



Commentary

Estimating Influenza Vaccine Efficacy From Challenge and Community-based Study Data

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In this paper, the authors provide estimates of 4 measures of vaccine efficacy for live, attenuated and inactivated influenza vaccine based on secondary analysis of 5 experimental influenza challenge studies in seronegative adults and community-based vaccine trials. The 4 vaccine efficacy measures are for susceptibility (VE_S), symptomatic illness given infection (VE_P), infection and illness (VE_{SP}), and infectiousness (VE_I). The authors also propose a combined (VE_C) measure of the reduction in transmission in the entire population based on all of the above efficacy measures. Live influenza vaccine and inactivated vaccine provided similar protection against laboratory-confirmed infection (for live vaccine: $VE_S = 41\%$, 95% confidence interval (CI): 15, 66; for inactivated vaccine: $VE_S = 43\%$, 95% CI: 8, 79). Live vaccine had a higher efficacy for illness given infection ($VE_P = 67\%$, 95% CI: 24, 100) than inactivated vaccine ($VE_P = 29\%$, 95% CI: -19, 76), although the difference was not statistically significant. VE_{SP} for the live vaccine was higher than for the inactivated vaccine. VE_I estimates were particularly low for these influenza vaccines. VE_{SP} and VE_C can remain high for both vaccines, even when VE_I is relatively low, as long as the other 2 measures of vaccine efficacy are relatively high.

communicable disease control; immunization; influenza, human; influenza vaccines; models, theoretical; research design

Abbreviations: AR, attack rate; CI, confidence interval; RR, relative risk; VE, vaccine efficacy; VE_C , combined vaccine efficacy; VE_I , vaccine efficacy for infectiousness; VE_P , vaccine efficacy for illness given infection; VE_S , vaccine efficacy for susceptibility; VE_{SP} , vaccine efficacy for infection-confirmed influenza illness.

A single measure of vaccine efficacy fails to capture the multidimensional protective effect of vaccination. Individual vaccination can prevent or reduce a number of outcomes, including laboratory-confirmed infection, symptomatic illness given infection, infectivity of infected individuals, or a combination of these. Vaccine efficacy (VE) is a measure of relative risk (RR) that generally takes the form $VE = 1 - RR$. The absolute efficacy of a vaccine compares relative risk in a vaccinated group with that in a control group. For the relative efficacy of one vaccine compared with another formulated against the same infectious agent, the relative risk is compared between 2 different groups receiving the 2 different vaccines against the same pathogen (refer to the Appendix).

Previously, Halloran et al. (1) defined several key vaccine efficacy parameters necessary to evaluate the ability of a vac-

cine to reduce infection, symptomatic illness, and infectivity. Both vaccine efficacy for susceptibility (VE_S) and vaccine efficacy for infection-confirmed symptomatic illness (VE_{SP}) are unconditional measures; that is, they are not conditional upon infection. Both take the form $VE = 1 - AR_1/AR_2$, where AR_1 and AR_2 are the attack rates (ARs) in the 2 comparison groups for infection in the estimation of VE_S or infection-confirmed symptomatic illness in the estimation of VE_{SP} . VE_{SP} is often the only efficacy measure reported by phase III community-based vaccine trials, although this terminology is not always applied.

Vaccine efficacy for illness given infection (VE_P) and vaccine efficacy for infectiousness (VE_I) are both measures in individuals who are already infected. VE_P estimates the degree to which the vaccine prevents an infected individual

from developing symptomatic illness, or the degree to which it successfully reduces the severity of symptoms among infected individuals. Here, we are interested in pathogenicity, which is the probability of illness given infection. We assume a multiplicative relation between VE_S and VE_P with respect to VE_{SP} . VE_I estimates the reduction in the probability that an infected, vaccinated person compared with an infected, unvaccinated person will infect another person (1).

Currently, both inactivated influenza vaccine and live, attenuated influenza vaccine are administered in the United States yearly to reduce the morbidity and mortality associated with seasonal influenza. Yet, there is a need to estimate the multidimensional measures of vaccine efficacy described for both of these influenza vaccines.

In this paper, we estimate VE_S , VE_P , VE_{SP} , and VE_I for the absolute efficacy of live, attenuated vaccine; for the absolute efficacy of inactivated vaccine; and for the relative efficacy of the 2 vaccines by using data from experimental influenza challenge studies. In addition, we categorize vaccine efficacy estimates reported by a number of community-based influenza vaccine trials and summarize the results based on each of the 4 measures of vaccine efficacy. Finally, we propose the relation between VE_S , VE_P , VE_{SP} , and VE_I in a composite measure VE_C , a measure of the reduction in transmission in the entire population.

MATERIALS AND METHODS

Challenge study identification

To identify recent, relevant influenza challenge studies, we conducted a search of publications indexed in PubMed (National Library of Medicine, National Institutes of Health, Bethesda, Maryland). The search criteria consisted of the following terms: (influenza, human *and* influenza vaccine) *and* (experiment* *or* challenge* *or* “wild type” *or* wildtype). We limited the search to articles published in English between January 1, 1980, and January 1, 2008, and indexed as research conducted in humans to obtain results. A total of 231 articles were returned in early 2008. In addition, influenza experts were consulted to seek out any additional influenza challenge studies.

