Evaluation of effectiveness of a vaccination program against an infectious disease at the population level

Tim E. Carpenter, PhD

Objective—To evaluate the application of a vaccine in a population of animals.

Sample Population—Field-trial data from the literature.

Procedure—A spreadsheet simulation model was constructed to estimate the impact of a vaccination program, assuming various population sizes, transmission rates, and vaccine efficacies.

Results—Total effectiveness (proportion of affected animals [i.e., cases] avoided) increased with the vaccinated proportion of the population. However, with a highly efficacious vaccine, this relationship continued after a sufficient vaccination proportion was reached, reflecting herd immunity. Evaluation of a case study indicated that what may be considered a poor vaccine on the basis of its low efficacy may protect a substantial portion of the population if the vaccine is administered to a sufficient number of susceptible animals. Further investigation of a case study of horses indicated that evaluating a vaccine based solely on its efficacy could greatly underestimate its value.

Conclusions and Clinical Relevance—When evaluating a vaccine applied to a population, in addition to the vaccine efficacy, the vaccination rate, cost of the vaccine, potential disease transmission rate, and cost of cases avoided must also be considered. Efficacy may underestimate vaccine value in terms of the reduction of indirect cases typically considered. Efficacy may underestimate vaccine value in terms of the reduction of indirect cases typically avoided when vaccination is applied in a population.


For a vaccine to be approved for usage, it must be safe. However, for its application to be justified in an animal population, its use should result in a net financial benefit (losses avoided exceed vaccination costs) or sufficient reduction in disease risk. The value or worth of a vaccine is often measured in terms of its efficacy. Vaccine efficacy (VE) may be calculated as the complement of a ratio, for example, relative risk (RR),

\[ \text{VE} = (1-\text{RR}) \times 100\% = (1-\text{IP}_v/\text{IP}_n) \times 100\% \]

or as the preventable fraction (PF),

\[ \text{VE} = \text{PF} = \frac{\text{IP}_n - \text{IP}_v}{\text{IP}_n} \times 100\% \]

where IP, is the incidence proportion (i.e., No. of affected animals/No. at risk) in the vaccinated (v) and nonvaccinated (nv) populations.

Regardless of the method used, the VE is calculated as a reduction in the IP. Consequently, basing a decision on the VE alone provides the decision-maker with useful but incomplete information. For example, a vaccine is 80% efficacious if the incidence proportions in the vaccinated and nonvaccinated groups are 0.10 and 0.50, 0.05 and 0.25, or 0.001 and 0.005, respectively. Therefore, although the VE is independent of disease incidence, the value derived from a population-based vaccination program is not. Consequently, in the evaluation of a vaccine, the absolute as well as the relative difference in disease incidence associated with different treatments must be considered simultaneously.

Whereas VE may accurately measure the ability of a susceptible animal that has been adequately exposed to an infectious agent to avoid, for example, clinical disease, VE may underestimate the value of applying the vaccine to a population. In other words, when vaccinating against an infectious disease, in addition to considering the VE (sometimes referred to as the direct effect), the indirect effect must also be considered. The indirect effect of vaccinating a population is the benefit derived from indirect, or secondary, exposure. It results from a reduction in the proportion of susceptible animals in a population that, as a result of vaccination, are vaccinal immune. Alternatively, an infected vaccinated animal, compared with an infected nonvaccinated animal, may shed the agent for a shorter period or in a lower amount. With this change in the susceptible population, all remaining susceptible animals, vaccinated or not, are at reduced risk of infection. In fact, if a vaccine provides 100% immunity in a given proportion of the vaccinated population, assuming the remaining vaccinates have no vaccinal immunity, these nonimmune vaccinates are at equal risk of infection as the nonvaccinated animals. These direct and indirect effects combine to create the total effect, or effectiveness of vaccination.

