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Distinguishing vaccine efficacy and effectiveness

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Abstract

Background—Mathematical models of disease transmission and vaccination typically assume that protective vaccine efficacy (i.e. the relative reduction in the transmission rate among vaccinated individuals) is equivalent to direct effectiveness of vaccine. This assumption has not been evaluated.

Methods—We used dynamic epidemiological models of influenza and measles vaccines to evaluate the common measures of vaccine effectiveness in terms of both the protection of individuals and disease control within populations. We determined how vaccine-mediated reductions in attack rates translate into vaccine efficacy as well as into the common population measures of 'direct', 'indirect', 'total', and 'overall' effects of vaccination with examples of compartmental models of influenza and measles vaccination.

Results—We found that the typical parameterization of vaccine efficacy using direct effectiveness of vaccine can lead to the underestimation of the impact of vaccine. Such underestimation occurs when the vaccine is assumed to offer partial protection to every vaccinated person, and becomes worse when the level of vaccine coverage is low. Nevertheless, estimates of 'total', 'indirect' and 'overall' effectiveness increase with vaccination coverage in the population. Furthermore, we show how the measures of vaccine efficacy and vaccine effectiveness can be correctly calculated.

Conclusions—Typical parameterization of vaccine efficacy in mathematical models may underestimate the actual protective effect of the vaccine, resulting in discordance between the actual effects of vaccination at the population level and predictions made by models. This work shows how models can be correctly parameterized from clinical trial data.

Keywords

vaccine; efficacy; effectiveness; mathematical model; infectious disease; parameterization

1. Introduction

Vaccination programs provide both direct and indirect protection against infectious diseases. Direct protection occurs by lowering the probability of vaccine recipients to become

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infected or by reducing the infectiousness of vaccinated individuals when breakthrough infections occur [1]. Indirect protection arises by reducing transmission within the population, thereby lowering the transmission rate for both vaccinated and unvaccinated individuals.

The interchangeable use of terms used to measure and parameterize vaccine efficacy and effectiveness can lead to inaccurate parameterization of epidemiological models and needs to be made explicit. *Vaccine efficacy* measures the protective effects of vaccination by the reduction in the infection risk of a vaccinated individual relative to that of a susceptible, unvaccinated individual [2]. In contrast, depending upon the study design of clinical trials, population-level vaccine effectiveness can be further categorized into the 'direct', 'indirect', 'total' and 'overall' impact of the vaccine [2–4] (Figure 1). Halloran et al. presented a seminal framework relating the different vaccination effects relevant study designs [5]. *Direct effects* compares the direct risk of a randomly selected individual with and without the vaccination program [1]. *Indirect effects* can be estimated from the difference in the degree of protection that unvaccinated individuals receive in the presence versus the absence of a vaccine program. *'Total' effectiveness* measures the relative infection risk in vaccinated individuals compared to the infection risk in unvaccinated individuals before a vaccination program is launched [6]. Thus, 'total' effectiveness of vaccination is the effect of the vaccination program combined with the effect of the person having been vaccinated [5]. However, 'total' effectiveness does not take into account indirect protection of unvaccinated individuals in partially vaccinated population. 'O*verall' effectiveness* of a vaccination program is defined as the reduction in the transmission rate for an average individual in a population with a vaccination program at a given level of coverage compared to an average individual in a comparable population with no vaccination program [5, 6]. Thus, the 'overall' effectiveness takes into account benefits accrued by both vaccinated and unvaccinated individuals, and it is the measure most commonly used to evaluate the impact of a mass vaccination program at the population level [7, 8].

We use a model of transmission dynamics to derive the expressions for the four protective effects of a vaccine (i.e. direct and indirect effects, and 'total' and 'overall' effectiveness) and to analyse the underlying dynamics of vaccine effectiveness regarding the control of an outbreak. We apply our analysis to two mechanisms of vaccine action, 'all-or-nothing' and 'leaky' vaccines [9]. An 'all-or-nothing' vaccine offers complete protection to a subset of the vaccinated individuals but does not take in the remainder of vaccinated individuals, whereas a 'leaky' vaccine offers partial protection to every vaccinated individual. We show potential discordance between the actual effects of vaccination at the population level and predictions made by mathematical models for 'leaky' vaccines, which often arises from incorrect parameterization of vaccine efficacy. We demonstrate how the vaccine efficacy as well as the four common measures of vaccine effectiveness ([2]) can be correctly estimated from typical attack rate data for influenza and measles, and determine the threshold vaccine coverage required to attain a specific level of effectiveness for each measure.

2. Materials and Methods

We use a simple population dynamic model of an acute directly transmitted disease to take into account indirect effects of mass vaccination. We assume that the transmission occurs from person to person based on random mixing. The population is divided into vaccinated and unvaccinated groups. We assume that N_U, N_V, and N denote the number of unvaccinated individuals, the number of vaccinated individuals, and the total population (i.e. $N = N_U + N_V$), where U and V represent unvaccinated and vaccinated groups, respectively. Each group is further divided into three subgroups based on their infection status: susceptible individuals who have not been infected (S), infectious individuals who have

been infected and are currently infectious (I), and immune individuals who have recovered from the infection and developed resistance to further infection (R). We assume no latency period. Our model also assumes a closed homogeneous population where there are no births, deaths, or migration.

