ESTIMATION OF THE POPULATION VACCINATION EFFECTIVENESS USING URN MODELS

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Abstract

The population vaccination effectiveness (PVE) is defined as the fraction of disease cases prevented by a vaccination campaign. We use occupancy urn models to estimate the PVE, and compare results for leaky, all-or-nothing and VEI (vaccine efficacy for infectiousness) vaccines using data of a measles outbreak and San Francisco current AIDS epidemic. This latter motivated by the current development of HIV vaccines of the VEI type. When applying our method to predict PVE for the San Francisco AIDS epidemic, our model predicts that PVE will be relatively low, even if the fraction of vaccinated and the efficacy of the vaccine are high.

Key words: vaccine efficacy, urn models, population vaccination.

1 INTRODUCTION

Human interest with epidemics of infectious diseases and their associated human mortality has a long history. However, the scientific study of epidemiology of infectious diseases started with the development of the 'germ theory of disease'[1]. The research on this field has produced many discoveries and developments including the creation of vaccines.

An evaluation of the performance of a vaccination program at the population level should at least involve a measure of the direct protective effect of the vaccine on every person, which has been measured by the so called vaccine efficacy (VE)[5-9, 11-13]. It also must incorporate its indirect effects such as those associated with herd immunity, that is, the reduction in disease probability (for vaccinees and non-vaccinees) resulting from the reduction in the proportion of infectious individuals[1, 5]. An index that considers these two factors is the Population Vaccination Effectiveness (PVE), which is ususally defined as

$$PVE = 1 - \frac{I_{ob}}{E[I]} \tag{1}$$

where I_{ob} denotes the observed attack rate in the population and $E[I]$ denotes the corresponding expected attack rate (in the same population) in the absence of vaccination.[5]. PVE measures the fraction of disease cases prevented by a vaccination programme, and thus, it can help public health authorities in the evaluation of the efficacy of a public health campaign. The above formula, as we will show, it can be used to predict the PVE of a vaccination campaign as a function of the VE and the vaccinated fraction.

The fraction of cases prevented by a vaccination campaign have been considered before by Struchiner et al, Halloran and Struchiner,(see Haber[5]).In the same article, Haber[5] (1997) coins the term 'population vaccination effectiveness' to describe the effect of a vaccination campaign at the population level. The main difficulty in the estimation of PVE in formula (1) arises from the term $E[I]$, the expected value of the number of infectives without vaccination campaign. It may be possible to estimate $E[I]$ from data collected prior to vaccination, or from observations on a similar unvaccinated population isolated from the study population. Even if such estimates exist, however, they would be unreliable in many cases(see Haber 1997).

In this work, we use occupancy urn models to estimate $E[I]$ and apply the approach based on this method to data from a measles outbreak in Scott

City, Kansas. We also apply this method to predict the PVE for the current AIDS epidemic in San Francisco, California. We discuss the effect of f, the fraction of the population vaccinated, and the effect of the VE on the PVE for three different types of vaccines, that can be distinguished according to their action[2, 7, 11].They are:all-or-nothing vaccines, leaky vaccines and VEI(vaccine efficacy for infectiousness) vaccines. *All-or-nothing vaccines afford complete protection to a fraction of the vaccinated people. Leaky vaccines reduce the probability of infection per contact for a vaccinated person to some (nonzero) value. We consider a vaccine under development whose purpose is to break the chain of infection of HIV (Human Immunodeficiency Virus). Its mode of action is called VEI because its goal is to reduce the infectiousness of an individual [2].

An important question arises regarding these vaccines: can we ever be able to stop the AIDS epidemic by means of these type of vaccines? When is it too late to implement them? We will analyze how successful the use of the VEI on the AIDS epidemic using data from the current AIDS epidemic in San Francisco could be.

2 METHODOLOGY

We present the basic framework on occupancy urn models that is required to understand our approach. Consider placing n balls in N urns, where N is assumed to be large. It is also assumed that every urn can hold an unlimited number of balls and that the probability that a ball falls in urn i, $i = 1, 2, 3, ..., N$, is N^{-1}. That is, the placements of balls in urns are independent events.

