^2}{2[(1-v)R_0-1][R_0-1]\gamma^2} + O(d^2,\delta^2) \tag{7}$$

which we expect to be relatively small (as both d and δ are small, and the level of vaccination is well above the erradication threshold $v > 1 - 1/R_0$).

We now wish to contrast ΔZ_v with $Z_v(I_0^*)$, that is the value calculated before the vaccination program begins, again assuming d and δ are small:

$$Z_v(I_0^*) \;=\; \frac{vd}{\gamma\delta} \;-\; \frac{d(1-v)R_0 + 2\delta}{2[(1-v)R_0-1]\gamma^2} \;+\; O(d^2,\delta^2) \tag{8}$$

Comparing the approximations for ΔZ_v and $Z_v(I_0^*)$ from equations 7 and 8, and assuming that the birth and death rate and also the discounting rate are small and of the same order, we find that ΔZ_v is expected to be small whereas $Z_v(I_0^*)$ is of order one. Hence, for much of parameter space, the differences due to the initial starting level of infection are minimal compared to the magnitude of Z_v itself, and such differences only arise through differences in the eigenvalues at the vaccinated and unvaccinated equilibria.

An alternative quantity to examine is the relative difference between the expected benefits of vaccination if it is calculated beginning at the vaccinated equilibrium compared to being calculated from the non-vaccinated equilibrium.

$$\frac{Z(I_v^*)}{Z(I_0^*)} = 1 + \frac{v\delta(d+2\delta)R_0}{[(1-v)R_0-1][R_0-1]\gamma d} + O(d^2,\delta^2) \tag{9}$$

Some what surprisingly, and against initial intuition, we find that $Z(I_v^*) > Z(I_0^*)$; that is the benefits of continuing vaccination are greater than the benefits of starting vaccination – assuming that we are above the eradication threshold.

Simple Analytics, at eradication threshold

It is clear that many of the above formula break down as we approach the critical vaccination threshold (that is $(1-v)R_0 \to 1$). We therefore explicitly consider this limit, noting that the dynamics about $I_v^* = 0$ are no-longer oscillatory. In this case, we find:

$$\Delta Z_v = \frac{d(R_0-1)}{(d+\delta)\gamma R_0} + O(d,\delta) \tag{10}$$

$$Z(I_0^*) = \frac{d^2(R_0-1)}{\delta(d+\delta)\gamma R_0} + O(d,\delta) \tag{11}$$

$$\frac{Z(I_v^*)}{Z(I_0^*)} = 1 + \frac{\delta}{d} + O(d,\delta) \tag{12}$$

Suggesting similar qualitative behaviour with $Z(I_v^*) > Z(I_0^*)$.

Numerical Results

While the analytic approximations (equations: 7 - 12) provide the insight that the impact of the initial conditions is likely to be small, only through numerical evaluation of either these approximations, or through numerical integration of the underlying ODEs, can we gain a full appreciation of the likely behaviour. Figure 2a shows the behaviour of $Z_v(I_v^*)$ against $Z_v(I_0^*)$ as the vaccination rate v changes, calculated from equation () using analytic

forms for the integrals. As expected from equation (9), for the majority of vaccine uptake levels (v) there is relatively little difference between the two values of Z_v; it is only as we approach $v = v_{max}$ when the eigenvalues becomes real, that large discrepancies appear – in particular $Z_v(I_0^*)$ first sharply decreases as $v \to v_{max}$ before increasing slightly for $v_{max} < v < v_c$. However, for values of v up to 95% of the eradication threshold (marked by black crosses), there is relatively little difference between the two values, although with $Z(I_0^*) < Z(I_v^*)$ as predicted by equation (9).

The obvious next-step is to numerically integrate the SIR ODEs (equation (1)) to understanding the role of assumptions needed to gain analytical traction: in particular, the implications of assuming that the dynamics are locally sinusoidal. Here we impose $S(0) = 1/R_0$, which matches our theoretical assumption that the dynamics are at the vaccinated or unvaccinated equilibria. Again we consider a range of vaccination levels up to the eradication threshold, with the greatest concentration of points near this threshold. For the true ODE dynamics, we find that the behaviour is much simplified. Throughout the entire range of vaccination rates, the two measures of vaccination benefit $Z(I_0^*)$ and $Z(I_v^*)$ calculated from the ODE solutions are in very close agreement, although as predicted by our theory $Z(I_0^*) < Z(I_v^*)$. For the three sets of (typical) epidemiological parameters used in figure 2, we find remarkably close agreement between the ODE results (Figure 2b) and the numerical evaluation of our approximations (Figure 2a) for all levels of vaccination up to 95% of the eradication threshold.