To be included in this analysis, studies had to be randomized, controlled trials involving an experimental influenza challenge in human subjects. At least 2 of the following groups were required for comparison: 1) participants receiving live, attenuated influenza vaccine; 2) participants receiving inactivated influenza vaccine; and 3) controls receiving placebo or no vaccine at all. All study participants had to be seronegative for the influenza challenge strain (defined as serum hemagglutination-inhibition antibody titer of $\leq 1:8$) prior to vaccination. If not all participants were seronegative, data for a seronegative subgroup had to be available. The dosage of live vaccine had to exceed 10^7 50% tissue culture infectious dose, the level used in licensed live vaccine. The challenge had to occur at least 2 weeks postvaccination, and the type of challenge strain and type of vaccine strain administered had to be identified. Furthermore, we required that the challenge strain be a wild-type virus (not

a vaccine strain) to more closely resemble natural infection. The data presented had to include the outcomes of interest (laboratory-confirmed influenza infection, viral shedding, and/or any influenza-like illness among infecteds) and provide enough detail to be able to estimate the vaccine efficacy parameters included in this secondary analysis. Each of 231 abstracts was reviewed to determine whether the inclusion criteria were met. The full-text articles for all abstracts that appeared to describe an influenza challenge study were then reviewed in detail. Any uncertainties about whether a study qualified were discussed by 2 of the authors and were resolved. In total, 5 studies met all of the inclusion criteria and were included in this analysis (2–6). For 1 study (6), a subset of the data reported in the manuscript that contained only seronegative volunteers was analyzed in accordance with the inclusion criteria.

Secondary analysis of challenge studies

Information about the sample size, treatment groups, type of influenza vaccine strain, type of influenza challenge strain, challenge strain dose, and time between vaccination and challenge was abstracted from each article, along with the number of participants in each treatment group for each of the outcomes. With these data, we calculated the following: 1) the absolute efficacy of live, attenuated vaccine; 2) the absolute efficacy of inactivated vaccine; and 3) the relative efficacy of live, attenuated vaccine compared with inactivated vaccine for each of the 4 vaccine efficacy measures described above (VE_S , VE_P , VE_{SP} , and VE_I).

To estimate VE_S and VE_{SP} , the formula $VE = 1 - RR$ was adapted so that the relative risk estimate pertained to the specific outcome of interest for each efficacy measure. For VE_S , infection was defined as laboratory-confirmed influenza infection, specifically evidenced by shedding of wild-type virus on any day postchallenge, at least a 4-fold rise in hemagglutination-inhibition antibody, or both. To estimate VE_{SP} , the outcome was defined as both laboratory-confirmed influenza infection and any illness consistent with influenza-like symptoms. To calculate $VE_P = 1 - (\text{relative pathogenicity})$, the outcome was defined as any illness consistent with influenza-like symptoms in those with laboratory-confirmed influenza infection postchallenge. For $VE_I = 1 - (\text{relative infectiousness})$, the ability of an infected individual to transmit infection was based on a surrogate measure, namely, the presence of viral shedding on any day postchallenge. All vaccine efficacy estimates are presented here as percentages.

Because the upper bound for positive efficacy estimates is 1 but the lower bound for negative efficacies is $-\infty$, each of the negative efficacy estimates was corrected. In the equation $VE = 1 - RR$, the reciprocal of the relative risk was used in place of the relative risk, and the resulting difference was multiplied by (-1) . To summarize the individual vaccine efficacy estimates, we calculated weighted averages for each efficacy measure by using the inverse of the variance as the value of the weight. In addition, 95% confidence intervals weighted by the inverse of the variance for each of these summary measures were calculated by using large-sample asymptotic methods.

Community-based vaccine trials

We reviewed the literature to identify several recent community-based influenza vaccine trials that used culture- or serologically confirmed influenza outcomes or validation sets to report at least 1 measure of vaccine efficacy. We categorized each reported measure of vaccine efficacy from the 11 studies identified according to the specific measure of efficacy to which it corresponded on the basis of the outcomes that the study recorded. A brief summary of these studies is presented in this paper.

Combined vaccine efficacy

We develop the composite vaccine efficacy measure, VE_C , similar to Halloran et al. (7), that measures how all the vaccine effects— VE_S , VE_P , VE_{SP} , and VE_I —combine to reduce transmission in the entire population (refer to the Appendix). In a fully susceptible population, a typical infected person will on average infect R_0 other people, where R_0 is the basic reproductive number. In a population, with a fraction f of the population vaccinated, a typical infected person will infect on average R_f other people, where R_f is the reproductive number with a fraction f of the population vaccinated. R_f is given in equation 7 in the Appendix. R_1 is defined as the reproductive number if the entire population is vaccinated. We define the combined efficacy as $VE_C = 1 - (R_1/R_0)$. The form of VE_C is given in equation 9 in the Appendix. Halloran et al. (7) previously referred to $1 - VE_C$ as the *immunologically naïve equivalent*, the fraction that a typical vaccinated person contributes to R_1 compared with an unvaccinated person to R_0 . In the calculations of VE_C and R_1 in the results, we assume that the pathogenicity is 67%, that is, $k = 0.67$ (8–10). In addition, we assume that unvaccinated, asymptomatic, infected people are half as infectious as symptomatic, infected people, that is, $m = 0.5$ (refer to the Appendix) (9, 10).