Under mild conditions, the distribution of the number of empty urns is well modeled by a Poisson distribution with parameter

$$\theta = Ne^{-n/N} \tag{2}$$

(Von Mises, 1939)[10]. The conditions are, that N and n tend to infinity in such away that θ remains bounded. Thus, the expected number of occupied urns is give by

$$N(1 - e^{-n/N}) \tag{3}$$

A variation in this type of model is the "leaky urn model". Under this model, once an urn receives a ball, it may escape inmediately with probability β, and the number of empty urns after attempting placing n balls tends also to a Poisson distribution with parameter[10] θ where

$$\theta = Ne^{-n\beta/N} \tag{4}$$

We use the following analogy to describe the role of a vaccine in reducing an epidemic: N in (2-4) corresponds to the total number of susceptible individuals in the population at the beginning of an epidemic. The number of occupied urns at the end of an epidemic corresponds to the total number of infected individuals, and thus, empty urns correspond to those individuals who remain susceptible. The role of n, the number of placed balls, is the total number of threats of infection. These threats may or not may result in an infection depending on the urn (being previously empty or occupied). An individual may receive any number of threats but its infectiousness does not depend on the number of threats (balls) received. Our model simply classifies individuals in two types, useful particulary when one looks infected (occupied) or susceptible (empty).

This analogy is at the final size of an epidemic, which is achieved when the last ball placed falls in an occupied urn. Since n, the number of threats of infection is proportional to the number of infected, n that is $n = c\ I$, where c is the number of *threats of infection that every infected produces*(c plays the role of the basic reproductive number or R_0[1]). Then the expected number of susceptible(empty urns) is given by

$$E[S] = N - E[I] = Ne^{-R_0\ \mathrm{I}/N} \tag{5}$$

where S is the number of empty urns and I is the number of occupied urns provided that each newly occupied urn produces itself (and throws) R_0 balls.

We can construct an estimate of R_0 by solving for R_0 in (5) and equating $E[I]$ to the observed number of occupied urns U, that is, an estimate $\hat{R}_0$ for R_0 is given by

$$\hat{R}_0 = -\frac{N}{U} Log\left(1 - \frac{U}{N}\right) \tag{6}$$

For a fixed (known) values of R_0, it is possible to estimate $E[I]$ by solving for R_0 this in (5). Numerical methods are required because there is no closed form for $E[I]$.

2.1 ALL-OR-NOTHING VACCINES

Suppose that at the beginning of the epidemic, there is only one infected individual (urn) and suppose that this urn disperses its R_0 balls randomly among N urns. Those urns that receive at least one ball become 'infected' and will disperse their respective R_0 balls among the remaining urns. When a fraction f of the population is vaccinated with an all-or-nothing vaccine with $VE = 1-\beta$, that is ,with a fraction β of those vaccinated not protected by the vaccine, then the immune fraction equals $f(1-\beta)$. The rest of the individuals remain susceptible. In terms of the urn model, this would be equivalent to have some of the urns covered, in the sense that they can receive balls, but without becoming infected.

As it can be seen in (1), it is required to estimate $E[I]$, but first we need to estimate R_0. We need to gather information on R_0 with a population that has been already vaccinated. We still can use (4), but we need to correct for the number of 'susceptible' urns. In the following, N_1, is the number of vaccinated individuals and $N_0 = N - N_1$. The number of susceptible individuals (or available urns) is then $N_0 + N_1\beta$.

A correction for the number dropped balls at the end of the epidemic is given by

$$n = R_0 I \left(\frac{N_0 + N_1\beta}{N} \right) \tag{7}$$

This last expression corrects for the fraction of balls that fall into susceptible urns. If I is the number of infected urns at the end of the epidemic, then from (5) we have that

$$E[I] = (N_0 + N_1\beta) \left(1 - e^{-\frac{n}{N_0+N_1\beta}} \right),$$

which simplifies to

$$E[I] = (N_0 + N_1\beta) \left(1 - e^{-\frac{R_0 I}{N}} \right). \tag{8}$$

Solving for R_0, we have

$$\hat{R}_0 = -\frac{N}{I}\log\left(\frac{I_{obs}}{N_0 + N_1\beta}\right) \tag{9}$$

where I_{obs}, is the observed number of infected individuals during an epidemic. This estimate of R_0 can be subsituted in (8) and then solve for I which becomes in fact the estimate of $E[I]$ in (1) yielding

$$E[I] = N\left(1 - e^{-\hat{R}_0 E[I]/N}\right) \tag{10}$$

that can be substituted in (1) to estimate the PVE.