We take this numerical assessment one stage further, by performing a sweep of parameter space. We therefore examine a wide region of parameter space for the two epidemiological parameters (β and γ, ensuring $1 < R_0 < 10$) and vary the level of vaccination v although ensuring it is above the critical threshold. We again compare $Z_v(I_0^*)$ with $Z_v(I_v^*)$ but do this through the percentage change between vaccinated and unvaccinated equilibria, captured by parameter P_v:

$$P_v = 100 \times \frac{Z_v(I_v^*) - Z_v(I_0^*)}{Z_v(I_0^*)} \tag{13}$$

which is also equal to the percentage change in the health benefit (discounted QALYs gained) calculated from the two equilibria. Figure 3 shows that this percentage change, is generally small and positive (as expected from the above theoretical calculations, equation (7)), and can be related to the dominant eigenvalue at the vaccinated equilibrium Λ_v. In particular, when both the real and imaginary parts of Λ_v are small (which happens when $v \approx v_c$) , the percentage change attains its highest value.

Finally, we return to the motivating question: comparing the benefit of vaccination before a campaign has begun and after it has been implemented for some finite time, T; relaxing the assumption that the calculations start from an equilibrium. We therefore modify the percentage change formulation and consider $Q_{v,T}$, the percentage change in the health benefit between starting at the non-vaccination equilibrium and starting once the vaccination scheme has been in operation for time T. Figure 4 shows these results for three different models. The top graph re-displays the results from Figure 3, noting that $P_v = Q_{v,\infty}$. The centre graph uses the same ODE formulation (equation (1), but considers finite time, T, between 1 and 10 years. Finally the lower graph uses an age-structured model (Schenzle, 1984) (see Supplementary Material for full formulation), and so is comparable to the types of model often used to address applied policy questions in the health economics of vaccination. In all three examples $Q_{v,T}$ is generally small and positive; for example using the simple ODE (figure 4b) model 95% of the values of $Q_{v,T}$ lie between -0.05% and 0.2%. For the age-structured model (figure 4c) the percentile range increases (95% of the values lie between -12% and 11%) which we attribute primarily to the delay between vaccination at birth and the peak of epidemiological transmission in school children. We also note that for this age-structured model, the majority of the declines in health benefit (negative values of $Q_{v,T}$) occur for low levels of vaccination and hence low levels of $Z_v(I_0^*)$, suggesting that these are of limited practical relevance.

Discussion

Using models of differing complexity – from analytical approximations to age-structured ODES – we have addressed the critical question of how a cots-benefit analysis of vaccination might be influenced by when this calculation in undertaken. Usually economic analyses are conducted prior to the start of a vaccination program to evaluate its value for money; however as new information becomes available it may be necessary to re-evaluate the program. There are two ways in which this can be done: a retrospective analysis that calculates costs and benefits from the start of the program, but includes the new information; or simply a contemporary analysis from the current point in time going forwards. Essentially it is these two different analyses that are compared here. We note that in some cases a the generation of new (finer resolution data) may mean that only a contemporary analysis is possible. There is understandable concern that a contemporary (rather than retrospective) re-evaluation could be biased by the lower levels of infection that arise from the presence of a vaccination program. This would mean that programs which were cost-effective at pre-vaccination disease prevalences might lose this cost-effectiveness over time, leading to a unstable situation where doing the most cost-effective action might lead to alternating patterns of vaccination and non-vaccination. In contrast, our analyses show the reassuring picture that the cost-benefit analysis is relatively unchanged due to an existing vaccination scheme; if anything there is a slightly greater benefit for retaining an existing scheme than starting a new one. In practical terms this means that once a decision to begin vaccination has been made, we do not enter a cycle of switching the program off and on as the levels of infection vary – rather the potential for future cases means that vaccination must be maintained. This finding is surprisingly robust to different epidemiological parameters, demographic rates, vaccine up-take and the economic discounting rate.

As with any modelling study there are elements of reality that are not captured. Mutliple important factors should be considered before this is applied to any practical problem. Firstly, this analysis only informs about a single vaccination program, it does not provide any information when there are two programs targeting different risk or age groups. For

example, suppose we consider vaccination of two risk groups: A and B; then whether or not group A has been part of an existing program will influence the cost-effectiveness of vaccinating group B. To place this in practical and current terms, the proposed vaccination of boys against HPV (Human Papilloma Virus) (Tam and Sturgis, 2016) is strongly influenced by the existing program in girls (Datta et al., 2017).

