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Direct, Indirect, Total and Population Vaccination Effectiveness in Pandemic influenza Vaccination

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An abstract of
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Abstract

Most vaccination effectiveness studies focus on the direct vaccination effectiveness (VEd), defined as one minus the ratio of attack rates in vaccinated and unvaccinated persons, and pay little attention to the indirect (VEi) and population (VEpop) effectiveness, which can be interpreted as proportion of cases prevented by vaccination. Here, we use a stochastic simulation model to estimate direct, indirect, total and population vaccination effectiveness using data from the 1957/1958 influenza pandemic To estimate VE_{pop}, which is unknown, from VEd and the vaccination fraction, which are known, linear regression modeling and estimation under the Susceptible-Infected-Removed (SIR) model were performed. From simulation results, we found the VEpop is usually higher, and in many cases much higher, than the VEd. In prediction studies, results from linear regression models showed that the estimates of population effectiveness were close to the simulated results when vaccination fractions were fixed, and that the estimation of population effectiveness can best approximate the simulated values when vaccine efficacy (VEs) is fixed and equals to 0.4. Our results also show that estimation of VEpop based on the SIR model provides a good approximation t0 the true population effectiveness even though, in the real world, the basic SIR model assumptions that the population is homogeneous and mixing is random are violated. We conclude that, due to the indirect vaccination effects, the VEpop is usually higher than the VEd. In addition, linear regression and SIR models can be applied to estimate VEpop.

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Direct, Indirect, Total and Population Vaccination Effectiveness in Pandemic influenza Outbreaks

Songli Xu

Introduction

Influenza is a seasonal infectious disease with annual epidemics that result in approximately 3 t0 5 million severe illnesses and 250,000 to 500,000 deaths worldwide (1). A report from National Institutes of Health (2008) indicated that seasonal influenza causes about 200,000 hospitalizations and 41,000 deaths annually in the US, making it the seventh leading cause of death in this country(2). Influenza pandemics, which occur approximately every 10-50 years, are associated with even higher morbidity and mortality (3). In the 20thcentury, there were three influenza pandemics occurring in 1918, 1957 and 1968 (4). The first influenza pandemic in the 21st century occurred in 2009 (5, 6). Influenza infections not only cause serious public health problems but also generate a huge economic burden. Rough estimation showed that seasonal influenza costs $87 billion per year in the United States (7).

Although several studies on multiple non-vaccination interventions showed various levels of decreasing infection rates, (8,9,10), and the U.S. Centers for Disease Control and Prevention (CDC) developed community-based guidance for non-pharmaceutical interventions to decrease the spread of the influenza virus (11), vaccination is still considered as the most effective and cost-saving method to control

influenza virus spread. The earliest report of the clinical effectiveness of vaccination against influenza-like illness appeared in Fedson's paper (12). The authors showed that 37% to 39% of hospitalizations for pneumonia, and 27 to 30% of relevant deaths, were prevented by influenza vaccination.A2002 meta-analysis of several studies showed similar estimates (13). All these studies suggested that vaccination is not only effective but also a cost-saving method for influenza control

Here are the concepts will be used in this thesis. The terms and definitions are consistent with those in Haber et al's1991 article (14).

1. Attack rate (AR): the cumulative incidence, over the entire outbreak, of influenza infection (for our study, we assume that infection and illness are the same events).
2. Vaccination fraction (f): the percent of vaccinated persons in the population, reflecting the coverage of vaccination.
3. Vaccine efficacy for susceptibility (VEs) is the vaccine-induced reduction, in the probability of influenza transmission from an infectious person to a susceptible person, i.e., the level of protection offered by the vaccine in a single contact.
4. $\text{Direct vaccine effectiveness (VEd)} = 1 - \frac{\text{ARv}}{\text{ARu}}$, where ARv is the attack rate amongst vaccinated individuals and ARu is the attack rate amongst unvaccinated individuals. This is a measure of the direct impact of the vaccine on vaccinated individuals, and it is the most commonly used definition of the concept 'vaccine effectiveness' (15).

5. Indirect vaccine effectiveness (VEi) $= 1 - \frac{\text{ARu}}{\text{ARc}}$, where ARc is the expected attack rate in the study population in the absence of any vaccination (i.e. when f=0).
6. Total vaccine effectiveness(VEtot) $= 1 - \frac{\text{ARv}}{\text{ARc}}$. This is a measure of the combined direct and indirect effects of vaccination..
7. Population vaccine effectiveness (VEpop) $= 1 - \frac{\text{ARo}}{\text{ARc}}$, where ARo reflects the overall attack rate in the population: ARo=(1-f)*ARu+f*ARv. This is a measure of the population preventive vaccine effectiveness.

Several groups performed theoretical studies to address vaccine effectiveness. Smith *et al* were the first group to use two models to describe the action of a vaccine (16). Under Model 1, the vaccine reduces the probability of infection in the entire vaccinated population. Under Model 2, vaccination offers complete protection to some of the vaccinated individuals and no protection to the rest of the vaccinated individuals. Later, Greenland *et al* explored a model combining the two types of actions (17). In the two studies, the authors only address the direct vaccine effectiveness, but not the indirect vaccine effectiveness since they assume the probability of a susceptible person to become infected remains the same during the whole epidemic period. To overcome this limitation, Haber *et al* (14) introduced the concepts of direct, indirect, total and population vaccine effectiveness (VE).The population VE is the proportion of cases prevented by vaccination, which accounts for both direct and indirect effects. The authors not only analyzed the four VE concepts under the two models described by Smith *et al* , but also illustrated the estimation of

the four types of VE from data on a mumps outbreak in a school. The results suggested that model 2 might be appropriate for mumps vaccine. Therefore, Haber et al and other groups' results suggested that the different vaccine models should be applied to different vaccines (14).

So far, most vaccine studies report only the direct effectiveness, which is one minus the ratio of the cumulative incidences or attack rates in vaccinated and unvaccinated persons, and do not pay attention to the estimation of the indirect and population-level effectiveness. In particular, there are only a few studies in which the population-level effectiveness of influenza vaccination is measured.