We assume that an unvaccinated, susceptible individual is infected at a rate proportional to β, the transmission rate among susceptible individuals. Upon infection, individuals are divided into two groups, $I_U(t)$ and $I_V(t)$; $I_U(t)$ represents the number of unvaccinated, infected individuals, and $I_V(t)$ represents the number of vaccinated, infected individuals. We define σ as the reduction of infectiousness among vaccinated people who become infected, τ_1 and τ_2 as the average length of infected period in unvaccinated and vaccinated individuals, respectively ($\tau_1 \geq \tau 2$), and $R_U(t)$ and $R_V(t)$ as the numbers of unvaccinated and vaccinated individuals who have recovered from infections. The time from the beginning of the epidemic is denoted t.

For 'leaky' vaccines, we assume that vaccination reduces the probability of infection. We also assumed that if individuals who received a 'leaky' vaccine are infected, their infectiousness will be reduced (see [10–15] for examples). Thus, vaccinated individuals (S_V) are assumed to be partially susceptible to infection. Here we define α as the vaccine efficacy for susceptibility, i.e. the relative reduction in the transmission rate among vaccinated individuals. On the other hand, for 'all-or-nothing' vaccines, we assume that a fraction α (vaccine efficacy) of the vaccinated individuals becomes immune and the remaining fraction, $1-\alpha$, is susceptible (see [15–21] for examples). We define σ as the vaccine efficacy for infectiousness for both 'leaky' and 'all-or-nothing' vaccines.

Using the definition of variables above, the flow of unvaccinated individuals between the different epidemiological classes in the presence of 'leaky' vaccination can be described by the following set of coupled, ordinary differential equations:

$$dS_U/dt = -\beta S_U\{I_U + (1-\sigma)I_V\}/N \quad \text{Eq. 1}$$

$$dI_U/dt = \beta S_U\{I_U + (1-\sigma)I_V\}/N - I_U/\tau_1 \quad \text{Eq. 2}$$

$$dR_U/dt = I_U/\tau_1 \quad \text{Eq. 3}$$

$$S_U(t) + I_U(t) + R_U(t) = N_U \quad \text{Eq. 4}$$

The initial conditions for Eqs (1)–(4) are $S_U(0) = N_U - \varepsilon$, $I_U(0) = \varepsilon$, and $R_U(0) = 0$ where $\varepsilon > 0$ is small. The differential equations for the vaccinated group are as follows:

$$dS_V/dt = -(1-\alpha)\beta S_V\{I_U + (1-\sigma)I_V\}/N \quad \text{Eq. 5}$$

$$dI_V/dt = (1-\alpha)\beta S_V\{I_U + (1-\sigma)I_V\}/N - I_V/\tau_2 \quad \text{Eq. 6}$$

$$dR_V/dt = I_V/\tau_2 \quad \text{Eq. 7}$$

$$S_V(t) + I_V(t) + R_V(t) = N_V \quad \text{Eq. 8}$$

The initial conditions for Eqs (5)–(8) are $S_V(0) = N_V - \varepsilon$, $I_V(0) = \varepsilon$, and $R_V(0) = 0$ where $\varepsilon>0$ is small. The effective reproductive ratio of this model (Eq. 1–8) is $R_C = (1-f)\beta\tau_1 + f(1-\alpha)(1-\sigma)\beta\tau_2$, which is reduced to $R_0 = \beta\tau_1$ in the absence of vaccination. By solving $R_C=1$ and assuming $\tau_1=\tau_2$, we can define the threshold vaccine coverage to prevent a disease outbreak, $f_C = (1-1/R_0)\{1/(1-(1-\alpha)(1-\sigma))\}$. The basic reproductive ratio (R_0) represents the number of new infectious cases by an index case introduced to a completely susceptible population.

To calculate the attack rate in both unvaccinated and vaccinated groups, we substitute Eq. 3 and Eq. 7 into Eq. 1:

$$dS_U(t)/dt = -\beta S_U(t)(\tau_1 dR_U(t)/dt + (1-\sigma)\tau_2 dR_V(t)/dt)/N. \quad \text{Eq. 9}$$

Because the population size and the length of the infectious period is finite, there exists a time T at which no new infections can occur and $I_U(T) = I_V(T) = 0$. Integrating Eq. 9 from 0 to T yields

$$S_U(T) = N_U \exp[-\beta\{\tau_1 R_U(T) + (1-\sigma)\tau_2 R_V(T)\}/N].$$

Similarly,

$$S_V(T) = N_V \exp[-(1-\alpha)\beta\{\tau_1 R_U(T) + (1-\sigma)\tau_2 R_V(T)\}/N].$$

Using $R_U(T) = N_U(T) - S_U(T)$ and $R_V(T) = N_V(T) - S_V(T)$, and dividing by N_U or N_V, respectively, yields

$$R_U(T)/N_U = 1 - \exp[-\beta\{\tau_1 R_U(T) + (1-\sigma)\tau_2 R_V(T)\}/N],$$
$$R_V(T)/N_V = 1 - \exp[-(1-\alpha)\beta\{\tau_1 R_U(T) + (1-\sigma)\tau_2 R_V(T)\}/N],$$

We define the attack rate (cumulative incidence) in the unvaccinated and vaccinated groups as $\Omega_{A0,1} = \frac{R_U(T)}{N_U}$ and $\Omega_{A1,1} = \frac{R_V(T)}{N_V}$, respectively. Using the vaccine coverage ($f = \frac{N_V}{N}$), gives

$$\Omega_{A0,1} = 1 - \exp[-\beta\{\tau_1(1-f)\Omega_{A0,1} + (1-\sigma)\tau_2 f\Omega_{A1,1}\}], \quad \text{Eq. 10}$$

$$\Omega_{A1,1} = 1 - \exp[-\beta(1-\alpha)\{\tau_1(1-f)\Omega_{A0,1} + (1-\sigma)\tau_2 f\Omega_{A1,1}\}]. \quad \text{Eq. 11}$$

Similarly, the expected attack rate in the pre-vaccine era, Ω_{B0}, is expressed in the following implicit equation: $\Omega_{B0} = 1 - \exp[-\beta\tau_1\Omega_{B0}]$ (see [22] for more generalized arguments).