RESULTS

Vaccine efficacy estimates from influenza challenge studies

The treatment groups available for comparison (including the type of influenza vaccine strain), the data for each outcome, the challenge dose, and the time interval between vaccination and challenge are provided in Table 1 for each of the studies analyzed. All studies identified were carried out among adult volunteers. In each study, participants were challenged with a wild-type strain of influenza virus homologous to 1 of the strains contained in the vaccine that they had received. The time between vaccination and challenge ranged from 4 weeks to 7 months.

Figure 1A–C presents both the point estimates for VE_S , VE_P , VE_{SP} , and VE_I and the weighted mean efficacies derived from each study for the absolute efficacy of live vaccine, the absolute efficacy of inactivated vaccine, and the relative efficacy of the 2 vaccines. In addition, the weighted summary vaccine efficacy point estimates and 95% confidence intervals are provided in Table 2.

The VE_S point estimates for the absolute efficacy of live ($VE_S = 41%$, 95% confidence interval (CI): 15, 66) and

inactivated ($VE_S = 43%$, 95% CI: 8, 79) vaccine were very similar, indicating that, on average, both vaccines offered a comparable level of protection against laboratory-confirmed influenza infection.

The VE_P for the absolute efficacy of live vaccine was $VE_P = 67%$, 95% CI: 24, 100, and the VE_P for the absolute efficacy of the inactivated vaccine was $VE_P = 29%$, 95% CI: –19, 76. The point estimate for VE_P of the live vaccine was higher than the estimate for the inactivated vaccine, although the confidence intervals were wide and overlapping.

Live vaccine appeared to offer modestly better protection against laboratory-confirmed influenza illness ($VE_{SP} = 77%$, 95% CI: 27, 100) when compared with a control group than inactivated influenza vaccine did ($VE_{SP} = 63%$, 95% CI: 11, 100). However, the confidence intervals were again wide and overlapping.

The point estimates for the absolute efficacy of the vaccine in reducing viral shedding (VE_I) were low for both live, attenuated vaccine ($VE_I = -1%$, 95% CI: –27, 25) and inactivated vaccine ($VE_I = -15%$, 95% CI: –51, 20). The point estimates for the relative efficacy against infection, illness given infection, laboratory-confirmed influenza illness, and infectivity of live vaccine compared with inactivated vaccine were all positive, indicating a trend toward better protection provided by the live vaccine, although the confidence intervals lacked precision (Table 2, column 3).

Categorizing vaccine efficacy estimates from community-based influenza vaccine trials

Community-based vaccine trials often report various measures of vaccine efficacy depending upon the specific outcome identified in the study, whether it is laboratory-confirmed infection, illness given infection, laboratory-confirmed influenza illness, or infectivity among infecteds. In this paper, we categorize community-based vaccine efficacy studies based on the specific component of vaccine efficacy that was reported: VE_S , VE_P , VE_{SP} , VE_I . All but 1 of the studies reviewed here provided VE_{SP} estimates. The type of circulating strain was categorized as homologous if the authors indicated that the strain was antigenically similar, well matched, or homologous. The type of circulating strain was categorized as heterologous if the authors reported that the strain was antigenically drifted or poorly matched for some other reason. Findings are summarized briefly, and informative comparisons between studies are highlighted.

Efficacy against homologous influenza strains in children

Evidence from community-based vaccine trials indicates that live, attenuated vaccine provides significantly better protection than inactivated vaccine against laboratory-confirmed influenza illness in children. In a randomized, double-blind comparison of live, attenuated and inactivated vaccine administered to 7,852 children aged 6–59 months during the 2004–2005 flu season, when 1 of the circulating influenza strains was homologous to the vaccine strain, VE_{SP} for the relative efficacy of live compared with inactivated vaccine against culture-confirmed influenza-like illness was 45% (95% CI:

Table 1. Data From the Experimental Influenza Challenge Studies Used in the Analysis of Influenza Vaccine Efficacy

First Author, Year (Reference No.)	Treatment Group (Influenza Strain)	Total No.	No. Infected	No. With Symptomatic Illness	No. With Viral Shedding	Time to Challenge, Challenge Dose
Clements, 1984 (2)	1. Live vaccine (H3N2)	16	3	0	2	5–8 weeks, 10 ^{6.0} TCID ₅₀
	2. Inactivated vaccine (H3N2)	16	10	2	10	
	3. Unvaccinated controls (H3N2)	24	23	11	20	
Clements, 1986 (3)	1. Live vaccine (H3N2)	16	11	2	11	7 months, 10 ^{6.0} TCID ₅₀ (H3N3), 10 ^{4.0} TCID ₅₀ (H1N1)
	2. Inactivated vaccine (H3N2)	16	11	1	11	
	3. Unvaccinated controls (H3N2)	27	25	12	22	
	4. Live vaccine (H1N1)	14	7	4	6	
	5. Inactivated vaccine (H1N1)	18	12	6	12	
	6. Unvaccinated controls (H1N1)	15	11	6	11	
Sears, 1988 (4)	1. Live vaccine (H1N1)	20	12	1	6	5–7 weeks, 10 ^{6.4} TCID ₅₀ (H1N1), 10 ^{7.0} TCID ₅₀ (H3N2)
	2. Inactivated vaccine (H1N1)	16	7	1	7	
	3. Unvaccinated controls (H1N1)	28	26	12	23	
	4. Live vaccine (H3N2)	11	5	0	5	
	5. Unvaccinated controls (H3N2)	10	10	3	10	
Clements, 1990 (5)	1. Live vaccine (B)	13	9	0	9	6 weeks, 10 ⁷ TCID ₅₀
	2. Unvaccinated controls (B)	12	10	5	8	
Treanor, 1999 (6)	1. Live vaccine (H1N1)	10	3	1	3	4 weeks, 10 ⁷ TCID ₅₀
	2. Inactivated vaccine (H1N1)	10	2	2	2	
	3. Placebo (H1N1)	12	7	6	6	
	4. Live vaccine (H3N2)	8	4	1	3	
	5. Inactivated vaccine (H3N2)	10	3	2	3	
	6. Placebo (H3N2)	4	3	3	1	
	7. Live vaccine (B)	7	2	0	1	
	8. Inactivated vaccine (B)	7	0	0	0	
	9. Placebo (B)	8	5	3	2	

Abbreviation: TCID₅₀, 50% tissue culture infectious dose.