In this analysis, stochastic simulations are used to study direct, indirect, total and population effectiveness of the influenza vaccine using data based on the 1958 influenza pandemic. Regression modeling is performed to predict the indirect and population vaccine effectiveness from the direct effectiveness and the vaccine coverage. The simulated results are compared with the estimated results based on model 1 under the Susceptible-Infected-Removed (SIR) model.

Methods

Simulation model

The Susceptible-Exposed-Infected-Removed (SEIR) model was applied in our simulation structure as described previously by Haber et al (14). Different from SIR, SEIR model includes latent period. An influenza outbreak was simulated in a small urban U.S. community with approximately 1000 households with a total of 2593

household members, using data from studies in U.S. influenza-associated rates of excess morbidity and mortality (18, 19, 20, 21). The data from the A(H2N2) Asian influenza pandemic in1957-1958 were used to calibrate the transmission parameters. All results are based on the assumption that age specific ARs are similar to their values in the 1957-58 influenza pandemic. Every person in the population belongs to one of four age-dependent groups: preschool children (0-4 years old, n=172, 6.63%), school children (5-18 years old, n=500, 19.28%), adults (19-64 years old, n=1752, 60.62%), seniors (65+ years old, n=300, 13.46%). In addition, every person also belongs to one or more mixing groups, such as households, daycare centers, schools, work places, long-term care facilities and the community. Final attack rates in the unvaccinated (ARu), in the vaccinated (ARv) and in the population (ARo) were obtained for each age-group in each simulation. Several special characteristics in our simulation model are different from other common simulation models (1). The probability of infection depends on the total time of contact between two individuals, not on the numbers of contacts. (2) The transmission parameters depend on the per-minute infection rate, and not on the population size (14).

In order to simplify our study, we applied the same vaccination fraction in each age group. We did not include any interventions, such as school closing, isolating ill individual and their household contact, etc. The simulated epidemic started with 12 influenza-infective individuals. The transmission process continued until there were no further infected individuals. In each simulation, the program provided us the attack rates (proportion of ill individuals) among vaccinated and unvaccinated

persons. We first conducted 200 simulations without vaccination to estimate the control AR (ARc).Then we conducted sets of 200 simulations for various combinations of the values of the vaccination fraction (f) and the vaccine efficacy (VEs), and obtained values of ARu, ARv and ARo by averaging over the 200 simulations. These attack rates were then used to calculate the direct, indirect, total and population vaccination effectiveness.

Linear regression model

In practice, it is usually impossible or very difficult to estimate ARc, as it is very difficult to find a control (unvaccinated) population that is identical to the study population. Therefore, only the direct effectiveness can be observed in a real-life study. We therefore wanted to see if the indirect and population vaccination effectiveness can be estimated when only the direct effectiveness and the vaccinated fraction are known. To establish a prediction model, linear regression methods were used to estimate the relationship between the vaccination fraction, the direct vaccination effectiveness and the indirect and population effectiveness. To select the final model, predicted results from linear regression model were compared with simulation results. R-square values and residuals were examined to obtain the best fitting model.

Assessing the accuracy of estimates of the population vaccination effectiveness via the SIR model.

Haber et al (1991) proposed a method for estimation of ARc and the population vaccination effectiveness based on a simple SIR model under the assumptions that

the population is homogeneous and its members mix at random. Under this method, one first estimates the basic reproductive number (teta) from $\text{teta} = -\frac{[\text{In}(1-\text{ARu})]}{\text{ARo}}$,. Under the SIR model, ARc can then be estimated as ARc_SIR=1-exp{-teta*(ARc_SIR)}. Then, under model 1, we can estimate $\text{indirect VE\_SIR} = 1 - \frac{\text{ARu}}{\text{ARc\_SIR}}$, and $\text{population VE\_SIR} = 1 - \frac{\text{ARo}}{\text{ARc\_SIR}}$. We compared the estimated population VE using the SIR-based method with the 'true' value of the population VE, obtained via simulations from a 'real-life' population where the assumptions of homogeneity and random mixing are violated.

Results

Baseline

Based on 200 simulations, ARc is 0.334 (95% confidence interval 0.257 to 0.411). We used 0.334 as the ARc value for all calculations of the true vaccination effectiveness.

Simulation estimated results

Figure 1 shows the direct, indirect, total and population vaccination effectiveness as function of VEs when vaccination fraction is fixed at the values of 0.4, 0.6 and 0.8 respectively. For f=0.4 the indirect and population vaccination effectiveness curves are very close to each other, but distinct from the total effectiveness curve. For f=0.6 and 0.8, all three curves are close to each other. The relationship between VEs and direct vaccination effectiveness (VEd) is almost linear. By contrast, the relationship between VEs and vaccination effectiveness are not linear for indirect (VEi), total

(VEtot) and population effectiveness (VEpop). For three different vaccination fractions, the values of vaccination effectiveness from the smallest to the largest are indirect, population and total. The curves of three effectiveness for f=0.6 and f=0.8 are similar and they are different from that of f=0.4. When f=0.4, the curves of the three effectiveness follow monotone trend and the curves increase gently. However, for f=0.6 and f=0.8, the curve of three effectiveness following monotone trend at the beginning and stabilize above certain value of vaccine fraction (VEs=0.6 and VEs=0.5, respectively). The curves for f=0.6 and f=0.8 increase sharply compared with that in f=0.4. Numerical results also show the different effectiveness when f equals to0.4 compared with f=0.6 and f=0.8 (table 1). For example, when f=0.4 and VEs=0.4, VEpop=0.622, while VEpop=0.822 when f=0.6 and VEpop=0.898 when f=0.8.