We can use the attack rates in the presence of vaccination among the unvaccinated and the vaccinated to define the direct effectiveness for a 'leaky' vaccine ($VE_{1,1}$):

$$VE_{1,1} = (\Omega_{A0,1} - \Omega_{A1,1})/\Omega_{A0,1}. \quad \text{Eq. 12}$$

Thus, it is clear that the resulting direct effectiveness is *not* equivalent to vaccine efficacy (α) as has typically been assumed. Instead, one can set a direct effectiveness of vaccine ($VE_{1,1}$) in Eq. 12, solve for $\Omega_{A0,1}$ (or $\Omega_{A1,1}$), and substitute it into Eqs. 10 and 11, which gives implicit equations for α and $\Omega_{A0,1}$ (or $\Omega_{A1,1}$). This substitution will correctly

parameterize protective vaccine efficacy (α) from the direct effectiveness of vaccine ($VE_{1,1}$).

The focus of clinical trials has been direct effectiveness of vaccine, which estimates how well vaccinated individuals are protected. The parameterization of vaccine efficacy in mathematical models of disease transmission has often been based on the assumption that vaccine efficacy is equivalent to direct effectiveness, resulting in incorrect estimation of the impact of mass vaccination (Figure 2). For instance, if we parameterize vaccine efficacy (α) with 0.625, the resulting direct effectiveness is predicted to range from 0.11 to 0.32 (not shown), depending on vaccine coverage and relative infectiousness of the vaccinated individuals when $\tau_1 = \tau_2 = 4$ days, and $R_0 = 3.2$.

Based on our mathematical model, we distinguish the different measures of vaccine effectiveness (Eqs. 1–8), and extend previous works ([2–5]) to present numerical simulations of the common measures of vaccine effectiveness. Furthermore, we identify potential sources for underestimation of the impact of vaccination at the population level, and demonstrate how to correct this underestimation. The indirect vaccine effectiveness ($VE_{IIA,1}$) refers to the relative decrease in cumulative incidence among *unvaccinated* individuals in the presence of vaccination programs, compared to that in a comparable population with no vaccination program. By contrast, the 'total' effectiveness ($VE_{IIB,1}$) is the relative reduction in cumulative incidence among the *vaccinated*, compared to that in a comparable population with no vaccination program. The 'overall' effectiveness of a vaccination strategy ($VE_{III,1}$) is the weighted average of the outcomes in the vaccinated and the unvaccinated people.

Accordingly, the common estimation of vaccine effectiveness are presented as one minus the respective measure of relative risk (Table 1) [5]:

$$\begin{aligned} VE_{1,1} &= (\Omega_{A0,1} - \Omega_{A1,1})/\Omega_{A0,1}, \\ VE_{IIA,1} &= 1 - \Omega_{A0,1}/\Omega_{B0}, \\ VE_{IIB,1} &= 1 - \Omega_{A1,1}/\Omega_{B0}, \\ \text{and} VE_{III,1} &= 1 - \{f\Omega_{A1,1} + (1-f)\Omega_{A0,1}\}/\Omega_{B0}. \end{aligned}$$

Therefore, the typical parameterization of the efficacy of 'leaky' vaccines often leads to misestimating the actual protective effect of the vaccine. By implicit differentiation of Eqs (10) and (11), it is noteworthy that $\partial\Omega_{A0,1}/\partial f$ and $\partial\Omega_{A1,1}/\partial f$ are non-positive as their denominators can be expressed as the secondary attack size when a fraction f of the population is vaccinated. Thus, the attack size among unvaccinated individuals decreases with higher vaccine coverage due to herd immunity.

In analyzing the efficacy of an 'all-or-nothing' vaccine - assuming that the vaccine coverage is denoted by f where $f = N_V/V$ and that a fraction α of the vaccinated individuals becomes immune and the remaining fraction, 1−α, is susceptible - the differential equations for the unvaccinated group are:

$$dS_U/dt = -\beta S_U\{I_U + (1-\sigma)I_V\}/N \quad \text{Eq. 13}$$

$$dI_U/dt = \beta S_U\{I_U + (1-\sigma)I_V\}/N - I_U/\tau_1 \quad \text{Eq. 14}$$

$$dR_U/dt = I_U/\tau_1 \quad \text{Eq. 15}$$

$$S_U(t) + I_U(t) + R_U(t) = N_U \quad \text{Eq. 16}$$

The initial conditions for Eqs (13)–(15) are $S_U(0) = N_U - \varepsilon$, $I_U(0) = \varepsilon$, and $R_U(0) = 0$ where $\varepsilon > 0$ is small. The differential equations for the vaccinated group are:

$$dS_V/dt = -\beta S_V\{I_U + (1-\sigma)I_V\}/N \quad \text{Eq. 17}$$

$$dI_V/dt = \beta S_V\{I_U + (1-\sigma)I_V\}/N - I_V/\tau_2 \quad \text{Eq. 18}$$

