Estimability and Interpretation of Vaccine Efficacy Using Frailty Mixing Models

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The authors consider estimability and interpretation of vaccine efficacy based on time to event data, allowing that some of the population might have a very low probability of acquiring disease, and the rest have partial, possibly continuously distributed, susceptibility. The efficacy parameters of interest in the frailty mixing model include the fraction highly unlikely to acquire the infection or disease due to the vaccine, the degree of partial protection in those still susceptible, and the average protection or summary measure of efficacy under heterogeneity. The efficacy estimates can still be usefully interpreted when the heterogeneity results from heterogeneity in contact patterns, contact rates, or infectiousness of the contacts, as long as these are equal in the vaccinated and unvaccinated groups. A likelihood-based method allows estimation of the efficacy parameters of interest from grouped time to event data. Simulated vaccine studies assuming different levels and distributions of efficacy demonstrate that ignoring heterogeneity in susceptibility or exposure to infection generally results in underestimation of vaccine efficacy as well as incorrect interpretation of the estimates. The approach is also applicable to other covariates affecting susceptibility or exposure to infection in infectious diseases. Exploitation of the dependent happening structure of infectious diseases to obtain a shape for the baseline hazard may help identifiability. The authors recommend fitting several models to time to event data in vaccine studies. Am J Epidemiol 1996; 144:83-97.

attributable risk; inference; randomization; study design; survival analysis; vaccines

A goal of vaccine field efficacy studies is to obtain interpretable estimates of the effect of the vaccine on susceptibility and infectiousness (1, 2). Protective vaccine efficacy (VE) is usually measured by VE = 1 - RR, where RR is some measure of relative risk of the vaccinated compared with the unvaccinated group. The measure could be based on some member of the transmission probability family, such as the household secondary attack rate if data on actual exposure to infection are available, on incidence or a Cox regression analysis if time to event data are available, or cumulative incidence if only final value data are available (3). Interpretation of the estimates depends on the choice of parameter and the distributions of susceptibility and exposure to infection in the population under study (4-7). Cox regression has been used to estimate vaccine efficacy in randomized trials of several types of vaccines, including high-dose Edmonston-Zagreb measles vacc-

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(8) and SPf66 malaria vaccine (9). The interpretation using this model is that the vaccine has a multiplicative effect on the underlying susceptibility in all of the people vaccinated. Under the assumption of homogeneous reduction in susceptibility induced by the vaccine, homogeneous susceptibility in the unvaccinated, as well as homogeneous exposure to infection in the vaccinated and unvaccinated groups, Rhodes et al. (3) showed that Cox regression, the proportional hazards model, yields a time-invariant estimate of the reduction in susceptibility to infection equivalent to the reduction in transmission probability.

As early as 1915, however, Greenwood and Yule (10) discussed possible heterogeneities in susceptibility in all of the people vaccinated. Under the assumption of homogeneous reduction in susceptibility induced by the vaccine, homogeneous susceptibility in the unvaccinated, as well as homogeneous exposure to infection in the vaccinated and unvaccinated groups, Rhodes et al. (3) showed that Cox regression, the proportional hazards model, yields a time-invariant estimate of the reduction in susceptibility to infection equivalent to the reduction in transmission probability.
susceptibility and protection induced by vaccines have been proposed (4, 5, 13, 14), but less has been done in estimating efficacy under heterogeneity (15) unless strata were identifiable (14, 16). Unmeasured heterogeneities can distort the estimated hazard and vaccine efficacy based on the hazard ratio if not taken into account in the analysis.

In this paper, we demonstrate estimation and interpretation of vaccine efficacy from time to event data under unmeasured heterogeneity based on frailty mixing models using a likelihood-based method presented by Longini and Halloran (17). This an extension of other frailty mixing models (18–22) and cure models (23–25). We discuss problems and assumptions necessary in distinguishing heterogeneity in susceptibility from heterogeneity in exposure to infection in the absence of exposure to infection data. Simulated vaccine efficacy studies show the bias and misinterpretation of the efficacy parameters when heterogeneity in the frailty distributions or in the protection conferred by the vaccine is incorrectly specified in the fitted model. We propose exploiting the dependent happening structure of infectious diseases (26–28) to estimate the shape of the baseline hazard curve in order to improve estimability of the parameters. In the discussion, we suggest fitting several different models and comparing the estimates and interpretations when using time to event data to estimate vaccine efficacy.

**ESTIMATING VACCINE EFFICACY WITH TIME TO EVENT DATA**

We are considering the specific case of vaccine studies with time to event data with vaccine efficacy based on survival analysis methods. In randomized trials, the assumption is generally made that the comparison groups are equally exposed to infection and are in other material aspects alike (10). Let \( \lambda_1(t) \) and \( \lambda_0(t) \) be the hazard rate or incidence, called force of infection in infectious diseases, in the vaccinated and unvaccinated groups, respectively. Under the Cox regression model (29), the proportional hazards assumption, the hazards in the two groups are related by a constant \( \theta \), so that \( \lambda_1(t) = \theta \lambda_0(t) \). Vaccine efficacy based on \( \theta \) is defined as

\[
VE_\theta(t) = 1 - \frac{\lambda_1(t)}{\lambda_0(t)} = 1 - \theta.
\]

The Cox regression parameter \( \theta \) can be estimated using a partial likelihood approach.

**Interpretation of hazard in infectious diseases**

In infectious diseases, we think of the hazard rate of infection as resulting from the combination of the exposure to infection and the susceptibility of the person being exposed, even if we cannot measure the components. Exposure to infection is a function of the rate of contacts, the mixing patterns, the type of contact, whether the contacts are with infectious sources, and the level of infectiousness of the infective contacts. The level of susceptibility is the probability of becoming infected or developing disease defined with respect to some specified exposure to infection (30). Under assumptions of simple random mixing that does not change over time, let \( c \) denote the number of contacts per time, \( p(t) \) be the probability that a contact is infectious, such as the prevalence of infectives, \( \pi \) be the transmission probability to an unvaccinated susceptible host during contact with an infectious person or other source of specified infectiousness, and \( \theta \) be the relative susceptibility of a vaccinated person compared with an unvaccinated person conditional on a specified exposure to infection. We can model the hazard rate based on these components in the unvaccinated and vaccinated persons as

\[
\lambda_0(t) = c \pi p(t),
\]

and

\[
\lambda_1(t) = \theta c \pi p(t) = \theta \lambda_0(t),
\]

respectively. The cumulative hazards and survival functions for the two groups are

\[
\Lambda_0(t) = \pi c \int_0^t p(\tau)d\tau, \quad \Lambda_1(t) = \theta \Lambda_0(t)
\]

\[
S_\nu(t) = \exp[-\Lambda_\nu(t)], \quad \nu = 0, 1.
\]

The estimate of \( \theta \) based on Cox regression, under the assumptions of equal (10) and homogeneous (3) exposure to infection and homogeneous susceptibility in each group, is interpreted to be the relative reduction in hazard due to the direct protective effects of the vaccine (30).