22, 61) for well-matched influenza strains (11). An earlier randomized, double-blind trial among 2,187 children aged 6–71 months with a history of recurrent respiratory infections reported similar results when the circulating influenza strain was also homologous to the vaccine strain (VE_{SP} = 53%, 95% CI: 22, 72) (12).

Several studies also reported a high VE_{SP} for the absolute efficacy of live vaccine in children. An analysis of the double-blind, randomized controlled trial conducted among 1,602 children aged 15–71 months by Belshe et al. (13, 14) found that the VE_{SP} for the absolute efficacy of live vaccine was 92% (95% CI: 89, 94). In a double-blind, randomized controlled trial of 1,616 children aged 6 to less than 36 months, Vesikari et al. (15) reported a VE_{SP} for the absolute efficacy of live vaccine as 85% (95% CI: 74, 92). Another double-blind, randomized controlled vaccine trial of 3,174 infants and young children found that the efficacy of live vaccine against homologous strains was similar (VE_{SP} = 73%, 95% CI: 63, 81) (16). In a community-based, nonrandomized field trial using surveillance cultures to estimate VE_{SP} for the absolute efficacy of live vaccine in children aged 18 months to 18

years, Halloran et al. (17) reported an efficacy of 79% (95% CI: 51, 91) against homologous strains of influenza.

Efficacy against heterologous influenza strains in children

In general, trials reporting vaccine efficacies for circulating influenza strains heterologous to the vaccine strains provided lower estimates than those reporting efficacy estimates against homologous strains. Two of the studies reported the absolute efficacy of live vaccine against heterologous strains. One study reported the absolute efficacy of live vaccine against antigenically dissimilar strains as VE_{SP} = 48%, 95% CI: –11, 76 (16), and 1 reported a VE_{SP} of 66% (95% CI: 9, 87) (17). In a community-based, nonrandomized field study of live, attenuated influenza vaccine in children aged 5–18 years during the 2003–2004 influenza season, when a drifted strain was circulating, the authors used surveillance cultures to estimate efficacy and reported a VE_{SP} of 56% (95% CI: 32, 75) for the absolute efficacy for live vaccine (18).

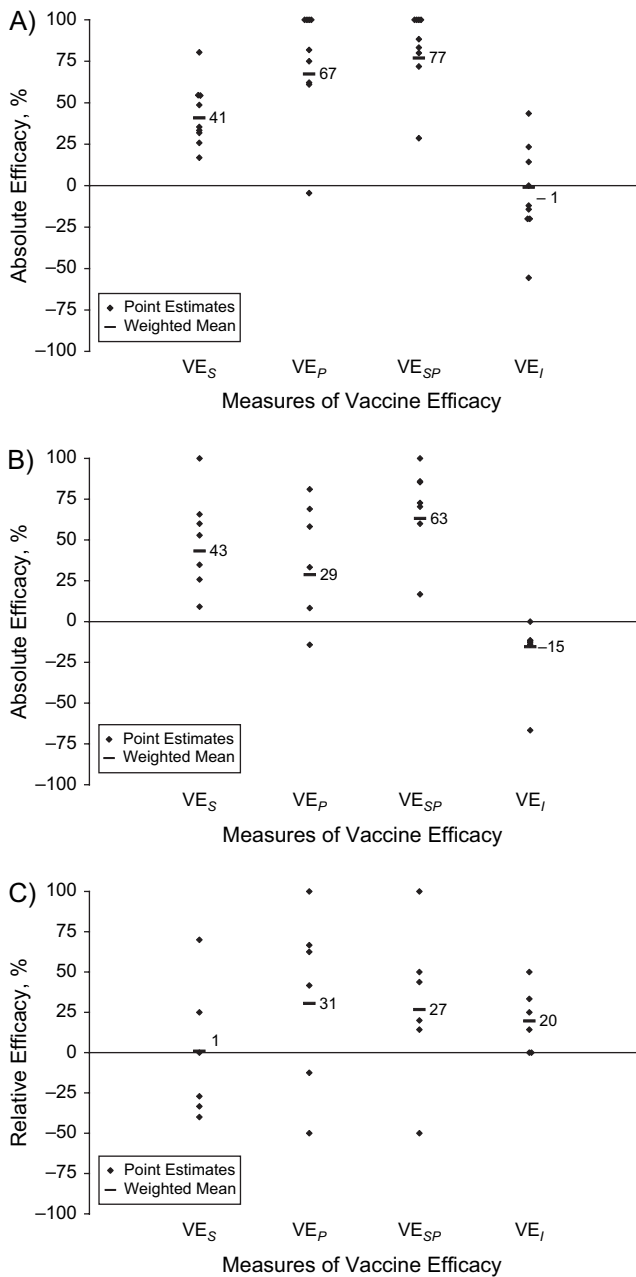


Figure 1. Point estimates and the weighted mean for the A) absolute efficacy of live influenza vaccine based on secondary analysis of the influenza challenge study data, B) absolute efficacy of inactivated influenza vaccine based on secondary analysis of the influenza challenge study data, and C) relative efficacy of live versus inactivated influenza vaccine based on secondary analysis of the influenza challenge study data. VE_I , vaccine efficacy for infection; VE_P , vaccine efficacy for illness given infection; VE_S , vaccine efficacy for susceptibility; VE_{SP} , vaccine efficacy for laboratory-confirmed influenza illness.