2.2 LEAKY VACCINES

This type of vaccine reduces the susceptibility of infection from 1 to β for all the vaccinated individuals, that is, every time the individual has a contact with the infectious agent, its probability of infection is reduced from 1 to β. Observe that the probability that a person do not become infected in k contacts is (1-β)$^{\mathrm{k}}$. Most of the last cosiderations are maintained. Nevertheless, for a leaky vaccine the number of infected at the end of the epidemic is similar to the number of occupied urns in the 'leaky urn model', where in every contact of infection, the ball has a probability β to stay in the urn, and 1-β to escape. Notice that the contact by itself do not produces infection, unless the ball remains in the urn.

We first consider the case of partial vaccination before the epidemic. In this case a fraction f of the population is vaccinated, and we define $\mathrm{N}_1 = Nf$, as the number of vaccinated individuals. We can consider that there are two type of urns, type 0 and type 1 for the non vaccinated and the vaccinated respectively. Thus the expected number of susceptible individuals at the end of the epidemic is the sum of the susceptibles vaccinated and unvaccinated. Provided that the Poisson limit applies, we have

$$E[\text{susceptibles type0}] = N(1-f)e^{-\frac{R_0 I}{N}} \tag{11}$$

and

$$E[\text{susceptibles type1}] = Nfe^{-\frac{R_0 I\beta}{N}} \tag{12}$$

Hence

$$\begin{aligned} E[\text{susceptibles}] &= E[\text{susceptibles type 0}] + E[\text{susceptibles type 1}], \\ &= N(1-f)\,e^{-\frac{R_0 I}{N}} + Nfe^{-\frac{R_0 I\beta}{N}}, \end{aligned}$$

and from (5) we have that

$$E[I] = N - N\left((1-f)\,e^{-\frac{R_0 I}{N}} + Nfe^{\frac{R_0 I\beta}{N}}\right) \tag{13}$$

Thus we can solve for R_0 in (13) to provide an estimate of R_0, from where we can estimate PVE using (1).

2.3 VEI TYPE VACCINES.

An analogous urn model for VEI type of vaccine would be one in which every infected individual reduces the amount of balls it can throw, R_0 to a fraction $R_0\,\alpha$, $0 < \alpha < 1$. Note that if α is very low αR_0 is very low and each individual is less infectious and the vaccine efficacy is VE=1-α.

For this type of vaccine we will study two cases: partial vaccination before the epidemic and partial vaccination of susceptible individuals during the epidemic.

Vaccination before the epidemic starts

In the case of partial vaccination before the epidemic we assume that, at the beginning of the epidemic, there is only one infected individual, and that this individual (urn) disperses its R_0 balls randomly. Those urns that receive at least one ball become infected and will in turn disperse αR_0 balls if they are vaccinated and R_0 if they are not. At the end of an epidemic there will be infected individuals of two types: the type 0 for unvaccinated individuals (I_0), and the type 1 for vaccinated individuals (I_1). Therefore the total of infected individuals is $I_0 + I_1$. From (2) we have

$$E[I_0] = N_0\left(1 - e^{-\frac{n_0}{N_0}}\right) \tag{14}$$

where the total number of balls dispersed n_0, will be a fraction of the total number of balls thrown, that is

$$n_0 = R_0 (I_0 + I_1\alpha)(1 - f) \tag{15}$$

where $R_0 (I_0 + I_1\alpha)$ is the total number of ball produced and $(1 - f)$ is the fraction that falls in the unvaccinated population. Hence

$$E[I_0] = (1 - f) N \left(1 - e^{-\frac{R_0(I_0+I_1\alpha)}{N}}\right) \tag{16}$$

On the other hand, the equation for I_1 is deduced similarly to that for I_0, therefore

$$E[I_1] = N_1 \left(1 - e^{-\frac{n_1}{N_1}}\right) \tag{17}$$

Therefore,

$$E[I_0 + I_1] = N \left(1 - e^{-\frac{R_0(I_0+I_1\alpha)}{N}}\right) \tag{18}$$

and from (18) we have the following estimate for R_0

$$\hat{R_0} = \frac{-N}{I_0 + I_1\alpha} \log\left(1 - \frac{I_0 + I_1}{N}\right). \tag{19}$$

which can be used to obtain $E[I_0 + I_1]$ for different values of f and α. Thus we obtain a predictor for the PVE.

Vaccination during the epidemic starts

If the vaccine is applied to a population that contains already infected individuals then we have to specify what kind of effect will the vaccine have in these infected (assumed infectious) individuals. In the worst case scenario, the vaccine will have no effect on them and thus the PVE would depend mainly on what happens to the new cases. This particular case is relevant to AIDS, in which that the epidemics can be driven by infections would generated in the primary infectious phase of the disease and therefore, a potential VEI vaccine will have little effect on those that have been infected for a long time. To simplify our model, we assume that the vaccine has no

effect on already infected individuals and study the evolution of an epidemic on the remaining susceptible individuals.