The value of a vaccination program is a function of the VE in addition to the disease dynamics in the population. Disease dynamics, in turn, are dependent on factors that contribute to the spread or control of the disease, including population size, the proportion of susceptible and immune animals, and the effective contact rate. To obtain an accurate measure of the value of vaccination in a population, the VE, expected disease incidence without vaccination, and the effect of alternative proportions of vaccination should be considered. For example, if the attack rate in a nonvaccinated population is 50%, what is the expected attack rate in a wholly or partially vaccinated population? As a result of the dynamics of an infectious disease, the attack rate is dependent on the susceptible, immune, and infectious animals in a population. Changing 1 of these subgroup sizes will, all other things being equal,
change the transmission dynamics of the disease. For example, if a critical portion of the population is vaccinated, a threshold or degree of herd immunity is reached, whereby all animals, vaccinated or nonvaccinated, are protected.\textsuperscript{1,4}

Case-control or cohort field studies may be used to measure VE.\textsuperscript{5,6} Basically, they may be based on information from a single population, where a portion (> 0 and < 1) of the population is vaccinated, or they may be conducted in 2 identical populations, 1 completely vaccinated and the other completely nonvaccinated. In the latter scenario, a necessary assumption is that the populations are identical with respect to disease dynamics, for example, population size, disease status, and transmission potential. In reality, this identical status is unlikely to develop. To obtain an accurate measure of VE, the investigator is thus faced with the first alternative, partial population vaccination. Although VE may be easily calculated from this type of trial, the effectiveness and, hence, value of the vaccination may still remain unanswered.

If a sufficient number of partial-herd vaccination trials were performed, VE could theoretically be estimated. However, this approach is expensive, time consuming, and potentially would have a negative effect on animal welfare. Alternatively, once a vaccine yields good results in an efficacy study, modeling may be performed to evaluate alternative vaccination strategy options.\textsuperscript{7,11} Modeling also avoids the problems associated with making the assumption that a susceptible animal's probability of infection remains constant throughout an epidemic.\textsuperscript{10}

Whereas much has been written recently on vaccination, it has not permitted a critical evaluation of the vaccine applied on a population level. An online computer search, using the MEDLINE/HealthSTAR database and the keyword vaccination, detected 1,514 journal articles published from 1995 through 1999. Of these, the abstracts of approximately 20% were examined. Most of those examined focused on the response of the animal to the vaccine, whereas a minority focused on the population impact. Similarly, there have been several recent articles in the veterinary literature evaluating the effect of vaccination in a variety of species, including \textit{Borrelia burgdorferi} in dogs,\textsuperscript{3} \textit{Actinobacillus pleuropneumoniae} in swine,\textsuperscript{12} and infectious upper respiratory tract disease in horses.\textsuperscript{13} Each of these studies focused on the individual animal efficacy of the vaccine while potentially underestimating its true value, as measured by its effectiveness in a population. The purpose of the study presented here was to develop a simple simulation model that could use readily available field-trial data to predict the total effectiveness and, hence, value of vaccination at the population level.

**Materials and Methods**

To evaluate the total effectiveness of a vaccine, it is first necessary to determine the attack rates in the vaccinated population (a portion or all) as well as in a nonvaccinated population. Although this may be attempted using 2 separate populations, the necessary assumption is unlikely true (ie, that the disease dynamics, specifically that the number and types of contacts in the 2 populations, are the same). Although replicating the trial in several randomly selected populations may minimize errors arising from this incorrect assumption, it is not preferable for several reasons, including cost and time considerations. Therefore, 1 alternative is available, where data from a single herd may be used to extrapolate the effect of vaccinating a previously nonvaccinated population or not vaccinating a partially or completely vaccinated population.

A modified Reed-Frost model\textsuperscript{19} was computerized in a spreadsheet format.\textsuperscript{15} The model calculates the number of new affected animals (ie, cases) in time, \( t+1 (C(t+1)) \), as follows:

\[
C(t+1) = S \times (1-q)^E,
\]

where \( S \) = the number of susceptible animals at time \( t \), \( C \) = the number of infectious cases at time \( t \), \( q \) = the probability of avoiding effective contact in a period, \( q = 1-p \), and \( E \) = the number of effective contacts in a period, and \( n \) = the population size. An assumption of the Reed-Frost model is that infected animals are infectious for 1 period and completely immune thereafter for life. In this model, an animal could become immune in this way or through vaccination. Furthermore, it was assumed here that the proportion of vaccinated animals becoming immune was equal to the VE. In other words, vaccinated animals that were immune had 100% immunity, equal to that of naturally infected animals, and the remainder of vaccinates had 0% immunity; that is, they would be fully susceptible and at equal risk of infection as those not vaccinated.\textsuperscript{16}