**FRAILTY MODELS AND VACCINE EFFECT MEASURES**

If susceptibility is heterogeneous in one or both of the comparison groups, either because the underlying population susceptibility is heterogeneous or the effect of the vaccine is heterogeneous, then the assumptions of the proportional hazards assumption are violated. Estimation of the Cox regression parameter to estimate vaccine efficacy would be incorrect. Frailty models or random effects survival models take unmeasured heterogeneity into account (18, 19, 31). In frailty models, all individuals in a cohort are assumed to experience
some common baseline hazard or force of infection, which is then multiplied by some factor for each individual depending on how susceptible that person is. The distribution of frailty is described by the random variable \( Z \). Thus, an individual whose frailty value is \( z \) in a cohort experiencing the baseline hazard \( \lambda(t) \) has an individual hazard rate of \( \lambda(t|z) = z\lambda(t) \). In a cohort with a frailty distribution experiencing a constant baseline hazard, the hazard will appear to decrease over time because the population will become enriched in resistant individuals as the frail individuals are depleted (31, 32).

Assume that the heterogeneity in susceptibility in the unvaccinated and vaccinated groups is described by the random variables \( Z_0 \) and \( Z_1 \), respectively. Combining the general frailty model with the concepts from infectious diseases, the conditional hazards for individuals in the unvaccinated and vaccinated groups are

\[
\lambda_0(t|Z_0) = Z_0\lambda_0(t) = Z_0c\exp(t),
\]

and

\[
\lambda_1(t|Z_1) = Z_1\lambda_1(t) = Z_1c\exp(t)\theta,
\]

respectively.

Although the term frailty suggests that the heterogeneity is in susceptibility, heterogeneity in the individual hazard rates could be due to heterogeneity in other components of the hazard rate, specifically, aspects of exposure to infection such as the contact rate, infectiousness of contacts, type of contacts, or the proportion of the contacts that are infected. An example of heterogeneous contacts would be in a pertussis vaccine trial in children, in which a fraction of the children stay at home and do not make regular contact with other children. They may never be exposed to infection, while other children attend day school and have the opportunity to be exposed to infection. Heterogeneity in contact rates might also play a role in human immunodeficiency virus vaccine trials. The prevalence of infection in the sexual contacts could also be heterogeneous in human immunodeficiency virus vaccine trials if people choose partners in different social settings (33). In malaria vaccine trials, local clustering of mosquitoes can influence the prevalence of infection in the biting mosquito vectors.

The role of randomization is to try to ensure that exposure to infection is equal in the vaccinated and unvaccinated groups. Even when the unvaccinated and vaccinated groups are equally exposed to infection, the exposure within groups could be heterogeneously distributed, however, distorting estimates based on a proportional hazards assumption (7). Thus, \( Z_0 \) and \( Z_1 \) could represent variation in hazard rates due to differential exposure to infection.

**Mixing models and vaccine efficacy**

In the following development, it is important to distinguish between heterogeneity in the distributions of the hazard rates and heterogeneity in vaccine effects. Assume that the distribution of susceptibility in each group is such that a proportion \( \alpha_0 \) of people are highly protected with frailty value \( Z_0 = 0 \), and the remainder have some homogeneous degree of susceptibility. Thus, the distribution is degenerate with two point masses. Then the frailty distributions \( Z_0 \) in the two groups are

\[
\Pr(Z_0 = 0) = \alpha_0, \quad \nu = 0.1,
\]

and

\[
Z_0|Z_0 > 0 = \text{constant}, \quad \text{with probability } 1 - \alpha_0.
\]

The difference \( \alpha_1 - \alpha_0 \) is the proportion of people highly protected by the vaccine. The relative susceptibility of those with \( Z_0 > 0 \) is the ratio \( \theta \) of the two constant susceptibilities. If the vaccine protects some people completely and some people not at all, the all-or-none vaccine (4), then the ratio of the constants in the susceptible groups is \( \theta = 1 \). We call a vaccine that protects some people quite well but confers only partial protection on others the degenerate mixed model of vaccine action.

Longini and Halloran (17) developed a more general model of heterogeneity that allows some proportion \( \alpha_0 \) of the people to be highly or completely protected so that \( Z_0 \) has point mass at 0, while susceptibility in the susceptible proportion can follow any continuous distribution \( f_s(\cdot) \) with probability \( 1 - \alpha_0 \). Thus,

\[
\Pr(Z_0 = 0) = \alpha_0,
\]

and

\[
Z_0|Z_0 > 0 = X_0 \sim f_s(\cdot), \quad \text{with probability } 1 - \alpha_0.
\]

The variance of the continuous part of the distribution is \( \text{Var}(X_0) = \delta_0 \), independent of the proportion completely susceptible. This reduces to the simple degenerate mixed models described above if \( \text{Var}(X_0) = \delta_0 = 0 \). The distribution \( f_s(\cdot) \) allows for the flexibility to model the shape and spread of the continuous part of the distribution of \( Z_0 \).

An example of the distribution of susceptibility in the vaccinated and unvaccinated groups if \( X_0 \) follows a gamma distribution is shown in figure 1. In this example, \( \alpha_0 = 0.1 \) and \( \alpha_1 = 0.5 \). The expectation of
the random variable in the susceptible proportion of each group is equal to one. In the vaccinated group, the susceptibility is reduced by the factor $\theta = 0.5$ in the people still susceptible. The area under each curve of susceptibles is $1 - \alpha_0$ and $1 - \alpha_1$ in the unvaccinated and vaccinated groups, respectively. In this example, both the distributions of susceptibility and the vaccine effects are heterogeneous.