Figure 2 shows the direct, indirect, and total and population vaccination effectiveness as function of vaccine fraction (f) when VEs is fixed at the value, 0.4, 0.6 and 0.8 respectively. Unlike Figure 1, the VEi and VEpop curves are always close to each other and distinct from that of VEtot. VEd is less than VEs. Similar to Figure 1, the curves of indirect (VEi) and population (VEpop) effectiveness when VEs=0.6 and VEs=0.8 are similar and they are different from that of VEs=0.4. When VEs=0.4, the curves of the two effectiveness follow a monotone trend with a small slope. For VEs=0.6 and VEs=0.8, the curves of the two effectiveness also follow monotone trend at the beginning and stabilize above certain value of vaccination fraction (VEs=0.6 and VEs=0.5, respectively). The curves for f=0.6 and f=0.8 increased sharply compared with that for f=0.4. Numerical results also showed the similar results that

the different effectiveness when f=0.4 compared with f=0.6 and f=0.8 (table 2). For example, when VEs=0.4 and f=0.8, VEpop=0.898, while VEpop=0.960 when VEs=0.6 and VEpop=0.976 when VEs=0.8.Interestingly, the curve of total effectiveness is very different from the other two. It dramatically increases when VEs increase from 0.4 to 0.8.More importantly, when f>0.2, the population vaccination effectiveness is always greater than the direct effectiveness. For example, when f=0.6 and VEs=0.6, VEpop=0.935 which is much larger that VEd=0.410 (Table 1-2).

Regression modeling

To address how to predict the indirect and population vaccination effectiveness which are unknown from vaccination fraction and direct vaccination effectiveness which are known, linear regression was applied. When the vaccination fraction (f)is fixed, VEi and VEpop were used as dependent variables and VEd was used as the independent variable. Since the residuals are large, an additional independent variable, square of VEd, was added to the regression model. The intercepts and coefficients of the final models are shown in Tables3-1a, 3-2a and 3-3a. In this case, the estimates of $\widehat{VEi}$ and $\widehat{VEpop}$ from the regression model approximate the simulated effectiveness well (R square is close to 1) (Tables 3-1b 3-2b and 3-3b).

When VEs was fixed, VEi and VEpop were again used as dependent variables and VEd and vaccination fraction (f) were used as independent variables. The intercepts and coefficients in the final models are shown in Tables4-1a, 4-2a and 4-3a. When VEs equal to 0.4, the estimation of $\widehat{VEi}$ and $\widehat{VEpop}$ from regression model approximate the simulated effectiveness best (R square is close to 1) (Table 3-1b). On

the other hand, when VEs equals to 0.6 or 0.8, the estimates of $\widehat{VEi}$ and $\widehat{VEpop}$from the regression model do not approximate the simulated effectiveness as well (R square is closed to about 0.8 and 0.65, respectively) (Tables 3-2b and 3-3b).

SIR model estimation

To compare the estimated population vaccination effectiveness from the SIR model (VEpop_SIR) with the value from simulation which we regard as the "true" value, we estimated VEpop_SIR when vaccination fraction (f) ranged from 0.2 to 0.8. Generally, the estimated VEpop_SIR approximates the simulated population effectiveness quite well, with the absolute difference between estimated and simulated values not exceeding 0.05 (Table 5). When the vaccination fraction (f) varies from 0.2 to 0.7, the VEpop_SIR estimates are somewhat below the simulated values. On the other hand, the VEpop_SIR estimates are slightly larger than the simulated values when VEs is at least 0.3. When vaccination fraction (f) is 0.8, the VEpop_SIR always overestimates the simulated value. Importantly, the results show that when VEs=0.3 or 0.4, the SIR estimates are closest to 'true' values.

Discussion

We used a stochastic SEIR simulation model, generating an influenza pandemic outbreak based on the 1957/1958 pandemic data, and estimated four measures of influenza vaccine effectiveness: direct (VEd), indirect (VEi), total (VEtot) and population (VEpop) vaccination effectiveness. We found that both the indirect and population vaccination effectiveness increase when the vaccination fraction (f) is

increased with fixed VEs. When VEs is increased, the trends of the indirect and population vaccine effectiveness become similar. For example, in order to achieve indirect and population vaccination effectiveness close to0.9, the vaccine fraction needs to be 0.6 with VEs=0.6, compared with f=0.5 for VEs=0.8. However, for VEs=0.4, f needs to be 0.9 to make indirect and population vaccination effectiveness close to 0.9.

In an influenza pandemic, exposure to infectious individuals increases after the beginning of the outbreak, and the population vaccination effectiveness (VEpop)does not only depend on direct vaccine effectiveness (VEd), but also on indirect vaccine effectiveness (VEi). Therefore, the estimation approach based on model 1 might be more appropriate than model 2 from Smith *et al*. We found that estimated population vaccination effectiveness from model 1can generally approximate the simulated population effectiveness well, although there is some overestimation when vaccination fraction are from 0.2 to 0.8. When VEs is 0.3-0.4 which is normally the case, the estimates from model 1 and the 'true' (simulated) values are closest. The overestimation could result from violations of the assumption that the population is homogeneous and mixing is at random (16, 14). However, in our simulation population (and in real life), the population is not homogeneous and each person belongs to several mixing groups, for example, household, daycare center, school, workplace, community, etc.

In this study, we successfully estimate four different kinds of vaccine effectiveness by using the same vaccine fraction in each age group. To maximize the

effectiveness, several factors need to be considered further. First, the vaccination coverage should be as high as possible. However, one also has to realize that sometimes there is a plateau situation where increasing the coverage does not further increase the effectiveness. For example, in our simulation results when f≥ 0.5 with VEs=0.6 or with VEs=0.8, the effectiveness remains almost constant. Second, using different vaccination coverage in different age groups can increase the effectiveness. For example, Weycker D.*et al* study showed that the most effective strategy for vaccination is to vaccinate as many children as possible (22). Third, we also need to consider the high risk populations, for example chronically ill patients, or the elderly, because WHO reports that most deaths associated with influenza in industrialized countries occur among people age 65 or older (1).

As mentioned above, there are many studies showing that non-vaccination intervention can result in reducing the influenza infectious rate. In practice, combining vaccination strategies with non-vaccination interventions will be a good direction for controlling future pandemics as well as seasonal influenza outbreaks.

In summary, our results indicate that (i) the population vaccination effectiveness (VEpop) which can be interpreted as proportion of cases prevented by vaccination, is usually higher, and in many cases much higher than the direct vaccination effectiveness (VEd). (ii) Even through the basic SIR model assumes that the population is homogeneous and mixing is random, the estimation of the population vaccination effectiveness based on this model still can provide a good approximation t0 the true population vaccination effectiveness even if the assumptions of the SIR

model are violated.