Secondly, the models used are deterministic and only work well away from the critical vaccination threshold, v_c. As the population nears herd-immunity when the infection may go locally extinct, re-introduction of the pathogen plays a major role as does the potential extra costs of a large sudden outbreak. The 2013 outbreak of measles in Swansea illustrates this point (Moore et al., 2015; Walsh et al., 2015), the ensuing epidemic that followed the stochastic introduction of measles into the local population had a devastating public-health impact, justifying the need for continued measles vaccination even when cases are low.

As shown in Figure 4c, the natural delays introduced by age-structure can influence the accuracy of the analysis, especially if there are long delays between the age of vaccination and the peak of transmission. Again, vaccination against HPV provides a prime example: vaccination is usually targeted at 12-year-old girls whereas the peak of transmission is generally in those aged around 20 – this lag means that even if vaccination is stopped, cases continue to decline for several year (Datta et al., 2017) which has a significant impact on the calculated cost-effectiveness.

Throughout we have implicitly assumed that the vaccine confers complete immunity throughout the programme. In practice no vaccine offers complete protection and therefore our vaccination level v should be considered as the proportion of new-borns that are successfully immunised generating life-long immunity. Of greater concern is the issue of vaccine escape (Pérez-Sautu et al., 2011) or strain replacement (Shiri et al., 2017), where the effectiveness of the vaccine may wane over time due to evolutionary adaptation, either in terms of the emergence of new strains or the increase in existing strains not covered by the vaccine. In such cases, the benefits of continuing a vaccination campaign may diminish through time, often prompting new broader range vaccines to be introduced.

The modelling and analytical results within this paper are all based upon the endemic equilibria and stability for SIR-type dynamics. The results from the age-structured model

(Figure 4c) indicate that the general results are also likely to hold for other more complex infection dynamics (such as SEIR) where there is lifelong immunity. Questions regarding SIS-type dynamics and waning immunity both from infection-derived and vaccine-derived immunity require more complex models, which may need to include differential rates of waning immunity and the implementation of booster vaccines. The analysis of this more complex scenario is beyond the scope of this paper and likely requires bespoke modelling matched to the situation under investigation.

A more complex situation where our analysis does provide an understanding is when there is an initially high cost at the beginning of the campaign; this lowers the cost-effectiveness of starting vaccination and hence increases the relative cost-effectiveness of maintaining vaccination once the programme is underway. This high initial difference could be because of the costs surrounding the start-up of a new program. Alternatively, many new programmes are associated with catch-up campaigns (which aim to rapidly increase herd immunity) but are less cost-effective than vaccination at birth.

Finally, in any practical situation, a bespoke model is generally needed to capture all the details of the epidemiology (e.g. (Trotter and Edmunds, 2002; Melegaro and Edmunds, 2004)) such as age-dependent susceptibility and costs (due to differential health impacts and risk factors of adverse effects) or the need for multiple booster vaccines to maintain immunity. Hence, while these results strongly suggest that health-economic findings are likely to be independent of current vaccination levels, full mechanistic models, carefully matched to available data, are needed to inform policy decisions.

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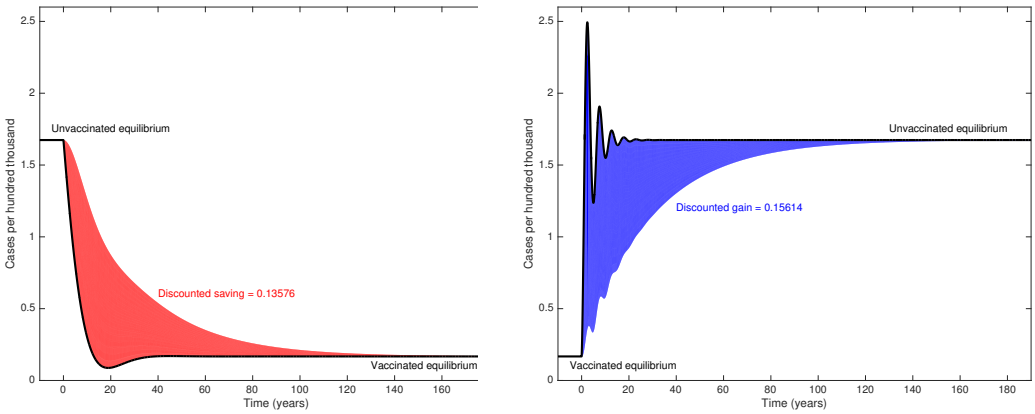