For a vaccine that highly protects some people while conferring partial protection on the rest, the efficacy measures of interest are the increase in the fraction highly protected by the vaccine, the relative reduction in the proportion susceptible, the expected relative reduction in susceptibility in the susceptibles, and the summary measure or average reduction in susceptibility induced by the vaccine (table 1). The difference between the proportion highly protected in each group, $VE_\alpha = \alpha_1 - \alpha_0$, would measure the fraction of the population highly protected due to vaccination. The relative reduction in the proportion susceptible is

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**FIGURE 1.** Schematic distribution of susceptibility in the (a) unvaccinated and (b) vaccinated. The proportion highly protected is $\alpha_0 = 0.1$ in the unvaccinated and $\alpha_1 = 0.5$ in the vaccinated. The expectation of the random variable in the susceptible proportion of each group is equal to one. The area under each curve of susceptibles is $1 - \alpha_0$ and $1 - \alpha_1$ in the unvaccinated and vaccinated groups, respectively. In the vaccinated group, the susceptibility is reduced by the factor $\theta = 0.5$. 

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Following Hougaard (18, 19, 22) and Aalen (20, 21),
each group from the survival curve of that group.
What can be estimated is the population hazard for
individual, and the individual hazards cannot be estimated.
Z is unknown for each individual measured, the value of
from several different sources into account to arrive at
could be used to take heterogeneity in the hazard rates
distribution of susceptibility. Thus, frailty models
frailty distribution could not be interpreted as the
expected relative reduction in susceptibility due to the
vaccine. The measure $VE_{\alpha} = 1 - \alpha_1 - \alpha_0$ is the efficacy of the vaccine in
ferring partial protection conditional both on a specified
exposure to infection and on remaining to some degree susceptible. The summary measure of protective vaccine efficacy is the expected relative reduction in susceptibility conferred by the vaccine, $VE_{\alpha} = \frac{1 - \alpha_1 - \alpha_0}{1 - \alpha_0}$.

Interpretation of the efficacy estimates does not depend on the source of heterogeneity in the hazard in the two groups as long as the heterogeneity is the same in both groups in the absence of intervention. In other words, $Z_0$ and $Z_1$ do not need to describe the distribution in susceptibility but could describe other sources of heterogeneity in the individual hazards. In the example above of the pertussis vaccine in which some children were not exposed to infection, if all of the unvaccinated children were susceptible, then $\alpha_0$ would give a measure of the proportion of children not exposed to infection. The measure $VE_{\alpha} = \frac{1 - \alpha_1 - \alpha_0}{1 - \alpha_0}$ would be the additional fraction highly protected by the vaccine. The measure $VE_{\alpha} = \frac{1 - \alpha_1 - \alpha_0}{1 - \alpha_0}$ would be the expected relative reduction in susceptibility due to the vaccine in those still susceptible, even though the frailty distribution could not be interpreted as the distribution of susceptibility. Thus, frailty models could be used to take heterogeneity in the hazard rates from several different sources into account to arrive at better efficacy estimates.

**Estimation and inference**

The problem is that when the heterogeneity is not measured, the value of $Z_0$ is unknown for each individual, and the individual hazards cannot be estimated. What can be estimated is the population hazard for each group from the survival curve of that group. Following Hougaard (18, 19, 22) and Aalen (20, 21), the population level survival functions at time $t$ in the vaccinated and unvaccinated groups under frailty is expressed as the expectation of the probability of survival

$$S_s(t) = E\{\exp[-Z_s \Lambda_s(t)]\}. \quad (8)$$

By including the model for the frailty distribution in the population survival function, estimates of the distribution and efficacy parameters of interest can be obtained. The population survival function for both the all-or-none vaccine and the degenerate mixed model is

$$S_s(t) = \alpha_s + (1 - \alpha_s)\exp[-\Lambda_s(t)], \quad \nu = 0, 1,$$

(9)

where $\Lambda_s(t)$ is the cumulative hazard as in equation 3, and with the all-or-none vaccine, $\theta = 1$. Longini and Halloran (17) developed the expression for the population survival function if $X_s$ follows a gamma distribution in the susceptible portion of the population (see Appendix).

Violation of the proportional hazards assumption (20) under frailty distributions is illustrated in figure 2. If the proportional hazards assumption is correct, the plots of $\ln(-\ln S_s(t))$ of the groups being compared will be parallel, where $\ln$ is the natural logarithm. Figure 2a plots $\ln(-\ln S_s(t))$ assuming that everyone in the unvaccinated group is homogeneously susceptible. The three distributions of vaccine protection are 1) homogeneous partial protection, so that the proportional hazards assumption holds and, in the presence of frailty, 2) the all-or-none vaccine, and 3) the degenerate mixed model. In the latter two cases, the plots deviate from parallel. Both vaccines with heterogeneous protection approach the asymptote of $\ln(-\ln(\alpha_s))$. The departure from proportional hazards under the two mixing models is also seen in the time-varying hazard ratios (figure 2b).

The efficacy parameters of interest in table 1 can be estimated using methods for grouped survival data (17, 20). The data are grouped with observations made at times $i_0(=0), i_1, \ldots, i_k$, with time intervals defined as
FIGURE 2. a, diagnostic natural log In (—In S(t)) survival plots checking the proportional hazards assumption for a vaccine conferring homogeneous partial protection, an all-or-none vaccine, and a mixed degenerate vaccine model compared with the unvaccinated group. b, plots of 1 - hazard ratios for homogeneous partial protection (θ = 0.5), the all-or-none vaccine (α = 0.5), and the mixed degenerate model (θ = 0.75, α = 0.33). VE<sub>sum</sub> = 0.5 at time t<sub>0</sub> = 0 in these three cases.