Not all estimates for the efficacy of live vaccine against heterologous strains were low, however. A double-blind, randomized controlled trial of 1,358 children aged 26–85 months reported a VE_{SP} for the absolute efficacy of live

vaccine against heterologous strains as 89% (95% CI: 81, 94) (14, 19), which was similar to the efficacy against homologous strains discussed above (14). In a randomized, double-blind comparison of live, attenuated vaccine with inactivated vaccine in children, the authors reported a relative efficacy against culture-confirmed influenza illness caused by poorly matched strains that was higher than that estimated for well-matched strains ($VE_{SP} = 58\%$, 95% CI: 47, 67) (11).

Other vaccine efficacy estimates in children

A true estimate of VE_I is difficult to obtain; as a result, VE_I is often estimated by using surrogate measures such as viral shedding. It is not known how well such a measure reflects true infectiousness in infected individuals. In an attenuated vaccine-strain challenge study in children, the authors reported a VE_I for the absolute efficacy of live, attenuated vaccine as 83% (95% CI: 60, 93) using viral shedding as a surrogate outcome (20). This value is likely to be an overestimate of the true VE_I because an attenuated vaccine strain was used in the challenge.

Efficacy against heterologous influenza strains in adults

Fewer recent studies have reported the efficacy of influenza vaccine in adults. In a community-based trial of 1,247 healthy adults randomized to receive live, attenuated vaccine, inactivated vaccine, or placebo during the 2004–2005 influenza season, when a drifted strain was circulating, Ohmit et al. (21) estimated the VE_{SP} against culture- or serologically confirmed infection and illness for the absolute efficacy of inactivated vaccine as 67% (95% CI: 16, 87) and for the absolute efficacy of live vaccine as 30% (95% CI: –57, 67).

As would be expected, the sensitivity of the laboratory methodology used to confirm infection affects the estimates of vaccine efficacy. In addition to reporting the vaccine efficacy against culture- or serologically confirmed influenza illness, Ohmit et al. (21) also reported the efficacy of live and inactivated vaccine against culture-positive, polymerase chain reaction–positive, culture- or polymerase chain reaction–positive, and serologically positive infection and illness. The estimates for the absolute efficacy (VE_{SP}) of live vaccine ranged from 28% (95% CI: –67, 67) to 57% (95% CI: –3, 82). The estimates for the absolute efficacy (VE_{SP}) of inactivated vaccine ranged from 74% (95% CI: 37, 89) to 78% (95% CI: 37, 93) when based on these additional laboratory measures (21).

Composite measure of vaccine efficacy

Figure 2A shows the contour lines for values of VE_{SP} as a function of VE_S and VE_P . Note that different pairs of values of VE_S and VE_P can give rise to the same value of VE_{SP} . However, the roles of VE_S and VE_P are very different, as Figure 2B–D shows. Figure 2B gives the combined vaccine efficacy VE_C as a function of VE_I for different pairs of values of VE_S and VE_P . Observe that, for low values of VE_I , the combined efficacy remains fairly high provided that the value of VE_S is high or the values of both parameters

Table 2. Weighted Mean Vaccine Efficacy Estimates and 95% Confidence Intervals From a Secondary Analysis of 5 Experimental Influenza Challenge Studies in Adults^a

	Live Vaccine: Absolute Efficacy		Inactivated Vaccine: Absolute Efficacy		Live vs. Inactivated Vaccine: Relative Efficacy	
	Weighted Mean %	95% CI	Weighted Mean %	95% CI	Weighted Mean %	95% CI
VE _S	41	15, 66	43	8, 79	1	-41, 43
VE _P	67	24, 100	29	-19, 76	31	-47, 100
VE _{SP}	77	27, 100	63	11, 100	27	-73, 100
VE _I	-1	-27, 25	-15	-51, 20	20	-15, 54

Abbreviations: CI, confidence interval; VE_I, vaccine efficacy for infectiousness; VE_P, vaccine efficacy for illness given infection; VE_S, vaccine efficacy for susceptibility; VE_{SP}, vaccine efficacy for infection-confirmed influenza illness.

^a The 5 experimental influenza challenge studies (2–6) are described in detail in Table 1.