The vaccination simulation model was constructed as a worksheet, using a computer spreadsheet program.\textsuperscript{17} The estimation of the unknown variable, \( k \), or the number of effective contacts/period, was performed, using an optimization spreadsheet add-in.\textsuperscript{18} The basis for selecting \( k \) is dependent on the data available for fitting. For instance, if incidence data are available by period, the optimal value for \( k \) is the value that minimized the difference between the observed and simulated epidemics over time. The fit can then be tested, using a \( \chi^2 \) goodness-of-fit test. Alternatively, only summary or cumulative incidence data without temporal reference may be available. In that instance, the optimal \( k \) is the value that enables the simulation model to generate the specified number of cases in the vaccinated and/or nonvaccinated populations during an arbitrary or specified period. For purposes of simplicity, this latter alternative was assumed for the present model. A final constraint was added to the model so that if \( < 0.5 \) cases were simulated, the epidemic was considered complete.

Vaccine efficacy may be assumed to be the result of imparting complete immunity on a given proportion of the vaccinated population, whereas the remaining vaccinated animals are at equal risk of infection as the nonvaccinated animals. Alternatively, it may be assumed that partial immunity is conferred to a portion of the vaccinated group. Finally, some combination of the 2 may be assumed, whereby a portion of the vaccinated population is completely immune, some are partially protected, and others are at risk similar to those not vaccinated. For the purpose of this paper, it was assumed that the first alternative, that is, a proportion of the vaccinated population, is fully protected, and this proportion is the efficacy.

To illustrate the evaluation of a vaccination program, 4 scenarios were examined assuming populations of 100 or 1,000 and number of effective contacts (\( k \)) that would mimic an explosive epidemic (affecting 90% of 100) or a long-lasting endemic (approx 1 new case/period) situation during 16 periods. Using these \( k \)-values, simulations were run, assuming that the only differences were in the proportion of the population vaccinated and the VE. The VE was coded in the model such that the proportion of the vaccinated population...
that was completely immune was equal to the VE. This modified the calculation of susceptible animals in period 1 (S₁) from the classic Reed-Frost model equation of

\[ S₁ = S₀ - C₁ \]

to

\[ S₁ = S₀ × (1 - vr × VE) - C₁ \]

where \( S₀ \) = initial number of susceptible animals and \( vr \) = vaccination rate.

Therefore, in a population of 100 susceptible animals, a 60% vaccination rate, and 50% VE; 30 animals would have complete vaccinal immunity. The remaining 30 vaccinated animals were assumed to be at equal risk as those that were not vaccinated.

**Results and Discussion**

Values of 2.53 and 1.10 were selected for \( k \), which generated the desired epidemic and endemic scenarios, respectively. Results for 0 or 20% vaccination rates and VE ranging from 20 to 100% are presented for the 4 populations and \( k \) combination scenarios (Table 1). If there were no vaccination program when there were a high number of effective contacts in a small population (\( k = 2.53, n = 100 \)), an explosive epidemic (90 cases) could be expected. However, if even a small percentage (20%) of the population were vaccinated, as VE ranged from 20 to 100%, between 10 and 53 cases could be avoided with a vaccine effectiveness of between 11 and 58%. Furthermore, even though only 20% of the population was effectively vaccinated (20% of those vaccinated were 100% immune), an additional 33 (the difference between 53 and 20) cases (of ineffectively vaccinated or nonvaccinated animals) were avoided as the result of the indirect effect of the vaccination reducing the susceptible population. Assuming a high contact rate (\( k = 2.53 \)), the proportion of cases and vaccine effectiveness in the 1,000-animal population were similar to those evident in the 100-animal population, especially with low and moderate VE. Furthermore, the vaccine effectiveness was approximately linearly proportional to the vaccine efficiency in both simulated populations.