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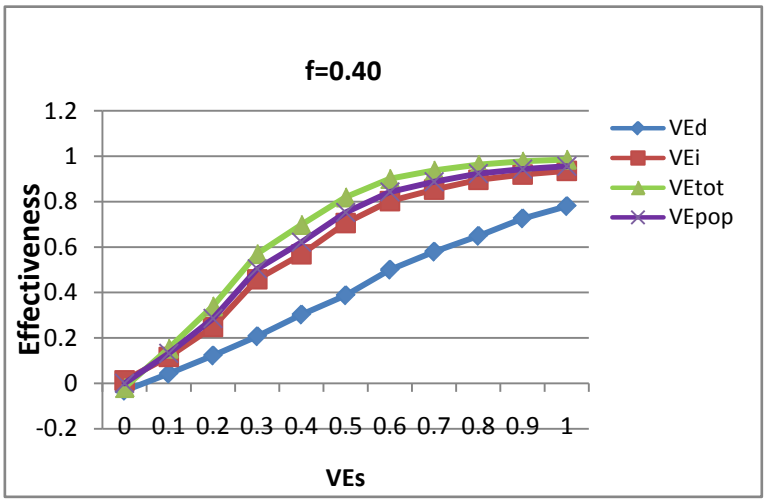
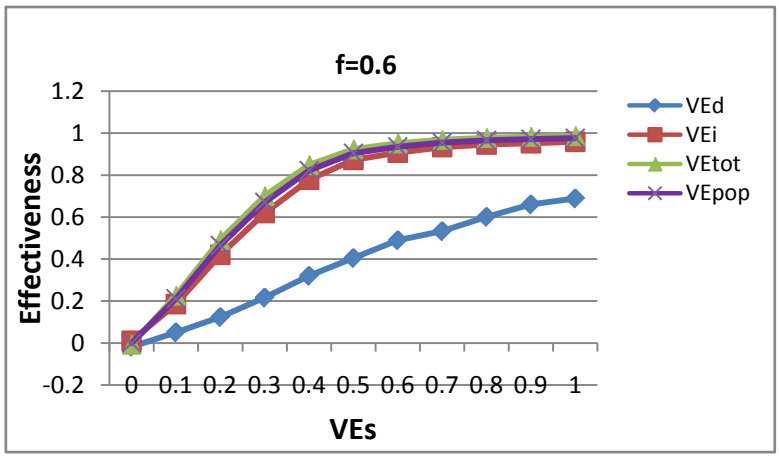
Figure 1 The Relationship Between VEs and effectiveness with fixed vaccine fraction





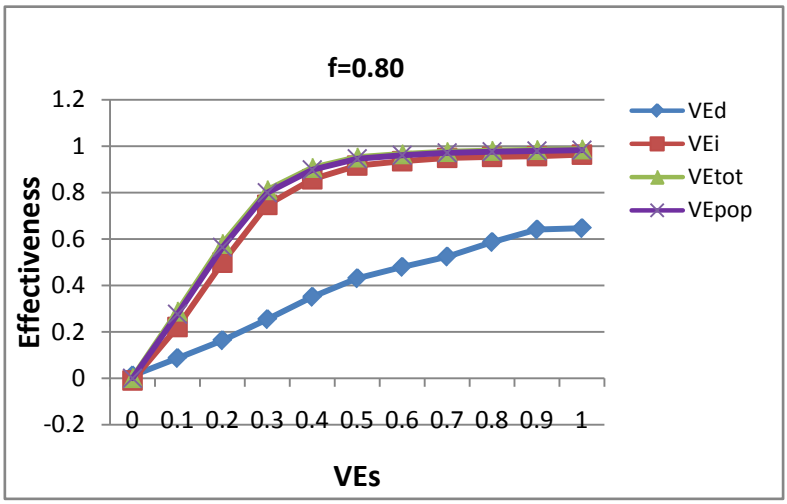


Table1-1 The effect of VEs on effectiveness with f=0.4

VEs	ARu	ARv	ARo	ARc	VEd	VEi	VEtot	VEpop
0.4	0.144	0.100	0.127	0.334	0.302	0.568	0.699	0.622
0.6	0.066	0.033	0.053	0.334	0.500	0.803	0.901	0.843
0.8	0.035	0.012	0.026	0.334	0.649	0.896	0.964	0.924

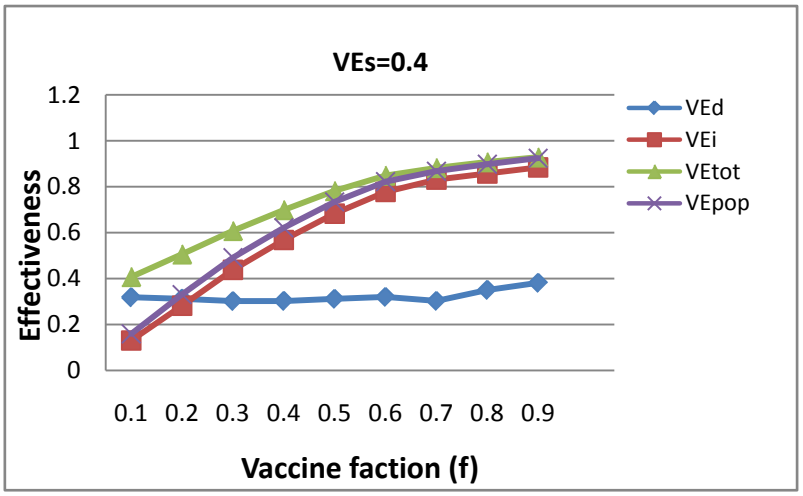
Table1-2 The effect of VEs on effectiveness with f=0.6