$$dR_V/dt = I_V/\tau_2 \quad \text{Eq. 19}$$

$$S_V(t) + I_V(t) + R_V(t) = N_V \quad \text{Eq. 20}$$

The initial conditions for Eqs (17)–(19) are $S_V(0) = (1-\alpha)N_V - \varepsilon$, $I_V(0) = \varepsilon$, and $R_V(0) = \alpha N_V$. where $\varepsilon > 0$ is small. Here, we assumed that the relative infectiousness of a vaccine failure is reduced by σ (e.g. pertussis and chickenpox vaccines [23, 24]). The effective reproductive ratio of this model (Eq. 13–20) is $R_C = (1-f)\beta\tau_1 + f(1-\alpha)(1-\sigma)\beta\tau_2$, which is reduced to $R_0 = \beta\tau_1$ in the absence of vaccination. By solving $R_C = 1$ and assuming $\tau_1 = \tau_2$, we can define the threshold vaccine coverage to prevent a disease outbreak, $f_C = (1 - 1/R_0)\{1/(1-(1-\alpha)(1-\sigma))\}$. Thus, both the effective reproductive ratio and the basic reproductive ratio for an 'all-or-nothing' vaccine are equal to those for a 'leaky' vaccine.

It follows from an analysis on an equivalent 'all-or-nothing' vaccine similar to the one performed in Model (1)–(8) that

$$\Omega_{A0,2} = 1 - \exp[-\beta\{\tau_1(1-f)\Omega_{A0,2} + (1-\sigma)\tau_2 f\Omega_{A1,2} + (1-\sigma)\tau_2\alpha f\}], \quad \text{Eq. 21}$$

$$\Omega_{A1,2} = (1-\alpha)\Omega_{A0,2}, \quad \text{Eq. 22}$$

$$\text{and}\Omega_{B0} = 1 - \exp[-\beta\tau_1\Omega_{B0}]. \quad \text{Eq. 23}$$

Here, $\Omega_{A0,2}$ and $\Omega_{A1,2}$ denote the cumulative incidence among the unvaccinated and vaccinated individuals respectively, in the presence of an immunization program using an 'all-or-nothing' vaccine. Ω_{B0} is defined as the expected cumulative incidence in pre-vaccine era. From these definitions, it follows that

$$VE_{1,2} = (\Omega_{A0,2} - \Omega_{A1,2})/\Omega_{A0,2} = \alpha.$$

Consequently, parameterization for protective vaccine efficacy (α) is equivalent to direct effectiveness of vaccine ($VE_{1,2}$) when vaccine-induced protection is based on an 'all-or-nothing' mechanism. For 'all-or-nothing' vaccines, different measures of vaccine effectiveness can be defined using cumulative incidence (Eqs. 21–23) in the same way as for 'leaky' vaccines (Table 1).

3. Results

Here, we estimated the measures of vaccination effectiveness (Table 1) in models of influenza and measles vaccination using the cumulative incidence approach. We let A_O and A_1 denote the unvaccinated and vaccinated individuals in population A, and B_O the unvaccinated individuals in population B, respectively. Equivalently, population B can be considered to be population A in pre-vaccine era. As an example, we parameterized our models for 'leaky' vaccine (Eqs 1–8) based on influenza, assuming α=0.7, σ =0.5, $\tau_1 = \tau_2$ = 4 (days), β=0.6, and R_0=2.4 [25]. As a baseline parameter set for measles, we assumed α =0.95, σ =0, $\tau_1 = \tau_2$ = 7 (days), β=2.143, and R0=15 [26–28].

We found that for an influenza vaccination coverage of 20%, the direct effectiveness of influenza vaccine is estimated at 52% (Fig 2). Thus, resulting direct effectiveness in our model was found to be much lower than vaccine efficacy, that is, the extent to which the vaccine reduces transmission (70% or α=0.7), which is often assumed to be equal.

Consistent with this example of influenza, we found that the resulting direct effectiveness of measles vaccine is lower than the input parameter of vaccine efficacy. Specifically, when the level of measles vaccine coverage is 60%, the resulting direct effectiveness is 63%, although the vaccine reduces the transmission rate by 95% (α=0.95). This direct effectiveness rose to 82% when the level of vaccine coverage was increased to 90%. Therefore, the discrepancy between the vaccine efficacy (α) and the resulting direct effectiveness fell with increasing vaccine coverage. These findings indicate that the typical parameterization of vaccine efficacy using direct effectiveness of vaccine in mathematical models generally leads to underestimation of the impact of mass vaccination. This underestimation, due to errors in parameterization of individual vaccine efficacy (α), is worse for the higher e fficacy vaccine of the more transmissible measles virus than for influenza.

The estimated indirect and 'total' effectiveness of vaccination compare the cumulative disease incidence in population A (with the vaccination program) and that in population B (without the vaccination program). For an influenza vaccine with coverage of 20%, indirect effect and 'total' effectiveness of vaccine are estimated at 8% and 56%, respectively. In addition, 'overall' effectiveness is estimated at 18%. Thus, the 'total' effectiveness of an influenza vaccine is usually higher than the 'indirect' or 'overall' effectiveness (Fig 2). When the vaccine coverage is increased to 40%, the direct effectiveness of the influenza vaccine is estimated to be 59%. Similarly, 'total', indirect and 'overall' effectiveness are estimated to be 71%, 29%, and 48% at the same level of vaccine coverage. In general, three estimates of indirect, 'total', and 'overall' effectiveness increase with vaccine coverage level, as was also shown to be the case for the measles vaccine. Specifically, with 20% vaccine coverage, the resulting indirect, 'total' and 'overall effectiveness' of the measles vaccine were 0%, 51%, and 10%, respectively. However, with 60% vaccine coverage, 'total' and 'overall effectiveness' increased to 63% and 38%, respectively. Finally, when the vaccine coverage is increased to 90%, indirect, 'total', and 'overall effectiveness' rose to 2%, 83%, and 75%, respectively.