(t<sub>i-1</sub>, t<sub>i</sub>), i = 1, .., k. Let r<sub>iv</sub> be the number of persons at risk in group v, v = 0,1, at the beginning of interval i, and let m<sub>iv</sub> be the number infected during that interval. Then the likelihood function is

\[
L = \prod_{i=1}^{k} \prod_{v=0}^{1} \left\{ \frac{S_v(t_i)}{S_v(t_{i-1})} \right\}^{r_{iv}} \left\{ 1 - \frac{S_v(t_i)}{S_v(t_{i-1})} \right\}^{m_{iv}}
\]

where S<sub>v</sub> is from either equation 9 or equation 19. We maximize equation 10 using standard methods. Given sufficient data and appropriate assumptions, estimates can be obtained for α<sub>0</sub>, α<sub>1</sub>, δ<sub>0</sub>, δ<sub>1</sub>, θ, and the baseline hazard. For the degenerate mixing models in which susceptibles are assumed to be homogeneous, we set δ<sub>0</sub> = δ<sub>1</sub> = 0. If all of the unvaccinated group is assumed to be susceptible, then α<sub>0</sub> is set equal to 0. The delta method is used to construct a confidence interval for VE<sub>sum</sub>.

SIMULATED EFFICACY STUDIES

To assess the role of heterogeneity in estimating efficacy, we simulated randomized vaccine efficacy trials with either 100, 1,000, or 10,000 individuals each in the vaccine and placebo arms. A cholera...
vaccine trial in Bangladesh, for example, had three groups, two vaccine and one placebo, with approximately 20,000 people in each arm (34). We performed stochastic simulations of different distributions of protection assuming a constant baseline hazard with varying levels of right censoring in the unvaccinated group. Different efficacy levels were simulated by varying $\alpha_1$, the proportion highly protected, from close to 0 to close to 1, and the expected relative residual susceptibility in the vaccinated group compared with the unvaccinated group, $\theta$, from 0 to 1. Everyone in the unvaccinated group was assumed to be susceptible, so $\alpha_0 = 0$. The levels of right censoring were either 50 percent or 5 percent in the unvaccinated group. The level of right censoring in the vaccinated group depended on the assumed vaccine efficacy in that simulation. For example, in a study with 1,000 people in each arm, 50 percent right censoring, $1 - \theta = 0.4$, and $\alpha_1 = 0.6$, for a VE$_{sum}$ = 0.76, there are about 500 events in the unvaccinated group and 135 events in the vaccinated group. The number of events is greater in the vaccinated group at lower efficacy levels, and vice versa. We also explored different groupings of the infection events.

We analyzed the simulated data assuming the mixture model using the grouped survival methods described above to estimate, as appropriate, VE$_{a}$ = $\alpha_1$, VE$_{d}$ = $1 - \theta$, VE$_{sum}$, $\delta_0$, and $\delta_1$. Confidence intervals in the figures and tables are based on the empirical estimates of 1,000 simulations and are in good agreement with those obtained from the likelihood. We present only a small fraction of the simulation results.

Comparison of the degenerate mixed model with misspecified models

We compared estimation of vaccine efficacy when the vaccine had a degenerate mixed effect in a population using the correctly specified model and three models based on incorrect assumptions (figures 3 and 4). The relative reduction in susceptibility is the same for all of the vaccinated susceptibles and is VE$_{d}$ = $1 - \theta = 0.40$. The proportion highly protected VE$_{a}$ = $\alpha_1$ varies from 0.2 to 0.8, so that the preset summary efficacy VE$_{sum}$ = $1 - (1 - \alpha_1) \theta$ varies from 0.52 to 0.88. There were 10,000 people in each simulated study group with 5 percent right censoring in the unvaccinated group in figure 3 and 50 percent in figure 4. Right censoring was due to ending the study before everyone had an event, not due to loss to follow-up. Infection events were grouped into 60 time units, and the constant baseline hazard was $\lambda = 0.05$. The average point estimates of the efficacy parameters of interest, VE$_{d}$ = $1 - \theta$, VE$_{a}$ = $\alpha_1$, and the VE$_{sum}$, are in such close agreement with the simulated values (figure 3a) that the plots overlap. This demonstrates that it is possible to estimate the efficacy parameters of interest using this method.

The first misspecified model assumes that all vaccinated people are partially susceptible by setting $\alpha_1$ to 0. We denote the efficacy estimated under this model by VE$_{pp}(t)$, where PP denotes partial protection. This is similar to the proportional hazards model. In this simulation, the estimated VE$_{pp}$ is higher than either the simulated VE$_{sum}$, $1 - \theta$, or $\alpha_1$ (figure 3b), giving a positively biased estimate of vaccine efficacy. Not only is the estimate biased but the interpretation that the vaccine has a multiplicative effect in all of the people vaccinated is incorrect for the simulated distribution. The heterogeneity of protection is not captured by the estimate.

The second misspecified model assumes the all-or-none effect of the vaccine by setting $\theta = 1$. We denote the efficacy estimated under this model by VE$_{ALL}(t)$, where ALL stands for all-or-none. The third model estimates vaccine efficacy from the final attack rates (AR$_{v}$, $\nu = 0.1$), the proportion in each group that acquires the infection during the study. We denote vaccine efficacy estimated in this way by VE$_{AR}(t)$, where VE$_{AR}(t)$ = $1 - AR_1(t)/AR_0(t)$. VE$_{AR}(t)$ is expected to give an unbiased, time-invariant estimate of the proportion completely protected if the vaccine has an all-or-none effect (4), an incorrect assumption in this case. In figure 3c, the estimated VE$_{ALL}$ is close to the true value of the proportion $\alpha_1$ that is highly protected. Not surprisingly, a similar result is found in figure 3d using the VE$_{AR}$. There is, however, no information about the partial protection, and it considerably underestimates VE$_{sum}$. For example, if the simulated distribution is 20 percent completely protected with 40 percent reduction in susceptibility in the others, for a preset VE$_{sum}$ = 0.52, the estimated efficacy would be only VE$_{AR}$ = 0.30, 95 percent confidence interval (CI) 0.27 to 0.33. This illustrates that misspecified models can give very precise estimates of the wrong answer (7).