(VE_S and VE_P) range between 40% and 60%. Figure 2C and D presents the combined vaccine efficacy as a function of VE_S and VE_P, respectively, both with VE_I = 20%. Note that the combined efficacy is not symmetric with respect to VE_S and VE_P. In fact, for high values of VE_S, regardless of the value of VE_P, the combined vaccine efficacy remains quite high. For example, when VE_S = 80% and VE_P = 20% (i.e.,

VE_{SP} = 84%; refer to Figure 2A), we obtain a combined efficacy of 85%. However, for low values of VE_S and high values of VE_P, the combined efficacy can be quite low. For example, if VE_P = 80% and VE_S = 20% (i.e., VE_{SP} = 84%), then the combined efficacy is 56%. According to the information presented in this paper, VE_S tends to range around 40% and VE_P in the 30%–70% range. This puts VE_{SP} in

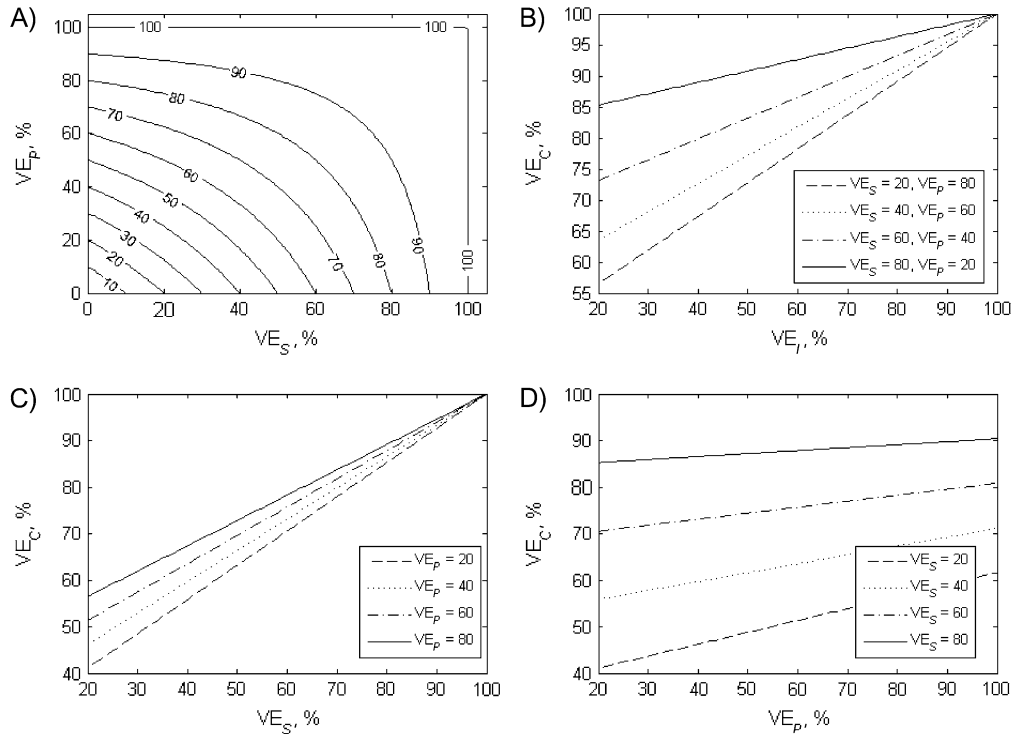


Figure 2. Vaccine efficacy for laboratory-confirmed influenza illness (VE_{SP}) and combined vaccine efficacy (VE_C) as functions of vaccine efficacy for susceptibility (VE_S), vaccine efficacy for illness given infection (VE_P), and vaccine efficacy for infectiousness (VE_I). A) The curves are contours for the VE_{SP} as a function of VE_S and VE_P. Note that the value of the VE_{SP} is constant along the contour curves at the value shown; B) VE_C as a function of VE_I for different pairs of values of VE_S and VE_P; C) VE_C as a function of VE_S for different values of VE_P when VE_I is held constant at 20%; D) VE_C as a function of VE_P for different values of VE_S when VE_I is held constant at 20%. It was assumed that the pathogenicity is 67%, that is, $k = 0.67$ (8–10) and that unvaccinated, asymptomatic, infected people are half as infectious as symptomatic, infected people, that is, $m = 0.5$ (9, 10) (refer to the Appendix).

the 40%–90% range, bringing VE_C into the 50%–80% range, even with modest values of VE_I .

Table 3 gives our expected vaccine efficacies for live and inactivated seasonal influenza vaccine in seasons when homologous and heterologous strains are circulating based on our best guesses from the information presented in this paper. We used the relative efficacy with $VE_{SP} = 50\%$ when comparing live with inactivated vaccine. We assumed that VE_S would be the same for live and inactivated vaccine. Then, VE_P was calculated by using the relation $VE_{SP} = 1 - (1 - VE_S)(1 - VE_P)$. Because all of the point estimates for the relative efficacy for VE_I in the challenge studies were non-negative and the mean was 20%, we assumed that VE_I for the live vaccine would be somewhat higher than that for the inactivated vaccine.

DISCUSSION

This analysis demonstrates the feasibility of estimating 4 components of vaccine efficacy simultaneously by using existing influenza challenge study data. Detailed, accurate, and reliable outcome data are needed to calculate these measures of vaccine efficacy with precision, and steps should be taken to incorporate the necessary data collection into the design of vaccine field trials, as noted before (1). In addition, our classification of vaccine efficacy measures from community-based vaccine trials highlights additional ranges of efficacy estimates observed and the importance of specifying the exact component of vaccine efficacy that is being reported, both to assess comparability between studies and to facilitate a more thorough understanding of the components of vaccine efficacy.