The infected population is composed of both old and newly infected individuals. Let the number of already infected individuals I_{ini}. This implies that I_{ini} have R_0 balls at the time the vaccination campaign starts. Thus, the I_{ini} individuals will continue to disperse their R_0 balls amongst the susceptible population. Suppose that a fraction f of the susceptible population S is vaccinated hence, if N_1 is the number of vaccinated individuals then at the end of an epidemic, there will be I_0 infected unvaccinated individuals and I_1 infected vaccinated individuals. Therefore, the total number of susceptibles becoming infected at the end of an epidemic is $I_0 + I_1$ and the expected number of infected among the non-vaccinated individuals is

$$E[I_0] = N_0 \left(1 - e^{-\frac{n_0}{N_0}}\right) \tag{20}$$

where the total number n_0 of balls dispersed is a fraction of the total number of balls thrown by all infected during the epidemic, that is

$$n_0 = R_0 \left(I_{ini} + I_0 + I_1\alpha\right) \frac{(1-f)\,S}{N} \tag{21}$$

where $R_0 \left(I_{ini} + I_0 + I_1\alpha\right)$ denotes the total number of threats of infection (balls), $\frac{S}{N}$ is the fraction of these balls that fall into susceptibles and $(1-f)$ the fraction that falls into the unvaccinated. Since

$$\frac{n_0}{N_0} = \frac{R_0 \left(I_{ini} + I_0 + I_1\alpha\right)}{(1-f)\,S} \frac{(1-f)\,S}{N} \tag{22}$$

we have that

$$E[I_0] = (1-f)\,S \left(1 - e^{-\frac{R_0\left(I_{ini}+I_0+I_1\alpha\right)}{N}}\right) \tag{23}$$

Similarly, we find that

$$E[I_1] = fS \left(1 - e^{-\frac{R_0\left(I_{ini}+I_0+I_1\alpha\right)}{N}}\right) \tag{24}$$

If R_0,or an estimate of R_0 is known, then we can use the last two expressions to estimate $E[I_0 + I_1]$ for different fraction of vaccinated and different α's, and then use these estimates to estimate PVE.

3 DISCUSSION AND RESULTS.

3.1 COMPARING ALL-OR-NOTHING AND LEAKY VACCINES.

Differentiation between leaky and all-or-nothing vaccines is difficult. As we have seen, the PVE depends on the mode of action of the vaccine and thus if this process is unknown, then we can only try to estimate the PVE under both modes of action. For the Scott City measles outbreak data[6], we found similar results for both all-or-nothing and leaky vaccines. In figures 1 and 2, it can be seen that there is a critical value of approximately 0.62, at which an increase in the fraction of vaccinated does not increase significatively the PVE. It can also be seen that there is an approximate linear relationship with the accinated fraction for both kinds of vaccines when f is below the critical value. Figure 1 shows the results for the effect of f on the PVE for the preschool group whereas Figure 2 is for elementary school population.

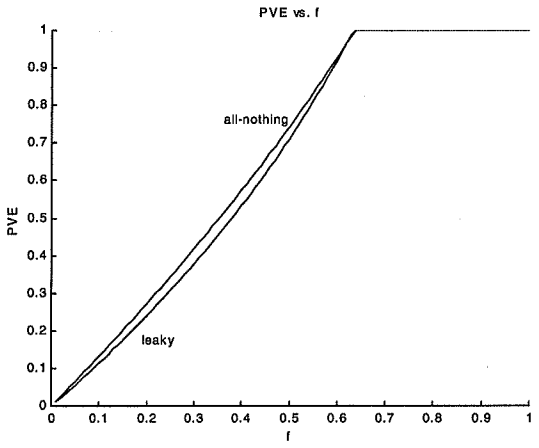

Figure 1. Graphs of PVE vs. vaccinated fraction (f) for preschool children effected by measles epidemic with a vaccine efficacy, $VE = 0.85$, N_0=119, N_1=193, I_{ob}=10, for all-or-nothing vaccine and leaky vaccine respectively.