We found that when vaccine-induced protection is based on an 'all-or-nothing' mechanism, the parameterization for protective vaccine efficacy (α) is equivalent to direct effectiveness of vaccine ($VE_{I,2}$) (Figure 4). In contrast, for 'leaky' vaccines, 'total' effectiveness is greater than the direct effectiveness at all levels of vaccine coverage. These differences among the measures arise because 'total' effectiveness measures the relative transmission rate among the vaccine recipients compared to a comparable population without a vaccination program, incorporating both the direct and indirect protection provided by vaccination. In addition, as a vaccine coverage level is increased, the 'overall' effectiveness increases faster than the

indirect effect, because ‘overall’ effectiveness incorporates both the direct and indirect effects of vaccination.

4. Discussion

In mathematical models, the protective vaccine efficacy is often incorporated as the reduction in the risk of infection at individual level. To evaluate the population level effects, the unit of observation becomes the population. In translating the individual-based measure of vaccine efficacy to population-level measures, mathematical models of infectious diseases typically assume that protective efficacy of vaccine, the relative reduction in the transmission rate among vaccinated individuals, is equivalent to direct effectiveness of vaccine. Our model shows that such parameterization of vaccine efficacy for ‘leaky’ vaccines can underestimate the protective effect of the vaccine computed by the relative attack rates. Varying vaccine coverage and the reduction of infectiousness among vaccinated individuals when vaccine breakthrough occurs affect the degree of underestimation. Specifically, underestimation tends to be greater as vaccine coverage or the reduction of infectiousness among vaccinated individuals decreases. We show how the common measures of vaccine effectiveness and vaccine efficacy can be correctly derived from typical attack rate data obtained in vaccine field studies. We also show how the threshold vaccine coverage required to attain a specific level of effectiveness for each measure can be calculated.

To evaluate population effects of a vaccination program, we presented mathematical models that incorporate the study designs for evaluating various types of vaccine effectiveness ([29]). Based on our model, the protective vaccine efficacy (i.e., the level of reduction in individual transmission rate) was an input into our mathematical models, from which the resulting direct, indirect, total, and overall effects of vaccine expected at different vaccination coverage levels were determined. Herd immunity changes the level of immunity in the population after vaccination, thereby increasing ‘total’ and ‘overall’ effectiveness of a vaccine. For both ‘leaky’ and ‘all-or-nothing’ vaccines, ‘total’ effectiveness is higher than indirect or ‘overall’ effectiveness at all levels of vaccine coverage. This is because ‘overall’ and indirect effect of vaccines account for the partial protection of unvaccinated individuals through herd immunity, which is often less than the direct protection for the vaccinated.

In conclusion, in this study, we reveal the potential pitfalls in the parameterization of mathematical models and the resulting underestimation of vaccination effects. The accurate parameterization of vaccine effectiveness is fundamental to model predictions, including projections of epidemic trajectories, the optimization of vaccination policies and cost-effectiveness analyses. The framework proposed here can provide more precise parameterization of mathematical models used to evaluate the effects of vaccination at individual and population levels.

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Highlights

- There are two mechanisms of vaccine action, ‘all-or-nothing’ and ‘leaky’ vaccines.
- Typical estimation of ‘leaky’ vaccine efficacy has been incorrect in mathematical models.
- We demonstrate how the common measures of vaccine can be correctly estimated.