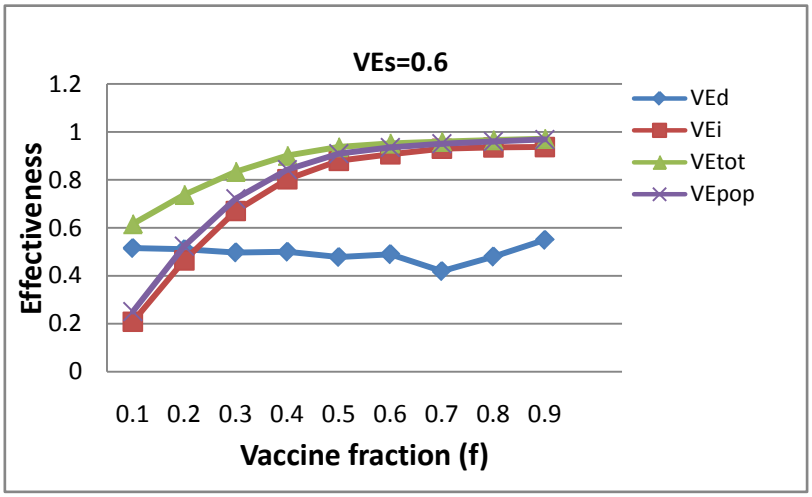
VEs	ARu	ARv	ARo	ARc	VEd	VEi	VEtot	VEpop
0.4	0.074	0.051	0.059	0.334	0.320	0.778	0.849	0.822
0.6	0.031	0.016	0.022	0.334	0.410	0.907	0.952	0.935
0.8	0.018	0.007	0.011	0.334	0.601	0.946	0.978	0.966

Table1-3 The effect of VEs on effectiveness with f=0.8

VEs	ARu	ARv	ARo	ARc	VEd	VEi	VEtot	VEpop
0.4	0.048	0.031	0.034	0.334	0.351	0.857	0.907	0.898
0.6	0.021	0.011	0.013	0.334	0.480	0.935	0.966	0.960
0.8	0.015	0.006	0.008	0.334	0.587	0.954	0.981	0.976

Figure 2 The Effect of vaccine fraction on effectiveness with fixed VEs





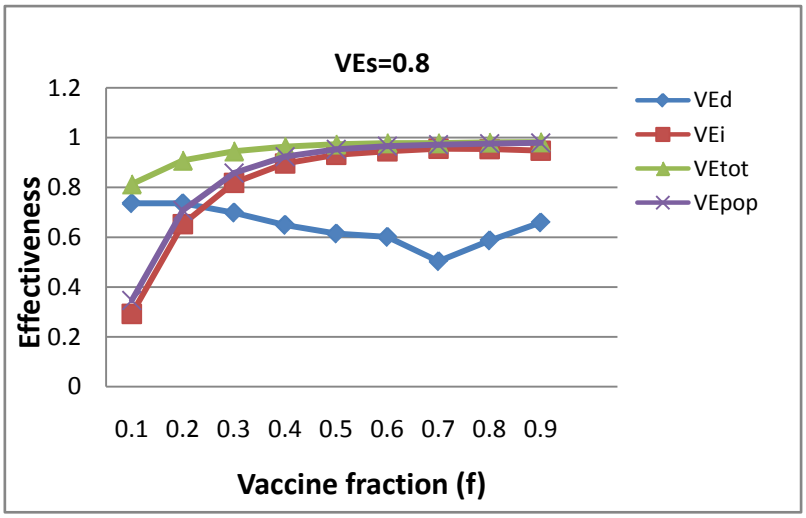


Table2-1 The effect of vaccine fraction on effectiveness with VEs=0.4

f	ARu	ARv	ARo	ARc	VEd	VEi	VEtot	VEpop
0.4	0.144	0.101	0.127	0.334	0.302	0.568	0.699	0.622
0.6	0.074	0.051	0.059	0.334	0.320	0.778	0.849	0.822
0.8	0.047	0.031	0.034	0.334	0.350	0.857	0.907	0.898

Table2-2 The effect of vaccine fraction on effectiveness with VEs=0.6

f	ARu	ARv	ARo	ARc	VEd	VEi	VEtot	VEpop
0.4	0.066	0.033	0.053	0.334	0.500	0.803	0.901	0.843
0.6	0.031	0.016	0.022	0.334	0.490	0.907	0.952	0.935
0.8	0.022	0.011	0.013	0.334	0.480	0.935	0.966	0.960

Table2-3 The effect of vaccine fraction on effectiveness with VEs=0.8

f	ARu	ARv	ARo	ARc	VEd	VEi	VEtot	VEpop
0.4	0.035	0.012	0.026	0.334	0.649	0.896	0.964	0.924
0.6	0.018	0.007	0.011	0.334	0.601	0.946	0.978	0.966
0.8	0.015	0.006	0.008	0.334	0.587	0.954	0.981	0.976

Table 3-1a Coefficients of regression model (VE vs VEd and VEd²) when f=0.4

	β0	β1	β2	R^2
VEi	0.05144	2.12161	-1.26464	0.9959
VEpop	0.0564	2.34294	-1.53733	0.9971

Note: $VE=\beta0+\beta1*VEd+\beta2*VEd^2$

Table 3-1b Estimation of VEi and VEpop based on regression model when f=0.4

VEs	VEd	VEd²	VEi	VEpop	$\widehat{VEi}$	e1	$\widehat{VEpop}$	e2
0.0	-0.03301	0.00109	0.01328	-0.00000	-0.01998	0.033256	-0.02262	0.022620
0.1	0.04228	0.00179	0.11654	0.13177	0.13889	-0.022344	0.15272	-0.020948
0.2	0.12212	0.01491	0.24827	0.28569	0.29167	-0.043402	0.31960	-0.033904
0.3	0.20695	0.04283	0.45827	0.50397	0.43634	0.021935	0.47542	0.028549
0.4	0.30245	0.09148	0.56828	0.62150	0.57743	-0.009159	0.62439	-0.002888
0.5	0.38733	0.15003	0.70614	0.75254	0.68348	0.022660	0.73326	0.019282
0.6	0.50014	0.25014	0.80260	0.84284	0.79621	0.006390	0.84365	-0.000809
0.7	0.57940	0.33570	0.85293	0.88767	0.85615	-0.003221	0.89781	-0.010142
0.8	0.64899	0.42119	0.89629	0.92373	0.89569	0.000599	0.92944	-0.005712
0.9	0.72583	0.52683	0.91960	0.94339	0.92512	-0.005519	0.94707	-0.003679
1.0	0.77994	0.60830	0.93571	0.95615	0.93688	-0.001168	0.94859	0.007564