We do not know of any community-based influenza vaccine trial that has provided estimates of all 4 vaccine efficacy components or of VE_I . It would be beneficial to design future phase III vaccine trials and phase IV vaccine studies to estimate all 4 components of vaccine efficacy. Better infection outcome measures could be used to separately estimate VE_S and VE_P . Inclusion of transmission groups, such as households, in the design could enable estimation of VE_I . All 4 components of protection have been successfully estimated for influenza antiviral agents from randomized household clinical trials (22). In addition, Preziosi and Halloran (23, 24) have successfully estimated VE_I and VE_P for pertussis vaccines.

Our estimates based on challenge study data indicate that live, attenuated influenza vaccine, as well as inactivated influenza vaccine, protected against influenza infection, VE_S , in seronegative adult volunteers. In addition, the point estimates for the absolute efficacy of live vaccine were higher for efficacy against symptomatic illness given infection, VE_P , than for the inactivated vaccine, which resulted in a higher VE_{SP} for the live vaccine.

The challenge studies did not yield particularly useful information for valid estimation of VE_I for either of these vaccines. Because of the difficulty of directly measuring the probability that an infected individual will infect a susceptible individual, studies such as this one often must use potential surrogate measures of infectiousness. The VE_I estimates drawn

Table 3. Expected Absolute Vaccine Efficacies (%) for Live and Inactivated Seasonal Influenza Vaccine in Homologous and Heterologous Seasons

	Live Vaccine		Inactivated Vaccine	
	Homologous	Heterologous	Homologous	Heterologous
VE_S	40	30	40	30
VE_P	83	57	67	14
VE_{SP}	90	70	80	40
VE_I	50	30	40	20
VE_C	83	68	78	56

Abbreviations: VE_C , combined vaccine efficacy; VE_I , vaccine efficacy for infectiousness; VE_P , vaccine efficacy for illness given infection; VE_S , vaccine efficacy for susceptibility; VE_{SP} , vaccine efficacy for infection-confirmed influenza illness.

from the challenge studies may be low for this very reason. Presence or absence of viral shedding was used as a surrogate measure of infectiousness, but information is lacking regarding its validity as a surrogate in this context, and it is likely that the dichotomous outcome does not fully capture an infected individual's ability to infect a susceptible individual. Furthermore, viral shedding was a component of the definition of laboratory-confirmed infection. Because VE_I is estimated for only those with laboratory-confirmed infection, these definitions overlap significantly. It may be that more detailed characteristics of viral shedding, including average number of days of shedding or peak mean titer, would provide better estimates of VE_I , and it would be beneficial to explore the usefulness of these measures. Yet, in the context of these challenge studies, neither of these outcomes would eliminate the issue stemming from the fact that viral shedding is part of the definition of laboratory-confirmed infection.

Overall, the combined efficacy, VE_C , was consistently higher for the live vaccine when compared with the inactivated vaccine. VE_C can remain high for these vaccines, with relatively low VE_I as long as the other 2 measures of vaccine efficacy are relatively high.

Although these results provide significant insight into the specific components of vaccine efficacy, more data are needed to assess additional factors key to estimating vaccine efficacy under other conditions. By combining the information from the challenge studies and the phase III community-based vaccine trials and observational studies, we find evidence that the VE_{SP} for the live vaccine is consistently higher than that for inactivated vaccine in children, but not necessarily in adults (11, 21). This disparity is probably due to prior immunity in adults, which is not present in very young children. The challenge studies included here were conducted among adults with little or no prior immunity to the challenge strain, which indicates that these results may also be somewhat applicable to children. The effects may be larger in children given that even adults seronegative for specific influenza strains have had greater previous exposure to seasonal influenza than young children have. In the event of an influenza pandemic caused by a novel influenza strain, everyone in the population should be immunologically naïve

to the emergent strain. Because the challenge study data used in this analysis challenged only those adult volunteers who were seronegative to the challenge strain, these vaccine efficacy results could be applicable to a pandemic situation, although, again, the effect may be larger given the novelty of the pandemic strain.

The challenge studies all administered homologous strains of influenza during the challenge. We were unable to identify influenza challenge studies that met our selection criteria in which the challenge strain was heterologous to the vaccine strain; therefore, it was not possible to estimate efficacy measures from experimental challenge study data when the vaccine was poorly matched for comparison. There is significant interest in estimating vaccine efficacy for poorly matched strains because the prepandemic vaccines currently being developed will likely be poorly matched to the pandemic strain when a pandemic strain emerges. On the other hand, data from community-based trials in years when poorly matched strains of influenza circulated in the community can provide insight into how well influenza vaccines protect against poorly matched strains.

In the absence of reliable estimates from vaccine trials, the vaccine efficacy values given in Table 3 could be used as rough guides in planning potential vaccination strategies for seasonal influenza in children and pandemic influenza in the community at large. This task could be accomplished by using mathematical models (10), a subject for further research (25).

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the vaccine efficacies, described in the text, as vaccine efficacy for susceptibility, $VE_S = 1 - \theta$, vaccine efficacy for infectiousness, $VE_I = 1 - \phi$, and vaccine efficacy for disease symptoms, conditioned on being infected, as $VE_P = 1 - \psi$. We assume a multiplicative model for the vaccine efficacy for symptoms and infections so that $VE_{SP} = 1 - \theta\psi$.