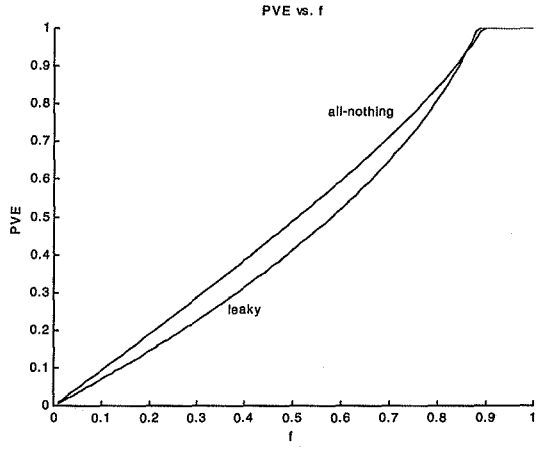

Figure 2. Graphs of PVE vs. vaccinated fraction (f) for elementary school children effected by measles epidemic with a vaccine efficacy, VE=0.927, N_0=76, N_1=459, I_{ob}=35, for all-nothing vaccine and leaky vaccine respectively.

3.2 ANALYSIS OF THE AIDS EPIDEMIC IN SAN FRANCISCO: EFFECT OF VEI ON PVE.

The goal of this section is to analyze the effect of a potential VEI vaccine applied to the population in San Francisco. The population size is N = 1,003,998[15], and the number of currently infected is I_{ini} = 7,921[14]. At this point, the efficacy of such a vaccine is unknown, and the vaccinated fraction plays an important role, specially since we have to consider that a lot of people may not be easily persuaded to take the vaccine[2].

To run our model, we need initial estimates of R_0. In our study we take R_0 = 2,6,8, and 12, whereas the VE of the potential VEI is from 0 to 1 at increments of 0.05. The fraction of vaccinated also varies from 0 to 1. Figures 12-15 show our results.

It can be seen that for R_0 values as low as 2, it is possible to obtain PVE's close to 1 if the VE is close to 1 and all the susceptibles are vaccinated, whereas for R_0 values as high as 12, the campaign will reach a PVE value smaller than 0.2 for a VE of 0.80 if all the susceptibles are vaccinated. If the vaccinated fraction is 0.80 (a rather optimistic fraction) no VEI vaccine will reach a PVE of 0.2. If the vaccinated fraction is less than 60 percent, then the campaign will be practicaly ineffective.

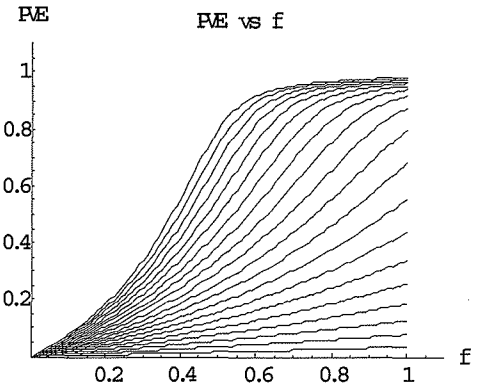

Figure 3. Effect of f on PVE for an VEI vaccine, while varying efficacy 1-α. Case $R_0 = 2$

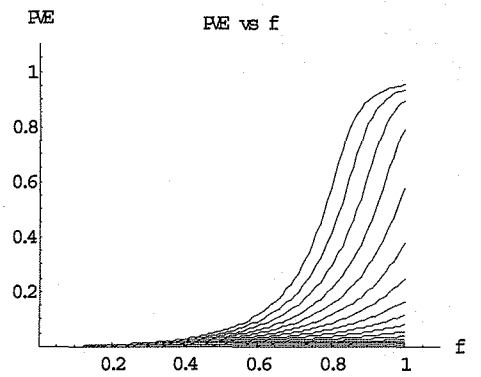

Figure 4. Effect of f on PVE for an VEI vaccine, while varying efficacy 1-α. Case $R_0 = 6$

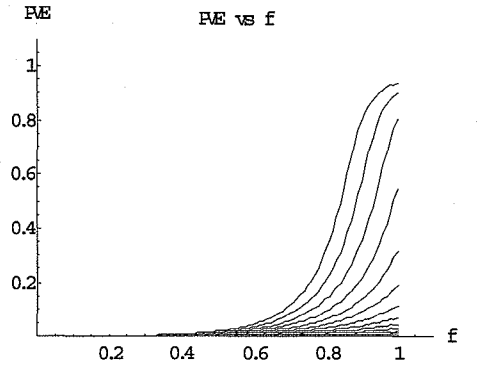

Figure 5. Effect of f on PVE for an VEI vaccine, while varying efficacy 1-α. Case $R_0 = 8$