With increasing right censoring, the point estimates of $1 - \theta$, $\alpha_1$, and VE$_{sum}$ are still quite good (figure 4a), while the efficacy estimates based on the misspecified models get closer to the values of the simulated VE$_{sum}$ (figure 4b–d). If right censoring were even greater, say close to 95 percent, the disease would become a rare disease. For rare diseases, it is well known that vaccine efficacy based on proportional hazards or attack rates will give similar estimates. Thus, it is not surprising that estimates of these parameters would approach each other at greater levels of censoring. It is interesting, however, that they also approach the actual VE$_{sum}$. 

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Tables 2 and 3 contain a summary of the comparison of the different efficacy estimators at varying values of $\alpha$ and $1-\theta$ with 10,000 in each simulated group at 5 percent right censoring. The values for $VE_{AR}$ have been left out of table 2 because they are nearly identical with those of $VE_{ALL}$.

Limits of estimation

We examined under what circumstances we can fit the frailty mixing model to the data and get stable estimates of $\alpha_1$, $1-\theta$, and $VE_{sum}$. In all cases, the constant baseline hazard was estimated accurately and precisely. The instability of the estimates was more sensitive to the degree of right censoring than the sample size in the ranges explored. Noteworthy is that good summary estimates of $VE_{sum}$ were generally obtained even when the two components $\alpha_1$ and $1-\theta$ were hard to estimate. With 10,000 people in each arm, estimation was very good in all 1,000 simulations at all levels of mixed effect when there was only 5 percent right censoring in the unvaccinated. Problems occurred on average 21 percent of the time at 50 percent censoring, again varying according to the assumed efficacy as with 1,000 people in each arm.

With 1,000 people in each arm and only 5 percent right censoring, estimation of the parameters of the correctly specified degenerate mixed model was possible in nearly all 1,000 of the simulations at all levels of efficacy. The value was indeterminate 3.6 percent of the time with a high proportion completely protected ($\alpha_1 = 0.8$) and low partial protection ($1 - \theta = 0.2$). With 50 percent right censoring, problems in estimation occurred as much as 33 percent of the time when there was a combination of a high proportion highly protected and low partial protection in the remaining susceptibles. Estimation was more dependable at low values of $\alpha_1$ and high values of partial protection. With 100 people in each arm, estimation of $\alpha_1$ and $1-\theta$ was unstable.

In general, if censoring is high, then the estimated VE from the proportional hazards model or cumulative incidence will give an estimate close to $VE_{sum}$. For any given summary vaccine efficacy, estimation using the frailty method will be more dependable with the combination of higher partial protection in the susceptibles with a lower proportion completely protected. That is, if $VE_{sum} = 0.88$, this could be from $\alpha_1 = 0.8$ and $1-\theta = 0.4$ or $\alpha_1 = 0.4$ and $1-\theta = 0.8$. Estimation in the latter case will be better. Whether it will be possible to estimate $\alpha_1$ and $1-\theta$ and the resulting $VE_{sum}$ will depend on the components of $VE_{sum}$ contributing to that particular value.

**Degenerate versus gamma distribution in mixed model**

To assess the effect of heterogeneity in the susceptibility of nonimmune persons on the estimate of vaccine efficacy, we repeated the simulations in the previous section, but with the variances of the gamma distributions set to one, i.e., \( \delta_0 = \delta_1 = 1 \). This introduces considerable variation, with the coefficient of variation for \( Z_v \) equal to one. We estimate the vaccine efficacy from fitting the correct full model with \( \delta_0 \) and \( \delta_1 \) treated as free parameters, and then the incorrect degenerate model, assuming \( \delta_0 = \delta_1 = 0 \). The results of the summary efficacy estimates are given in table 4. The summary vaccine efficacy based on the full model is well estimated for all parameter combinations. For example, when \( \alpha_1 = 0.2 \), \( 1 - \theta = 0.2 \), and, thus, \( \text{VE}_{\text{sum}} = 0.36 \), the estimated \( \text{VE}_{\text{sum}} \) is also 0.36 (95 percent CI 0.32–0.40). In this example, the estimates of \( \delta_0 \) and \( \delta_1 \) are both 1.00 (95 percent CIs 0.96–1.04 and 0.91–1.11), and the estimates of \( \alpha_1 \) and \( 1 - \theta \) are both 0.20 (95 percent CIs 0.19–0.21 and 0.15–0.25), respectively (results not shown). Thus, at this level of censoring in the unvaccinated arm, i.e., 5 percent, all of the parameters of the full model are estimable. Incorrectly assuming the degenerate model yields poor estimates of vaccine efficacy. In the example above, with preset \( \delta_0 = \delta_1 = 1 \) but assuming incorrectly that \( \delta_0 = \delta_1 = 0 \), \( \bar{\text{VE}}_{\text{sum}} = 0.25 \) (95 percent CI 0.24–0.26), a considerable underestimate. In addition, the confidence interval is unrealistically narrow reflecting that the degenerate model does not allow for the actual variability in the data. For the incorrectly assumed degenerate model, \( \alpha_1 \) is well estimated for all parameter values, but \( 1 - \theta \) is generally estimated to be near zero (results not shown). Thus, the misspecified degenerate model is unable to identify the partial reduction in susceptibility conferred by the vaccine when there is considerable heterogeneity in individual hazard rates. This results in the substantial underestimate of the summary vaccine efficacy.

We repeated the simulations above with a smaller coefficient of variation of \( Z_v \) equal to 0.25, i.e., \( \delta_0 = \delta_1 = 0.0625 \). The results (not shown) were similar as in the previous example, except for improved, though still biased, estimation for combinations of high values of \( 1 - \theta \) and low values of \( \alpha_1 \) using the degenerate model.

**Effect of increasing heterogeneity with everyone susceptible**

To assess the degree of increasing heterogeneity in the frailty distribution that produces an important bias...
in estimating vaccine efficacy, we compared the estimates of \( VE_{\theta} = 1 - \theta \) using the degenerate model and the full model while varying the variances of the gamma distribution from 0 to 1 (table 5). Everyone was assumed to be susceptible, \( \alpha_1 = \alpha_0 = 0 \), so in the degenerate case, the proportional hazards model would be appropriate. With increasing heterogeneity in susceptibility in both the vaccinated and unvaccinated groups, the degenerate model increasingly underestimated the vaccine efficacy to a surprising degree. With a coefficient of variation of 0.7, or \( \sigma = 0.5 \), the estimate of a preset value of \( VE_{\theta} = 0.5 \) was just 0.44 (95 percent CI 0.42–0.46). The baseline hazard was also underestimated (not shown). The correct full model produced good estimates of \( VE_{\theta} \), \( \delta_0 = \delta_1 \), and the baseline hazard.