We follow the format from Longini et al. (26) and Hill and Longini (27) to derive functions of the efficacy measures. We define the basic reproductive number for a given infectious disease as the expected number of secondary infections resulting from a single, typical infectious individual in a completely susceptible population. We let r_0 be the basic reproductive number for an unvaccinated, infectious, symptomatic individual. Then, the overall basic reproductive number, R_0 , for the disease is

$$R_0 = (1 - k)mr_0 + kr_0 \quad (1)$$

$$R_0 = ((1 - k)m + k)r_0. \quad (2)$$

We are interested in computing the expected number of secondary infections produced by a *typical* infected person during his or her entire infectious period, at the beginning of the epidemic. We let f be the fraction of the susceptible population that receives vaccine; I_0 and I_1 are the number of secondary unvaccinated and vaccinated cases, respectively. From equation 2 and the law of total probability, we find that

$$E(I_0) = \{(1 - k)(1 - f)mr_0 + (1 - f)kr_0\} + \{\phi(1 - \psi k)fmr_0 + \phi\psi kfr_0\}. \quad (3)$$

The expression in the first set of brackets represents the probability of being infected by an unvaccinated, infectious, asymptomatic person (the first summand) plus the probability of being infected by an unvaccinated, symptomatic person (the second summand).

The expression in the second set of brackets represents the probability of being infected by a vaccinated person and again has 2 summands, each representing an asymptomatic and a symptomatic, vaccinated, infectious person. In both summands, the probability of being infected is reduced by a factor of ϕ because of the vaccine efficacy for infectiousness. The first summand represents the probability of being infected by a vaccinated, asymptomatic person. In this instance, the probability that he or she will be asymptomatic is $1 - \psi k$. The last summand represents the probability of being infected by a vaccinated, symptomatic person, so it is reduced by ψ .

Rearranging terms, we have

$$E(I_0) = r_0(1 - f)\{(1 - k)m + k\} + r_0f\phi\{(1 - \psi k)m + k\psi\}. \quad (4)$$

Similarly, the number of secondary infections among the vaccinated susceptible population is

APPENDIX

Relative efficacy

We compute relative efficacy by comparing the vaccine efficacy estimates for the live, attenuated vaccine with those for the inactivated vaccine. In the case of VE_{SP} , we have $VE_{SP1} = 1 - (AR_1/AR_0)$ for the live vaccine and $VE_{SP2} = 1 - (AR_2/AR_0)$ for the inactivated vaccine, where AR_1 and AR_2 are the illness attack rates in the 2 respective vaccine arms and AR_0 is the illness attack rate in the placebo arm if there is one. Then, for a particular vaccine effect, the relative efficacy is $VE_{rel} = 1 - (AR_1/AR_2) = 1 - \beta$. Note that VE_{rel} is defined even if there is no placebo arm. The relation between the 2 vaccines is $VE_1 = 1 - \beta(1 - VE_2)$. So, for example, if $\beta = 0.5$ and if $VE_2 = 0.8$, then $VE_1 = 0.9$, and, if $VE_2 = 0.4$, then $VE_1 = 0.7$. The same logic applies to the conditional measures of vaccine efficacy.

Combined efficacy

To derive a simple, tractable expression, we assume that people mix homogeneously. We assume that an infected person will become symptomatic with probability k , $0 \leq k \leq 1$, that is, pathogenicity. Furthermore, we assume that being infectious and asymptomatic will have a multiplicative effect on infectiousness in the sense that an infectious, asymptomatic person will be relatively m times as infectious as a symptomatic person, where $0 \leq m \leq 1$. We parameterize

$$\begin{aligned}
E(I_1) &= \theta\{(1-k)(1-f)mr_0 + (1-f)kr_0\} \\
&\quad + \theta\{\phi(1-\psi k)fmr_0 + \phi\psi kfr_0\} \\
&= r_0\theta(1-f)\{(1-k)m+k\} \\
&\quad + r_0\theta\phi f\{(1-\psi k)m+\psi k\}. \tag{5}
\end{aligned}$$

We define the next generation matrix as

$$\mathbf{M}_f = r_0 \begin{pmatrix} (1-f)((1-k)m+k) & \phi f((1-\psi k)m+\psi k) \\ \theta(1-f)((1-k)m+k) & \theta\phi f((1-\psi k)m+\psi k) \end{pmatrix}. \tag{6}$$

We have given a heuristic derivation of the next-generation matrix, equation 6, but the matrix can also be derived from local stability analysis around the initial conditions based on the system of differential equations for the system by using a construction similar to that given in Hill and Longini et al. (27); also refer to Farrington (28).

The largest eigenvalue of \mathbf{M}_f is the reproductive number with the fraction f of the population vaccinated, where

$$R_f = r_0\{(1-f)((1-k)m+k) + \theta\phi f((1-\psi k)m+\psi k)\}. \tag{7}$$

If nobody is vaccinated, that is, $f = 0$, then $R_f = R_0$, in agreement with our previous definition. If $R_f > 1$, the epidemic grows, whereas, if $R_f \leq 1$, the epidemic will die out. We define the combined efficacy, VE_C , by examining the reproductive number when everyone in the population is vaccinated, that is, $f=1$, which is

$$R_1 = r_0(\theta\phi((1-\psi k)m+\psi k)). \tag{8}$$

Then, the combined efficacy is

$$VE_C = 1 - \frac{R_1}{R_0} = 1 - \frac{\theta\phi((1-\psi k)m+\psi k)}{(1-k)m+k}. \tag{9}$$

VE_C is a useful index because it assesses the combined effect of all 3 vaccine efficacy components, that is, $VE_S = 1 - \theta$, $VE_I = 1 - \phi$, and $VE_P = 1 - \psi$.