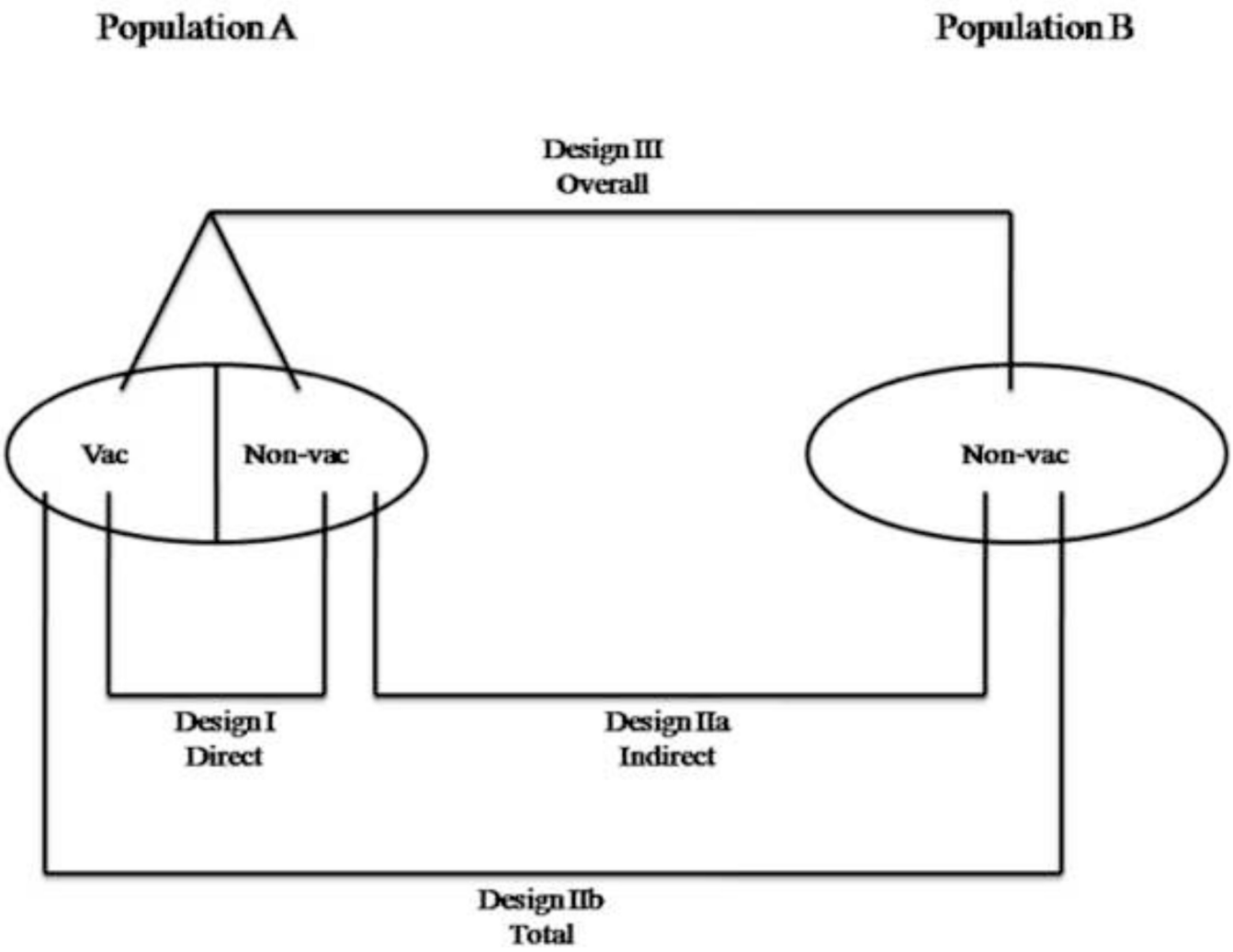

Figure 1.
Measures of vaccination effectiveness and study designs for the evaluation of each measure based on comparison populations. Population A and B are separated in every way relevant to transmission dynamics. In population A, some but not necessarily all individuals are vaccinated. In population B, all individuals are unvaccinated (Adapted from [29])