### DEPENDENT HAPPENINGS AND BASELINE INFECTION RATE

Farewell (35) and Aalen (20, 21) as well as others warn about the problem of nonidentifiability in mixture models. Nonidentifiability refers to the inability to differentiate the baseline hazard function from the frailty distribution, because many different combinations of baseline hazard and frailty distributions will give the same observed population survival function. This problem is aggravated when censoring is heavy. In infectious diseases, the baseline hazard can be thought of as a function of the prevalence of infectives, as illustrated in equation 2. This dependent happening structure of events in infectious diseases might help to stabilize estimation and to improve identifiability if we are able to derive some information about the shape of the baseline hazard function over time from the number of people who are infectious.

As defined above, \( p(t) \) is the probability that a contact is infectious. Under certain assumptions about random mixing and time-invariant transmission probability, \( p(t) \) could be estimated by the prevalence of infectives in the population. If \( n \) is the size of the population, with \( n_0 \) and \( n_1 \) the number of unvaccinated and vaccinated people, respectively, and \( I_0(t) \) and \( I_1(t) \) the proportion of people infective in each group, respectively, then the proportion of infectives in the population is the weighted average of the proportion infected in each group:

**TABLE 2. Estimated vaccine efficacy using the summary model (VE\(_{\text{SUM}}\)), partial protection model (VE\(_{\text{PP}}\)) and all-or-none model (VE\(_{\text{ALL}}\)) for data simulated with 10,000 people in both the vaccinated and unvaccinated groups, 60 time periods, 5% right censoring in the unvaccinated group, baseline hazard \( \lambda_0 \) (t) = 0.05 and \( \delta_0 = \delta_1 = 0 \)**

<table>
<thead>
<tr>
<th>( \alpha_1 ) model</th>
<th>1 - ( \theta ) = 0.2</th>
<th>1 - ( \theta ) = 0.4</th>
<th>1 - ( \theta ) = 0.6</th>
<th>1 - ( \theta ) = 0.8</th>
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</thead>
<tbody>
<tr>
<td>( \alpha ) set†</td>
<td>Point estimate‡</td>
<td>Empirical 95% CI‡</td>
<td>Point estimate‡</td>
<td>Empirical 95% CI‡</td>
</tr>
<tr>
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<td>0.34–0.38‖</td>
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<td>0.2</td>
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<td>0.50–0.53</td>
<td>0.61</td>
</tr>
<tr>
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</tr>
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<td>0.50–0.54</td>
<td>0.64</td>
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<td>0.4</td>
<td>VE(_{\text{PP}})</td>
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<td>0.41–0.43</td>
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</tr>
<tr>
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<td>Preset</td>
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<td>0.66–0.70</td>
<td>0.76</td>
</tr>
<tr>
<td>0.6</td>
<td>VE(_{\text{SUM}})</td>
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<td>0.83–0.84</td>
<td>0.86</td>
</tr>
<tr>
<td>0.6</td>
<td>VE(_{\text{PP}})</td>
<td>0.52</td>
<td>0.50–0.53</td>
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<tr>
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<td>Preset</td>
<td>0.84</td>
<td>0.83–0.85</td>
<td>0.88</td>
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<tr>
<td>0.8</td>
<td>VE(_{\text{SUM}})</td>
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<td>0.93–0.93</td>
<td>0.94</td>
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<tr>
<td>0.8</td>
<td>VE(_{\text{PP}})</td>
<td>0.81</td>
<td>0.80–0.82</td>
<td>0.82</td>
</tr>
</tbody>
</table>

* \( \alpha_1 \), proportion completely protected in vaccinated group.
† \( \theta \), relative residual susceptibility of vaccinated susceptibles compared with the unvaccinated group.
‡ Average point estimate based on 1,000 simulations per \( \alpha_1 \), 1 - \( \theta \) combination.
§ CI, confidence interval.
‖ Preset value of VE\(_{\text{SUM}}\) in the simulation model = 1-(1 - \( \alpha_1 \))\( \theta \).
|| Empirical 95% confidence intervals based on 1,000 simulations per \( \alpha_1 \), 1 - \( \theta \) combination.
TABLE 3. Estimates of $\alpha_i$ and $1 - \theta_i^*$ using the summary model for data simulated with 10,000 people in both the vaccinated and unvaccinated groups, 60 time periods, 5% right censoring in the unvaccinated group, baseline hazard $\lambda_0(t) = 0.05$ and $\delta_0 = \delta_i = 0$

<table>
<thead>
<tr>
<th>$1 - \theta$</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
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</thead>
<tbody>
<tr>
<td>0.2</td>
<td>$\alpha_1$</td>
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<td>0.19-0.21</td>
<td>0.19</td>
<td>0.18-0.22</td>
<td>0.20</td>
<td>0.16-0.23</td>
<td>0.20</td>
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<td></td>
<td>$1 - \theta$</td>
<td>0.20</td>
<td>0.17-0.23</td>
<td>0.40</td>
<td>0.37-0.43</td>
<td>0.60</td>
<td>0.57-0.63</td>
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<td>0.4</td>
<td>$\alpha_1$</td>
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<td>0.39-0.41</td>
<td>0.40</td>
<td>0.39-0.42</td>
<td>0.40</td>
<td>0.37-0.43</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>$1 - \theta$</td>
<td>0.20</td>
<td>0.16-0.24</td>
<td>0.40</td>
<td>0.36-0.44</td>
<td>0.60</td>
<td>0.56-0.64</td>
<td>0.80</td>
</tr>
<tr>
<td>0.6</td>
<td>$\alpha_1$</td>
<td>0.60</td>
<td>0.59-0.61</td>
<td>0.60</td>
<td>0.58-0.61</td>
<td>0.60</td>
<td>0.57-0.62</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>$1 - \theta$</td>
<td>0.20</td>
<td>0.15-0.25</td>
<td>0.40</td>
<td>0.35-0.44</td>
<td>0.60</td>
<td>0.55-0.65</td>
<td>0.80</td>
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<tr>
<td>0.8</td>
<td>$\alpha_1$</td>
<td>0.80</td>
<td>0.79-0.81</td>
<td>0.80</td>
<td>0.79-0.81</td>
<td>0.80</td>
<td>0.79-0.82</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>$1 - \theta$</td>
<td>0.20</td>
<td>0.14-0.26</td>
<td>0.40</td>
<td>0.34-0.46</td>
<td>0.60</td>
<td>0.54-0.66</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* $\alpha_i$, proportion completely protected in vaccinated group.
† $\theta_i$, relative residual susceptibility of vaccinated susceptibles compared with the unvaccinated group.
‡ Average point estimates and empirical confidence intervals based on 1,000 simulations per $\alpha_i, 1 - \theta$ combination.
§ CI, confidence interval.