Note: $e1=VEi-\widehat{VEi}$; $e2= VEpop-\widehat{VEpop}$

Table 3-2a Coefficients of regression model (VE vs VEd and VEd²) when f=0.6

	β0	β1	β2	R^2
VEi	0.06705	2.9987	-2.52318	0.9971
VEpop	0.007737	3.19521	-2.81034	0.9945

Note: $VE=\beta0+\beta1*VEd+\beta2*VEd^2$

Table 3-2b Estimation of VEi and VEpop based on regression model when f=0.6

VEs	VEd	VEd²	VEi	VEpop	$\widehat{VEi}$	e1	$\widehat{VEpop}$	e2
0.0	-0.01800	0.00032	0.01117	-0.00000	0.01224	-0.001078	-0.05068	0.05068
0.1	0.05078	0.00258	0.18555	0.21150	0.21287	-0.027326	0.16274	0.04876
0.2	0.12345	0.01524	0.42052	0.46541	0.39893	0.021595	0.35935	0.10606
0.3	0.21648	0.04686	0.61915	0.67087	0.59821	0.020933	0.56773	0.10315
0.4	0.32019	0.10252	0.77766	0.82233	0.76890	0.008761	0.74269	0.07964
0.5	0.40484	0.16390	0.87236	0.90478	0.86798	0.004376	0.84068	0.06409
0.6	0.48965	0.23976	0.90663	0.93532	0.93099	-0.024354	0.89847	0.03684
0.7	0.53272	0.28379	0.93314	0.95549	0.94909	-0.015950	0.91234	0.04315
0.8	0.60108	0.36129	0.94555	0.96609	0.95859	-0.013042	0.91295	0.05314
0.9	0.66020	0.43586	0.95161	0.97165	0.94780	0.003804	0.89229	0.07936
1.0	0.68849	0.47401	0.95869	0.97654	0.93640	0.022296	0.87546	0.10108

Note: $e1=VEi-\widehat{VEi}$; $e2=VEpop-\widehat{VEpop}$

Table 3-3a Coefficients of regression model (VE vs VEd and VEd²) when f=0.8

	β0	β1	β2	R^2
VEi	-0.04986	3.80693	-3.532813	0.9931
VEpop	-0.01846	3.92522	-3.75664	0.9890

Note: $VE=\beta0+\beta1*VEd+\beta2*VEd^2$

Table 3-3b Estimation of VEi and VEpop based on regression model when f=0.8

VEs	VEd	VEd^2	VEi	VEpop	$\widehat{VEi}$	e1	$\widehat{VEpop}$	e2
0.0	0.01167	0.00014	-0.00956	-0.00000	0.14236	-0.15192	0.02685	-0.026850
0.1	0.08683	0.00754	0.22103	0.27591	0.40232	-0.18129	0.29404	-0.018132
0.2	0.16335	0.02668	0.49792	0.56447	0.62600	-0.12808	0.52249	0.041979
0.3	0.25442	0.06473	0.74726	0.79944	0.83828	-0.09101	0.73702	0.062413
0.4	0.35068	0.12297	0.85749	0.89804	0.99896	-0.14147	0.89605	0.001985
0.5	0.43071	0.18551	0.91645	0.94565	1.08271	-0.16626	0.97528	-0.029628
0.6	0.47963	0.23004	0.93526	0.96045	1.11161	-0.17635	1.00000	-0.039543
0.7	0.52420	0.27478	0.94951	0.97098	1.12323	-0.17372	1.00687	-0.035885
0.8	0.58681	0.34434	0.95416	0.97599	1.11584	-0.16168	0.99132	-0.015330
0.9	0.64078	0.41060	0.95706	0.97939	1.08724	-0.13018	0.95427	0.025114
1.0	0.64662	0.41812	0.96379	0.98279	1.08291	-0.11911	0.94895	0.033842

Note: $e1=VEi-\widehat{VEi}$; $e2=VEpop-\widehat{VEpop}$

Table 4-1a Coefficients of regression model (VE vs VEd and f) when VEs=0.4

	β0	β1	β2	R^2
VEi	0.9981	-2.99787	1.14934	0.9833
VEpop	1.08703	-3.14664	1.15560	0.9778

Note: $VE=\beta0+\beta1*VEd+\beta2*f$

Table 4-1b Estimation of VEi and VEpop based on regression model when VEs=0.4

f	VEd	VEi	VEpop	$\widehat{VEi}$	e1	$\widehat{VEpop}$	e2
0.1	0.31867	0.13064	0.15949	0.15771	-0.027066	0.19985	-0.040356
0.2	0.31209	0.28209	0.33065	0.29235	-0.010263	0.33609	-0.005439
0.3	0.30210	0.43823	0.49125	0.43724	0.000989	0.48309	0.008158
0.4	0.30245	0.56828	0.62150	0.55114	0.017137	0.59756	0.023947
0.5	0.31200	0.68317	0.73422	0.63744	0.045732	0.68306	0.051159
0.6	0.32019	0.77766	0.82233	0.72782	0.049836	0.77285	0.049481
0.7	0.30290	0.83119	0.86779	0.89460	-0.063404	0.94282	-0.075026
0.8	0.35068	0.85749	0.89804	0.86631	-0.008820	0.90804	-0.010006
0.9	0.38166	0.88418	0.92438	0.88836	-0.004176	0.92611	-0.001731

Note: $e1=VEi-\widehat{VEi}$; $e2=VEpop-\widehat{VEpop}$

Table 4-2a Coefficients of regression model (VE vs VEd and f) when VEs=0.6

	β0	β1	β2	R^2
VEi	1.09713	-1.51255	0.79434	0.8170
VEpop	1.08376	-1.37718	0.7607	0.7973