Figure 1: Schematic examples of (a) the discounted savings accrued over time starting at the unvaccinated equilibrium and introducing vaccination at time zero (b) the discounted costs accrued over time starting at the vaccinated equilibrium and stopping vaccination at time zero. In both figures oscillatory dynamics are observed, but these are more pronounced in graph b. (Parameters are $B = d = 0.122$ per year, $R_0 = 2$, $\gamma = 10$ per day, $\delta = 3.5\%$ per year.)

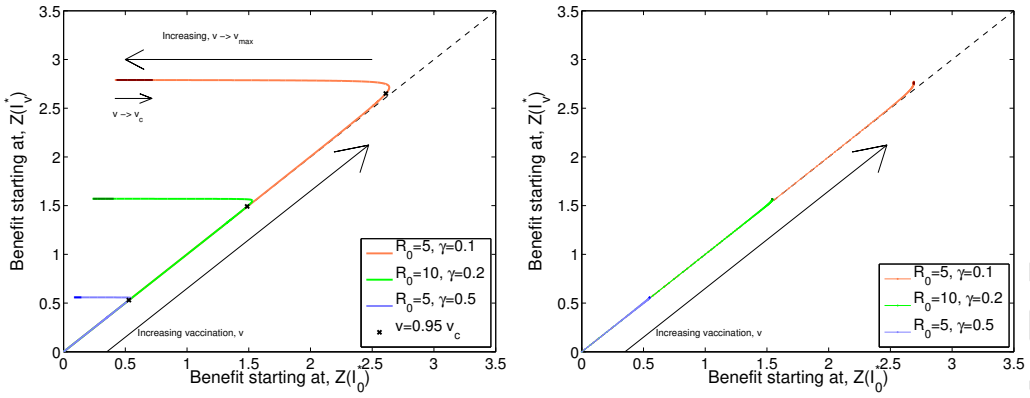

Figure 2: The difference in the discounted benefits of vaccination; plotting the benefit of introducing vaccination to an unvaccinated population (x-axis) and the benefit of retaining vaccination for a population that is at its vaccinated equilibrium (y-axis). (a) Theoretical results from equations 9 and 12; (b) Numerical results from solving the ODEs over the same parameter ranges. The point at which 95% of the critical vaccination level ($0.95v_c$) is marked with a cross, and points between v_{max} and v_c are darker coloured. For the numerical results (b) it is clear that the theoretical behaviour close to v_c does not occur, and the benefit of vaccination is relatively independent of the initial condition. (Parameters are $B = d = 0.0122$ per year, $\delta = 3.5\%$ per year.)

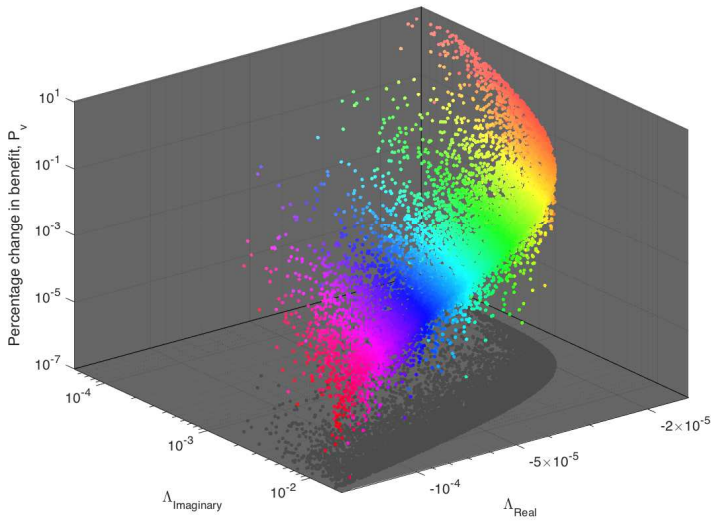

Figure 3: Relative percentage difference in the benefit of vaccination depending of the initial condition (vertical axis), against the real and imaginary components of the eigenvalue at the vaccinated equilibrium. From this graph it is clear that the eigenvalue is the major determining factor, and that the benefits for remaining at the vaccinated equilibrium are consistently greater than the benefits of starting vaccination from the unvaccinated equilibrium. (Parameters are $B = d = 0.0122$ per year, $\delta = 3.5\%$ per year, $\gamma \in (0, 1)$, $R_0 \in (1, 10)$, $v \in (0, v_c)$.)