TABLE 4. Estimated vaccine efficacy using the degenerate summary model ($V_{ESUMD}$) and the full summary model ($V_{ESUM}$) for data simulated with 10,000 people in both the vaccinated and unvaccinated groups, 60 time periods, 5% right censoring in the unvaccinated group, baseline hazard $\lambda_0(t) = 0.325$ and $\delta_0 = \delta_i = 1$

<table>
<thead>
<tr>
<th>$1 - \theta$</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
<th>Average point estimate</th>
<th>Empirical 95% CI</th>
</tr>
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<tbody>
<tr>
<td>0.2</td>
<td>Preset</td>
<td>0.36</td>
<td>0.32-0.40</td>
<td>0.52</td>
<td>0.49-0.55</td>
<td>0.68</td>
<td>0.66-0.70</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>$V_{ESUM}$</td>
<td>0.36</td>
<td>0.24-0.26</td>
<td>0.26</td>
<td>0.25-0.27</td>
<td>0.39</td>
<td>0.37-0.42</td>
<td>0.63</td>
</tr>
<tr>
<td>0.4</td>
<td>Preset</td>
<td>0.52</td>
<td>0.48-0.65</td>
<td>0.64</td>
<td>0.61-0.67</td>
<td>0.76</td>
<td>0.74-0.78</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>$V_{ESUM}$</td>
<td>0.52</td>
<td>0.43-0.45</td>
<td>0.45</td>
<td>0.44-0.46</td>
<td>0.54</td>
<td>0.52-0.57</td>
<td>0.72</td>
</tr>
<tr>
<td>0.6</td>
<td>Preset</td>
<td>0.68</td>
<td>0.65-0.71</td>
<td>0.76</td>
<td>0.74-0.78</td>
<td>0.84</td>
<td>0.82-0.85</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>$V_{ESUM}$</td>
<td>0.68</td>
<td>0.61-0.63</td>
<td>0.63</td>
<td>0.62-0.64</td>
<td>0.70</td>
<td>0.68-0.71</td>
<td>0.81</td>
</tr>
<tr>
<td>0.8</td>
<td>Preset</td>
<td>0.84</td>
<td>0.82-0.86</td>
<td>0.88</td>
<td>0.86-0.89</td>
<td>0.92</td>
<td>0.91-0.93</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>$V_{ESUM}$</td>
<td>0.84</td>
<td>0.80-0.82</td>
<td>0.82</td>
<td>0.81-0.82</td>
<td>0.85</td>
<td>0.83-0.86</td>
<td>0.91</td>
</tr>
</tbody>
</table>

* $\alpha_i$, proportion completely protected in vaccinated group.
† $\theta_i$, relative residual susceptibility of vaccinated susceptibles compared with the unvaccinated group.
‡ Average point estimate based on 1,000 simulations per $\alpha_i, 1 - \theta$ combination.
§ CI, confidence interval.
‖ Preset value of $V_{ESUM}$ in the simulation model = $1 - (1 - \alpha_i)\delta$.
¶ Empirical 95% confidence intervals based on 1,000 simulations per $\alpha_i, 1 - \theta$ combination.

$$p(t) = \frac{n_0d_0(t) + n_1d_1(t)}{n_0 + n_1}.$$  (11)

In the vaccine cohort study described here, if the population is closed or is a random sample of the population, then $p(t)$ would either be, or be estimated by, the number of infectives in the cohort at time $t$ divided by the number of people in the cohort.

In the grouped survival setting, assume that the proportion of the population that is infective in interval
TABLE 5. Estimates of vaccine efficacy $(1 - \theta)$, $\delta_0$ and $\delta_1$ using the degenerate summary model and the full summary model for data simulated with 10,000 people in both the vaccinated and unvaccinated groups, 60 time periods, 5% right censoring in the unvaccinated group, $\alpha_0 = \alpha_1 = 0$, $1 - \theta = 0.5$, and varying levels for $\delta_0$ and $\delta_1$.

<table>
<thead>
<tr>
<th>True $\delta_0$, $\delta_1$ model</th>
<th>$1 - \theta^*$ Average estimate</th>
<th>Empirical 95% CI</th>
<th>$\delta_0^*$ Average estimate</th>
<th>Empirical 95% CI</th>
<th>$\delta_1^*$ Average estimate</th>
<th>Empirical 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerate $\delta_0 = \delta_1 = 0$</td>
<td>0.50</td>
<td>0.48-0.51</td>
<td>0.01</td>
<td>0.00-0.03</td>
<td>0.01</td>
<td>0.00-0.06</td>
</tr>
<tr>
<td>Full $\delta_0 = \delta_1 = 0.0625$</td>
<td>0.49</td>
<td>0.48-0.51</td>
<td>0.06</td>
<td>0.03-0.09</td>
<td>0.06</td>
<td>0.01-0.12</td>
</tr>
<tr>
<td>Degenerate $\delta_0 = \delta_1 = 0.10$</td>
<td>0.49</td>
<td>0.47-0.50</td>
<td>0.10</td>
<td>0.07-0.13</td>
<td>0.10</td>
<td>0.05-0.15</td>
</tr>
<tr>
<td>Full $\delta_0 = \delta_1 = 0.25$</td>
<td>0.47</td>
<td>0.45-0.48</td>
<td>0.25</td>
<td>0.22-0.28</td>
<td>0.25</td>
<td>0.20-0.30</td>
</tr>
<tr>
<td>Degenerate $\delta_0 = \delta_1 = 0.50$</td>
<td>0.44</td>
<td>0.42-0.46</td>
<td>0.50</td>
<td>0.46-0.53</td>
<td>0.50</td>
<td>0.45-0.54</td>
</tr>
<tr>
<td>Full $\delta_0 = \delta_1 = 0.75$</td>
<td>0.42</td>
<td>0.39-0.44</td>
<td>0.75</td>
<td>0.71-0.79</td>
<td>0.75</td>
<td>0.70-0.79</td>
</tr>
<tr>
<td>Degenerate $\delta_0 = \delta_1 = 1.00$</td>
<td>0.39</td>
<td>0.37-0.42</td>
<td>1.00</td>
<td>0.96-1.04</td>
<td>1.00</td>
<td>0.95-1.05</td>
</tr>
</tbody>
</table>