Note: $VE=\beta 0+\beta 1*VEd+\beta 2*f$

Table 4-2b Estimation of VEi and VEpop based on regression model when VEs=0.6

f1	VEd	VEi	VEpop	$\widehat{VEi}$	e1	$\widehat{VEpop}$	e2
0.1	0.51532	0.20827	0.25076	0.39705	-0.18878	0.45016	-0.19941
0.2	0.51081	0.46430	0.52360	0.48330	-0.01900	0.53245	-0.00884
0.3	0.49690	0.67038	0.72154	0.58378	0.08660	0.62768	0.09386
0.4	0.50014	0.80260	0.84284	0.65830	0.14430	0.69928	0.14356
0.5	0.47793	0.87973	0.90941	0.77133	0.10839	0.80595	0.10347
0.6	0.48965	0.90663	0.93532	0.83303	0.07360	0.86587	0.06945
0.7	0.41921	0.92999	0.95100	1.01901	-0.08902	1.03896	-0.08796
0.8	0.47963	0.93526	0.96045	1.00706	-0.07180	1.03182	-0.07136
0.9	0.54948	0.93719	0.96857	0.98083	-0.04364	1.01169	-0.04312

Note: $e1=VEi-\widehat{VEi}$; $e2=VEpop-\widehat{VEpop}$

Table 4-3a Coefficients of regression model (VE vs VEd and f) when VEs=0.8

	β0	β1	β2	R^2
VEi	1.19145	-0.93050	0.45644	0.6771
VEpop	1.13292	-0.78083	0.44513	0.6560

Note: $VE=\beta 0+\beta 1*VEd+\beta 2*f$

Table 4-3b Estimation of VEi and VEpop based on regression model when VEs=0.8

f1	VEd	VEi	VEpop	$\widehat{VEi}$	e1	$\widehat{VEpop}$	e2
0.1	0.51532	0.20827	0.25076	0.39705	-0.18878	0.45016	-0.19941
0.2	0.51081	0.46430	0.52360	0.48330	-0.01900	0.53245	-0.00884
0.3	0.49690	0.67038	0.72154	0.58378	0.08660	0.62768	0.09386
0.4	0.50014	0.80260	0.84284	0.65830	0.14430	0.69928	0.14356
0.5	0.47793	0.87973	0.90941	0.77133	0.10839	0.80595	0.10347
0.6	0.48965	0.90663	0.93532	0.83303	0.07360	0.86587	0.06945
0.7	0.41921	0.92999	0.95100	1.01901	-0.08902	1.03896	-0.08796
0.8	0.47963	0.93526	0.96045	1.00706	-0.07180	1.03182	-0.07136
0.9	0.54948	0.93719	0.96857	0.98083	-0.04364	1.01169	-0.04312

Note: $e1=VEi-\widehat{VEi}$; $e2=VEpop-\widehat{VEpop}$

Table 5a Estimation of VEpop by SIR model when f=0.2

VEs	ARu	ARv	ARo	ARc	VEd	VEpop	teta	ARc_SIR	VEpop_SIR	difference
0.0	0.332	0.341	0.334	0.334	-0.027	0.000	1.208	0.324	-0.032	-0.032
0.1	0.316	0.301	0.313	0.334	0.046	0.065	1.213	0.330	0.050	-0.015
0.2	0.284	0.248	0.276	0.334	0.126	0.173	1.210	0.326	0.153	-0.020
0.3	0.266	0.209	0.253	0.334	0.212	0.242	1.222	0.340	0.256	0.014
0.4	0.240	0.165	0.224	0.334	0.312	0.331	1.225	0.344	0.348	0.017
0.5	0.204	0.119	0.185	0.334	0.415	0.445	1.233	0.353	0.475	0.030
0.6	0.179	0.088	0.159	0.334	0.511	0.524	1.240	0.360	0.559	0.035
0.7	0.151	0.056	0.130	0.334	0.626	0.610	1.259	0.381	0.659	0.049
0.8	0.116	0.031	0.098	0.334	0.736	0.708	1.258	0.380	0.742	0.034
0.9	0.096	0.015	0.079	0.334	0.844	0.764	1.278	0.401	0.803	0.039
1.0	0.077	0.004	0.061	0.334	0.954	0.818	1.314	0.436	0.860	0.042

Note: Difference=VEpop_ VEpop_SIR

Table 5b Estimation of VEpop by SIR model when f=0.3

VEs	ARu	ARv	ARo	ARc	VEd	VEpop	teta	ARc_SIR	VEpop_SIR	difference
0.0	0.332	0.340	0.334	0.334	-0.024	0.000	1.208	0.324	-0.032	-0.032
0.1	0.303	0.288	0.298	0.334	0.049	0.109	1.211	0.327	0.089	-0.020
0.2	0.268	0.234	0.258	0.334	0.127	0.229	1.209	0.325	0.206	-0.023
0.3	0.235	0.185	0.220	0.334	0.213	0.343	1.218	0.335	0.344	0.001
0.4	0.188	0.131	0.170	0.334	0.302	0.491	1.225	0.344	0.505	0.014
0.5	0.146	0.087	0.128	0.334	0.406	0.618	1.233	0.353	0.637	0.019
0.6	0.110	0.055	0.093	0.334	0.497	0.722	1.253	0.375	0.752	0.030
0.7	0.078	0.032	0.063	0.334	0.593	0.810	1.289	0.412	0.847	0.037
0.8	0.061	0.018	0.047	0.334	0.698	0.858	1.339	0.460	0.898	0.040
0.9	0.047	0.010	0.035	0.334	0.786	0.895	1.375	0.491	0.929	0.034
1.0	0.035	0.005	0.026	0.334	0.859	0.923	1.370	0.486	0.947	0.024

Table 5c Estimation of VEpop by SIR model when f=0.4

VEs	ARu	ARv	ARo	ARc	VEd	VEpop	teta	ARc_SIR	VEpop_SIR	difference
0.0	0.330	0.341	0.334	0.334	-0.033	0.000	1.199	0.313	-0.068	-0.068
0.1	0.295	0.283	0.290	0.334	0.042	0.132	1.205	0.320	0.094	-0.038
0.2	0.251	0.221	0.239	0.334	0.122	0.286	1.209	0.325	0.264	-0.022
0.3	0.181	0.144	0.166	0.334	0.207	0.504	1.203	0.318	0.477	-0.027
0.4	0.144	0.101	0.127	0.334	0.302	0.622	1.224	0.342	0.629	0.007
0.5	0.098	0.060	0.083	0.334	0.387	0.753	1.243	0.364	0.772	0.019
0.6	0.066	0.033	0.053	0.334	0.500	0.843	1.288	0.411	0.871	0.028
0.7	0.049	0.021	0.038	0.334	0.579	0.888	1.322	0.444	0.914	0.026
0.8	0.035	0.012	0.026	0.334	0.649	0.924	1.370	0.486	0.947	0.023
0.9	0.027	0.007	0.019	0.334	0.726	0.943	1.441	0.542	0.965	0.022
1.0	0.021	0.005	0.015	0.334	0.780	0.956	1.415	0.523	0.971	0.015