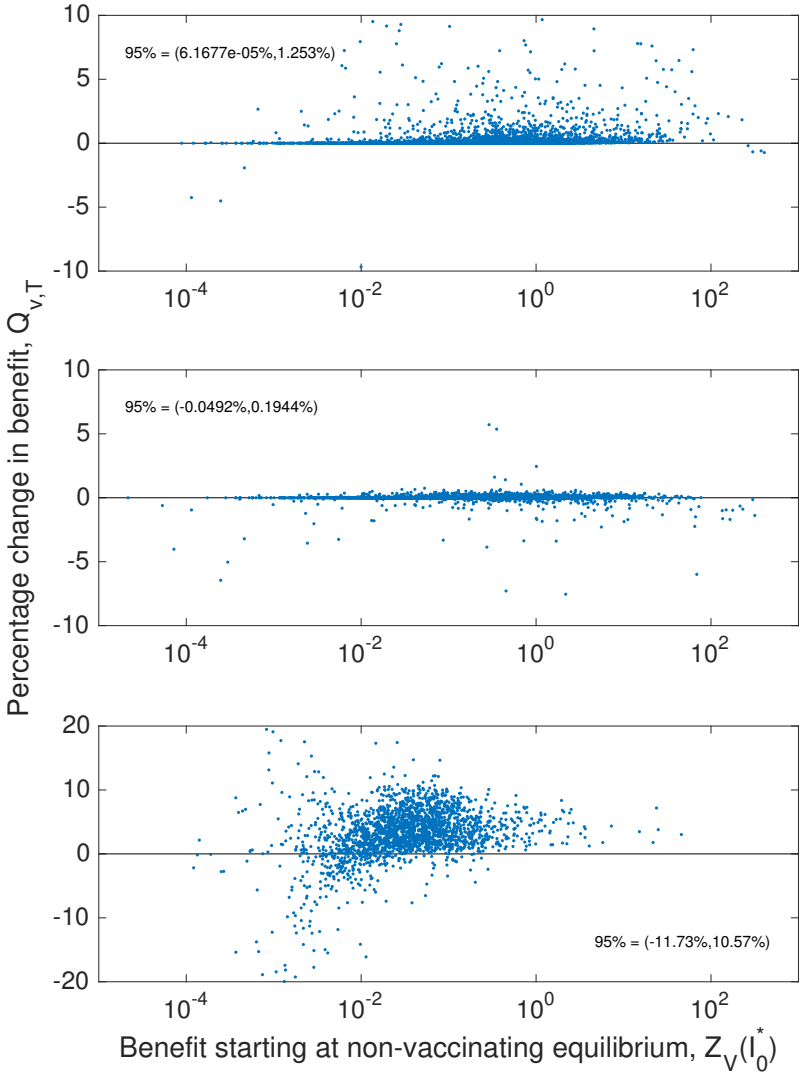

Figure 4: Relative percentage difference in the benefit of vaccination depending of the initial condition (y-axis), against the benefit of vaccination starting at the initial conditions (x-axis). Graph (a) compares vaccinated and unvaccinated equilibria of a simple SIR model (as in Figure 3); graph (b) compares the unvaccinated equilibria with the state arrived at if vaccination campaign has been operating for a time T, for a simple SIR model; graph (c) is the equivalent of graph (b) for an age-structured SEIR model, using POLYMOD mixing matrix. For models (a) and (b) there is relatively limited effect of initial conditions, such that the 95% of the simulations are between 0 and 1.3% for (a) and between -0.05% and 0.2% for (b). For the more complex model (c) greater variation is seen, but again the relative impact of the initial conditions are limited with 95% of the parameter choices leading to changes between -12% and 11%. (Parameters are $B = d = 0.0122$ per year, $\delta = 3.5\%$ per year, $\gamma \in (0, 1)$ per day, $R_0 \in (1, 10)$, $v \in (0, v_c)$, $T \in (1, 10)$ years.)

Highlights. The impact of current infection levels on the cost-benefit of vaccination

- Cost-effectiveness of vaccine programmes before vs after implementation is considered
- Simple analytical models and numerical solutions used to quantify differences
- Benefits of maintaining vaccination at least equal to starting a programme.
- Successfully immunising individuals does not devalue the vaccination program