Alternatively, when an endemic situation (\( k = 1.10 \)) was assumed when there was no vaccination, the proportion of cases simulated in the 2 populations differed greatly. In fact, although the number of new cases was similar in large and small herds, the IP in the large herd was approximately a tenth of that observed in the small herd. The VE increased rapidly in small and large populations as the VE increased initially and slowly when the VE exceeded 60%. This suggests that vaccination is more effective in large herds where the disease is highly transmissible.

If there were no vaccination in an epidemic situation (\( k = 2.53; \) Fig 1), the vaccination effectiveness associated with different VE and vaccination proportions were determined for a small population (\( n = 100 \)). It can be seen that at low VE (up to 30%), there is a linear relationship between the VE and vaccine effectiveness. However, as with the dynamics of interaction between a population of hosts and an infectious agent when the VE increases (≥ 30% in this example), a nonlinear relationship develops as the vaccination proportion increases. As the VE increases, the vaccination proportion necessary to create this nonlinear relationship decreases.

There has been a great deal of discussion about the total (direct + indirect) effect of vaccination and herd immunity.\(^{4,17-19}\) That is, when vaccinating an animal, not only is that animal protected, others in the herd are protected, vaccinated and nonvaccinated alike, by reducing the number of susceptible animals in the herd. However, the emphasis has focused on the critical amount of herd immunity necessary to achieve eradication or elimination of a disease from a population or herd and not on sub-eradication.

The results presented here indicate that although quantification of the VE is necessary to evaluate a vaccine, it is not a sufficient condition. For example, identical vaccination scenarios (same vaccination proportion

![Figure 1](image-url)
and VE) will have substantially different results for an endemic disease, depending on whether the herd is large or small. If 20% of the population was vaccinated, and the VE was 60%, 17 versus 30 cases could be avoided in a small versus large herd. However, the ratio of animals vaccinated to cases avoided in the small herd would be 1.1 (20/17) versus 0.067 (200/30) in the large herd. This may mean, for example, that vaccination could be justified in the small, but not large, herd.

Recently, the VE of infectious upper respiratory tract disease in horses was correctly reported to be 27%. Incidence proportions were 0.22 and 0.16 for the nonvaccinated and vaccinated horses, respectively. It was concluded that the vaccine was not sufficiently efficacious, because it did not exceed 50%. This failure of the VE to exceed 50% was further interpreted as the vaccine’s inability to reduce the number of cases observed during an influenza epidemic by at least 50%. However, as discussed here, the VE does not necessarily equate to the percentage of cases avoided.

To properly evaluate the protection afforded by vaccination, the disease dynamics in a nonvaccinated population as well as in a partially or wholly vaccinated population must be considered. Specifically, the herd-level impact of vaccination must be considered. The authors further concluded that the expected vaccination benefit would only be approximately 1 fewer influenza virus infection for every 20 horses that are vaccinated, a reduction in disease risk that would not be substantial enough for vaccination to be cost-effective. However, as discussed here, not only is the vaccination effect in a population incidence dependent, the vaccination effect is also dependent on the proportion of the population that is vaccinated. Failure to account for these factors will result in an underestimate, or even exclusion, of the indirect effect of vaccination.

The simulation model developed here was used to estimate the number of effective contacts (k) 1.58, on the basis of the data presented in the manuscript. For this example, the additional constraint was that 44 cases (18/113 vaccinated and 26/120 nonvaccinated) developed during the outbreak. The model predicted that without vaccination, a total of 87 cases would have developed instead of the 44 observed when there was a 48.5% vaccination rate. Therefore, at the studied vaccination rate, 43 (49%) cases were avoided. Furthermore, if the entire population of 233 horses was vaccinated, the model predicted that only 18 cases would have developed. Consequently, a 100% vaccination proportion with a vaccine having a VE of 27% would have avoided 79% of the cases that would have otherwise developed if there were no vaccination. Hence, instead of only 7 horses apparently being protected, whole-herd vaccination could have protected 79% (69 horses) of the cases that were expected to develop if there were no vaccination.

In conclusion, although it is necessary and important to consider VE when evaluating a vaccine, it is equally important to remember that VE is only 1 of the components that determine the overall value of a vaccine. This value may be more accurately measured with the application of a simple model such as the one presented here.

A free copy of the model may be obtained from the author via electronic mail (tecarpenter@ucdavis.edu).

References