Table 5d Estimation of VEpop by SIR model when f=0.5

VEs	ARu	ARv	ARo	ARc	VEd	VEpop	teta	ARc_SIR	VEpop_SIR	difference
0.0	0.331	0.338	0.334	0.334	-0.021	0.000	1.204	0.319	-0.048	-0.048
0.1	0.284	0.270	0.277	0.334	0.050	0.172	1.206	0.321	0.138	-0.034
0.2	0.228	0.200	0.214	0.334	0.123	0.361	1.209	0.325	0.341	-0.020
0.3	0.163	0.129	0.146	0.334	0.211	0.565	1.219	0.337	0.566	0.001
0.4	0.106	0.073	0.089	0.334	0.312	0.734	1.259	0.381	0.766	0.032
0.5	0.061	0.037	0.049	0.334	0.398	0.854	1.284	0.407	0.880	0.026
0.6	0.040	0.021	0.030	0.334	0.478	0.909	1.361	0.479	0.937	0.028
0.7	0.031	0.013	0.022	0.334	0.563	0.935	1.431	0.535	0.959	0.024
0.8	0.023	0.009	0.016	0.334	0.615	0.953	1.454	0.552	0.971	0.018
0.9	0.018	0.006	0.012	0.334	0.670	0.964	1.514	0.592	0.980	0.016
1.0	0.017	0.004	0.011	0.334	0.738	0.968	1.559	0.619	0.982	0.014

Table 5eEstimation of VEpop by SIR model when f=0.6

VEs	ARu	ARv	ARo	ARc	VEd	VEpop	teta	ARc_SIR	VEp_SIR	difference
0.0	0.331	0.337	0.334	0.334	-0.018	0.000	1.204	0.319	-0.048	-0.048
0.1	0.272	0.258	0.264	0.334	0.051	0.211	1.202	0.316	0.166	-0.045
0.2	0.194	0.170	0.179	0.334	0.123	0.465	1.205	0.320	0.441	-0.024
0.3	0.127	0.100	0.110	0.334	0.216	0.671	1.235	0.355	0.690	0.019
0.4	0.074	0.051	0.059	0.334	0.320	0.822	1.303	0.426	0.861	0.039
0.5	0.043	0.025	0.032	0.334	0.405	0.905	1.373	0.489	0.935	0.030
0.6	0.031	0.016	0.022	0.334	0.490	0.935	1.431	0.535	0.959	0.024
0.7	0.022	0.010	0.015	0.334	0.533	0.955	1.483	0.572	0.974	0.019
0.8	0.018	0.007	0.011	0.334	0.601	0.966	1.651	0.668	0.984	0.018
0.9	0.016	0.005	0.009	0.334	0.660	0.972	1.792	0.729	0.988	0.016
1.0	0.014	0.004	0.008	0.334	0.688	0.977	1.762	0.718	0.989	0.012

Table 5f Estimation of VEpop by SIR model when f=0.7

VEs	ARu	ARv	ARo	ARc	VEd	VEpop	teta	ARc_SIR	VEpop_SIR	difference
0.0	0.329	0.336	0.334	0.334	-0.023	0.000	1.195	0.308	-0.085	-0.085
0.1	0.264	0.250	0.254	0.334	0.055	0.241	1.207	0.322	0.212	-0.029
0.2	0.170	0.147	0.154	0.334	0.131	0.540	1.210	0.326	0.528	-0.012
0.3	0.102	0.079	0.086	0.334	0.221	0.744	1.251	0.373	0.769	0.025
0.4	0.056	0.039	0.044	0.334	0.303	0.868	1.310	0.433	0.898	0.030
0.5	0.033	0.020	0.024	0.334	0.379	0.928	1.398	0.509	0.953	0.025
0.6	0.023	0.014	0.016	0.334	0.419	0.951	1.454	0.552	0.971	0.020
0.7	0.018	0.010	0.012	0.334	0.466	0.963	1.514	0.592	0.980	0.017
0.8	0.015	0.007	0.009	0.334	0.504	0.972	1.679	0.682	0.987	0.015
0.9	0.013	0.006	0.008	0.334	0.535	0.976	1.636	0.661	0.988	0.012
1.0	0.012	0.005	0.007	0.334	0.611	0.979	1.725	0.702	0.990	0.011

Table 5g Estimation of VEpop by SIR model when f=0.8

VEs	ARu	ARv	ARo	ARc	VEd	VEpop	teta	ARc_SIR	VEpop_SIR	difference
0.0	0.338	0.334	0.334	0.334	0.012	0.000	1.235	0.355	0.059	0.059
0.1	0.260	0.238	0.242	0.334	0.087	0.276	1.244	0.365	0.337	0.061
0.2	0.168	0.140	0.146	0.334	0.163	0.564	1.260	0.382	0.618	0.054
0.3	0.084	0.063	0.067	0.334	0.254	0.799	1.310	0.433	0.845	0.046
0.4	0.048	0.031	0.034	0.334	0.351	0.898	1.447	0.547	0.938	0.040
0.5	0.028	0.016	0.018	0.334	0.431	0.946	1.578	0.630	0.971	0.025
0.6	0.022	0.011	0.013	0.334	0.480	0.960	1.711	0.696	0.981	0.021
0.7	0.017	0.008	0.010	0.334	0.524	0.971	1.715	0.698	0.986	0.015
0.8	0.015	0.006	0.008	0.334	0.587	0.976	1.889	0.764	0.990	0.014
0.9	0.014	0.005	0.007	0.334	0.641	0.979	2.014	0.801	0.991	0.012
1.0	0.012	0.004	0.006	0.334	0.647	0.983	2.012	0.800	0.993	0.010