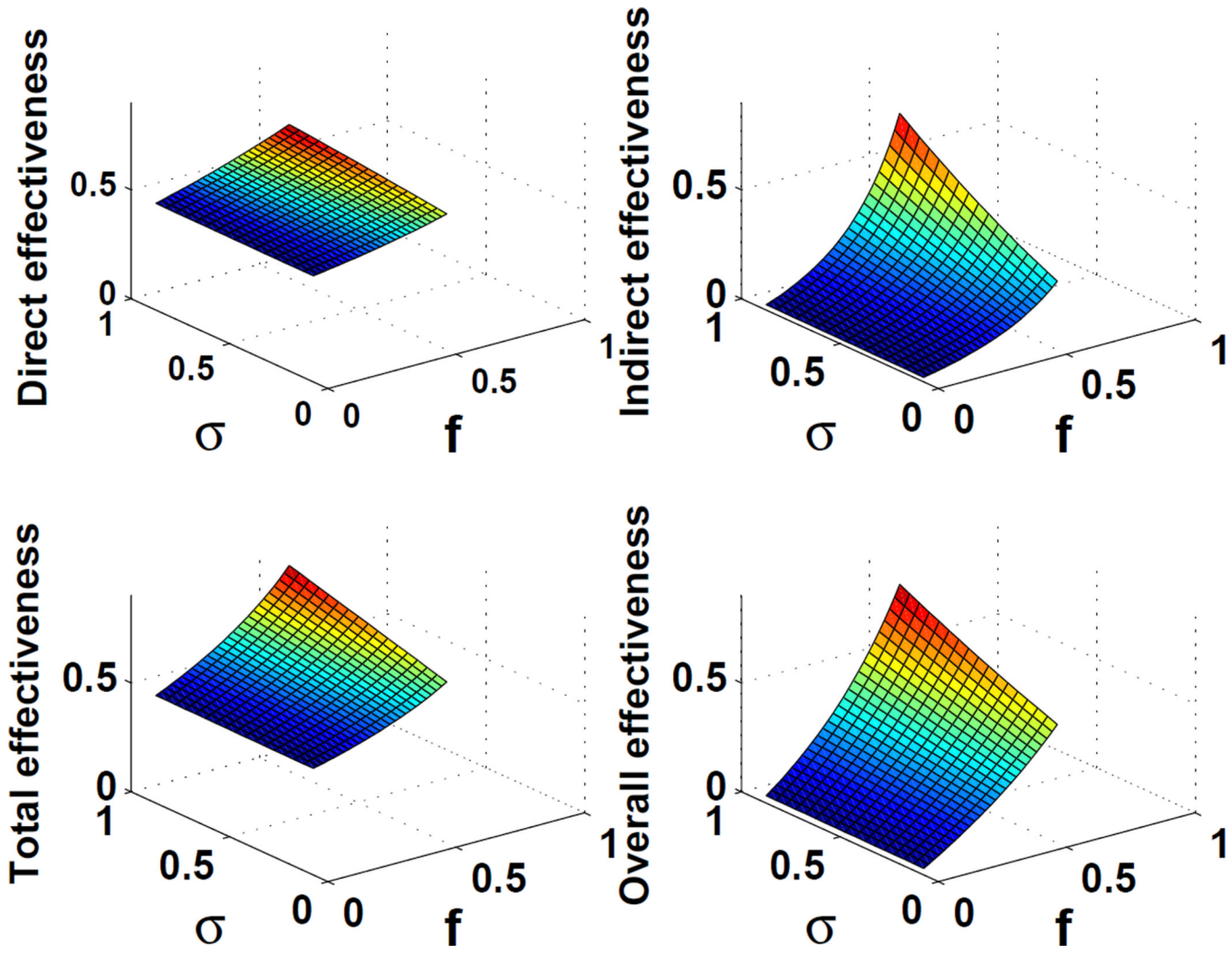

Figure 2.

Four types of vaccine effectiveness (VE_I, VE_{IIA}, VE_{IIB}, and VE_{III}) produced by a mathematical model for influenza. Parameters specific to influenza were used: α=0.7, τ_1 = τ_2 = 4 (days), β=0.6, and R_0=2.4 [25]. The vaccine coverage (f) and the reduction in infectivity among the vaccine breakthrough cases (σ) compared to unvaccinated infections were varied. Vaccine effectiveness produced by the model were often much lower than the protective vaccine efficacy, α. The discrepancy between the value of α and resulting direct effectiveness (VE_I) indicates the potential underestimation in the predicted impact of vaccination produced by mathematical models arising from common approaches in parameterization of vaccine efficacy.

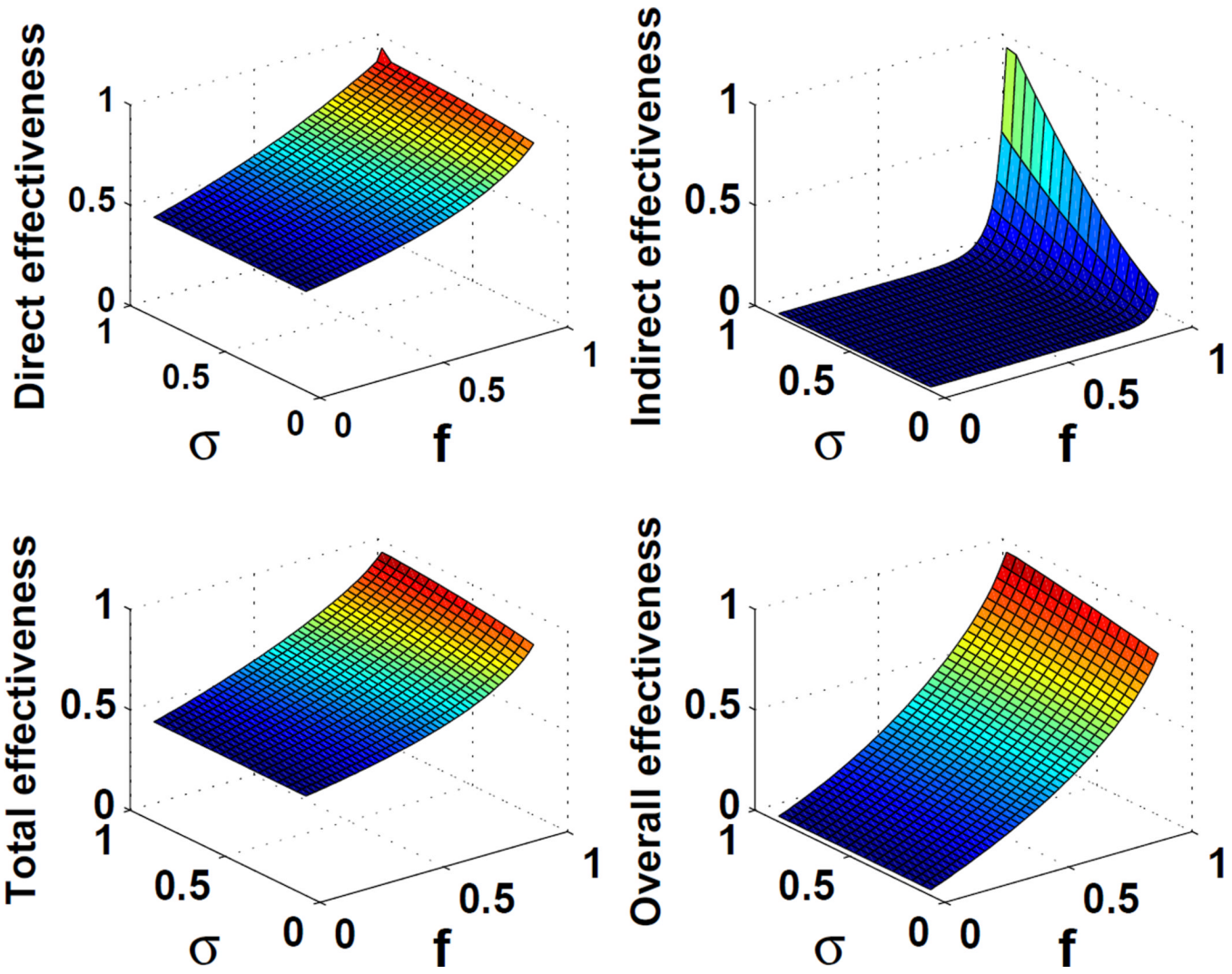

Figure 3.