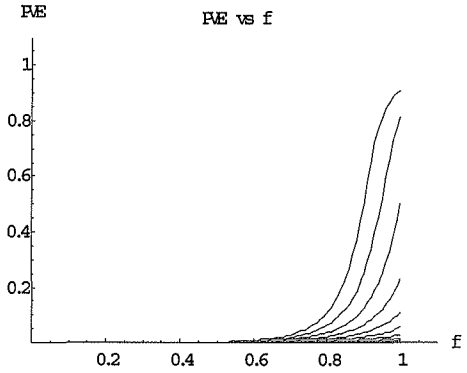

Figure 6. Effect of f on PVE for an VEI vaccine, while varying efficacy 1-α.
Case $R_0 = 12$

3.3 ANALYSIS OF THE AIDS EPIDEMIC IN SAN FRANCISCO: COMPARING PONTENTIAL ALL-OR-NOTHING, LEAKY, AND VEI VACCINES.

Figures 7 and 8 show the comparison between the predicted PVE for the three kinds of vaccines: all-or-nothing, leaky and VEI for α=0.2 and α=0.4 respectively, with R_0=8.We can see that the PVE of the all-or-nothing vaccine is far above of the PVE of the leaky vaccine for the same fraction of vaccinated, and that the PVE of the VEI vaccine is below the PVE of a leaky vaccine. A interesting result arises: even if the VE of the VEI vaccine is relatively high (around 0.8) and the fraction of vaccinated is optimistically high (90 %), the predicted PVE is below 0.4.

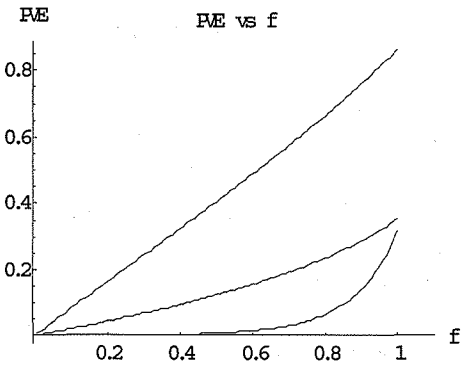

Figure 7. Comparison between all-or-nothing, leaky and VEI vaccines.
R_0=8 , α=0.2.

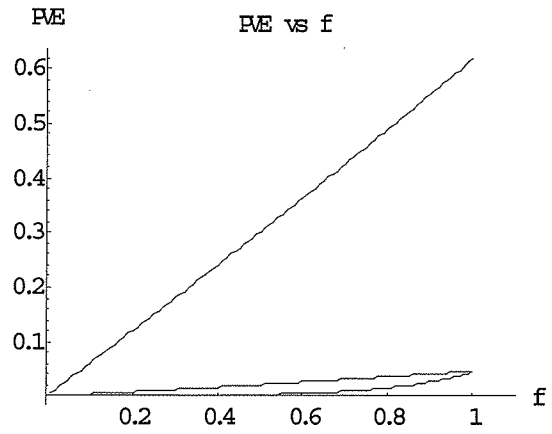

Figure 8. Comparison between all-or-nothing, leaky and VEI vaccines. R_0=8 , α=0.4.

4 CONCLUSIONS

Estimation of PVE is a valuable tool to assess the quality of previous vaccination programmes, or in the prediction of the effects of a disease in a population under a vaccine campaign.

Occupancy urn models provide a simple way to derive PVE estimate for different types of vaccines. It is also an ideal framework to develop confidence intervals, which could in turn be used to assess the level of confidence of the predictions. More research needs to be done regarding the ditributional properties of the PVE.

For the specific measles outbreak that we considered, it is seen that in order to obtain a valuable vaccination programme, it is needed to vaccinate most of the population and to have an efficient vaccine, both implemented vaccines showed similar impact on the PVE.

One important conclusion derived from our model is that more research is required towards the development of alternative all/nothing or leaky vaccines that could halt the AIDS epidemic, since according to our estimates, the predicted population vaccination effectiveness of a VEI type vaccine (even assuming a high VE and a high fraction of vaccinated), is low. This is especially disturbing since it is expected that it would be difficult to convince people to be vaccinated with a vaccine that does not confer them immunity -total o partial-, but instead protects other people from being infected.[2] Besides is also covenient to consider the sector of the population

that is vaccinated, since people in certain groups are more exposed to become infected. Moreover, it should be considered that vaccination may cause changes in the behaviour of vaccinated, a topic already considered elsewhere, thus, vaccinated people could increase their contact rate and thus the effects of vaccination could be reversed.

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