Four types of vaccine effectiveness (VE_I, VE_{IIA}, VE_{IIB}, and VE_{III}) predicted for measles by using a mathematical model (Eqs. 1–8). We parameterized our model based on measles epidemiology and its vaccine: α =0.95, $\tau_1 = \tau_2 = 7$ (days), β=2.143, and R_0=15 [26–28]. The vaccine coverage (f) and the reduction in infectivity among the vaccine breakthrough cases (σ) compared to unvaccinated infections were varied. In general, the resulting vaccine effectiveness are lower than the reduction in individual infection risk by vaccination, α. Such discrepancy was highlighted with lower vaccine coverage or with lower vaccine efficacy in reducing infectivity among vaccinated individuals when vaccine breakthrough occurs.

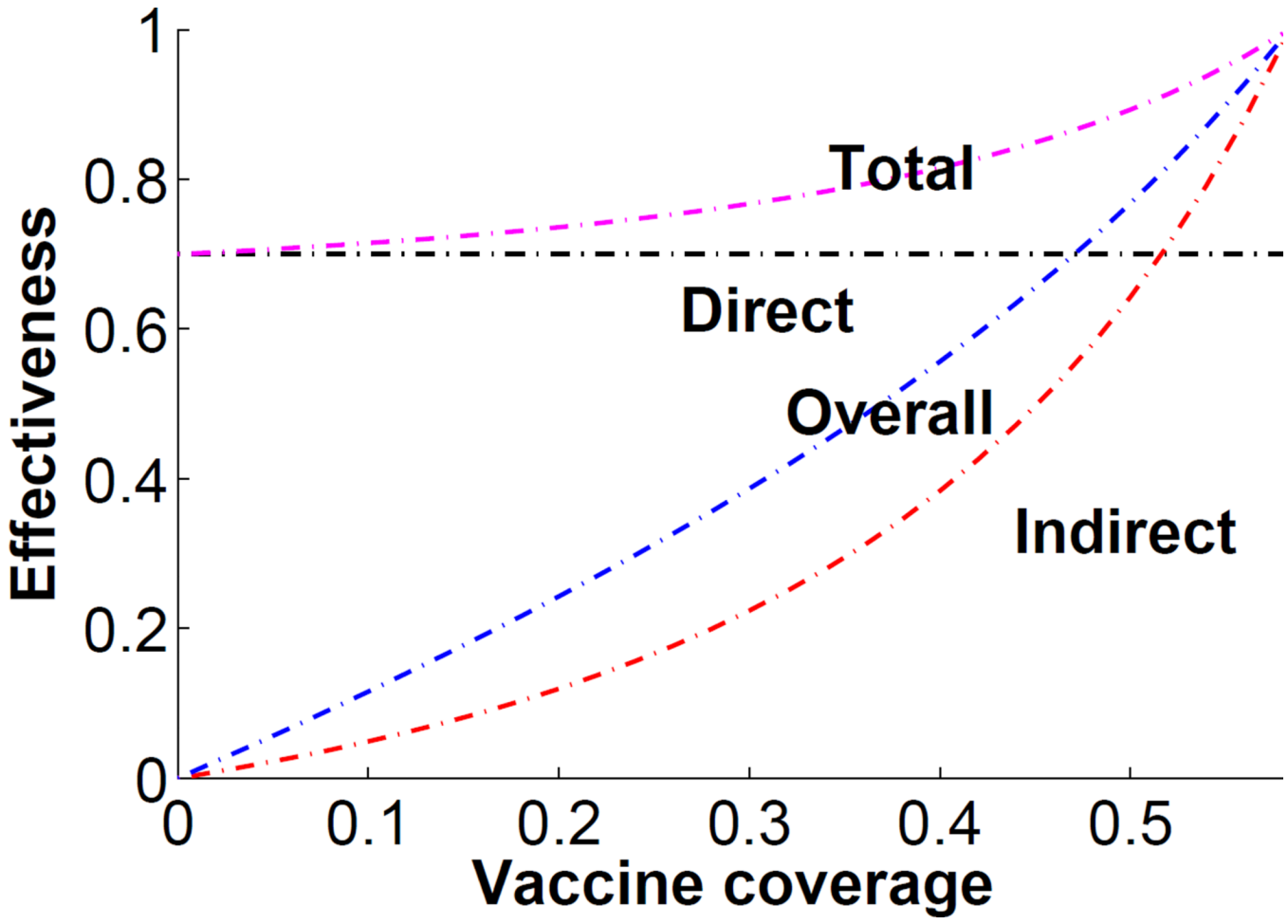

Figure 4.
Four types of vaccine effectiveness (VE_I, VE_{IIA}, VE_{IIB}, and VE_{III}) predicted for influenza and 'all-or-nothing' vaccine (Eqs. 13–20). We used parameters that are influenza-specific: $\alpha=1$, $\tau_1 = \tau_2 = 4$ (days), $\beta=0.6$, and $R_0=2.4$ [25].

Table1

Measurements of vaccination effectiveness

Study Design			
I Direct	**IIA Indirect**	**IIB Total**	**III Overall**
$VE_I = 1 - \frac{\Omega_{A1}}{\Omega_{A0}}$	$VE_{IIA} = 1 - \frac{\Omega_{A0}}{\Omega_{B0}}$	$VE_{IIB} = 1 - \frac{\Omega_{A1}}{\Omega_{B0}}$	$VE_{III} = 1 - \frac{f \cdot \Omega_{A1} + (1-f) \cdot \Omega_{A0}}{\Omega_{B0}}$