* Average point estimates and empirical confidence intervals based on 1,000 simulations per $\delta_0$, $\delta_1$ combination.
† CI, confidence interval.

$i$ is constant. Then $p(t) = p_i$ in interval $i$. We can approximate $p_i$ by some function of the number of observed infections in interval $i$ and the total number of people in the interval, under the assumption that the period of infectiousness is shorter than the interval used in grouping the data. If the degree of infectiousness of vaccinated and unvaccinated infectives is assumed to be equal, then the prevalence $p_i$ is proportional to the sum of the number of people $m_{i\nu}$ becoming infected in interval $i$, $\nu = 0, 1$:

$$p_i \propto \frac{m_{i0} + m_{i1}}{n_0 + n_1}.$$  \hfill (12)

We can put this quantity into the expression for the cumulative hazard to improve identifiability. The baseline hazard is assumed to be equal for both the vaccinated and unvaccinated groups under the assumption of equal exposure to infection in the two groups (10), and the $p_i$s give the baseline hazard its underlying shape. Assume that a person is infective for a fraction $\kappa$ of the time interval. Assume also that the contact rate and transmission probability are constant. Then the cumulative hazard enters the likelihood as

$$\Lambda_0(i) = c\pi\kappa \int_0^t p(\tau) d\tau = c\pi\kappa \sum_{j=1}^i (t_j - t_{j-1})p_j + (t_i - t_j)p_{i+1}] \cdot \delta(t_i, t_{i+1}). \hfill (13)$$

The quantity $\alpha = c\pi\kappa$ becomes one of the quantities to estimate. The quantities $c$ and $\pi$ cannot be separately estimated from time to event data (3), and the $\kappa$ term depends on the grouping. Longini and Halloran (17) used this method in estimating vaccine efficacy in an outbreak of measles. There are differences between this method of estimating the cumulative hazard and the usual Nelson or Breslow estimates of cumulative hazard (36) that deserve additional investigation.

We can also build into the likelihood that vaccinated infectives could be less infectious or of shorter duration than unvaccinated infectives (1, 37). If we assume that a vaccinated infective is only the fraction $\phi$ as infectious as an unvaccinated infective, then we can reduce the contribution of vaccinated infected persons to the hazard in equation 2:

$$\lambda_0(t) = c\pi p(t) = c\pi \frac{n_{0f_0(t)} + \phi n_{1f_1(t)}}{n_0 + n_1}. \hfill (14)$$
The effective prevalence of infection would be proportional to the weighted average of the number of infectives in the unvaccinated and vaccinated groups:

$$p_{\text{eff}} \propto \frac{m_0 + \phi m_1}{n_0 + n_1}. \quad (15)$$

**DISCUSSION**

We have demonstrated that under certain conditions, it is possible to estimate the vaccine efficacy parameters from time to event data in the presence of unmeasured heterogeneity in the hazard rates and vaccine effects. Meaningful estimates can be obtained for the fraction highly protected, the relative reduction in susceptibility in those remaining susceptible, and the summary efficacy measure under heterogeneity. The methods are applicable to situations in which either susceptibility or exposure to infection is distributed heterogeneously within comparison groups, as long as these are equal in the absence of vaccine effects. Under the assumption of equal though possibly heterogeneous exposure to infection in the vaccinated and unvaccinated groups, the efficacy parameters can be interpreted as the distribution of protection conferred by the vaccines. As with any vaccine efficacy study, if exposure to infection in the comparison groups is not equal, then estimates of the effect of the vaccine on susceptibility will be biased. Although the use of frailty models improves estimation under certain conditions, interpretation of the estimates should be done with the underlying assumptions in mind.

Fitting the wrong model gives vaccine efficacy estimates that are biased and have the wrong interpretation. Interestingly, at high levels of censoring when the rare disease assumption holds, estimates from misspecified models based either on the assumption of homogeneous partial protection or on the all-or-none model not only approach each other, but also approach the value for the correctly specified summary vaccine efficacy measure. Sample size calculations for vaccine efficacy studies should take possible heterogeneities and consequences for confidence intervals into account to avoid being underpowered.

There are limitations to the likelihood approach presented here, including nonidentifiability of the parameters, especially at high degrees of censoring, and lack of formal methods for choosing among different models. The simulated efficacy studies presented here have much less censoring than most vaccine efficacy studies. We suggest that improvement in identifiability might be achieved by incorporating information from the epidemic process into estimation of the baseline cumulative hazard. Other models of vaccine action would have to be used for more complex distributions of vaccine protection such as threshold effects. We have confined our discussion to estimating the vaccine effect on susceptibility, not on infectiousness, indirect effects, or how the vaccine might change the incubation period (38).

We have presented a couple of possible distributions here. Another distribution with point mass at 0 and continuous distribution in the susceptibles is the compound Poisson distribution (20, 21). However, in the compound Poisson distribution, as \( \alpha \), the proportion highly protected, increases, the tail of the distribution of those partially protected becomes more susceptible where we would expect it to become less. Another approach to modeling degenerate mixing distributions in survival analysis literature are cure models (23–25). This method also has nonidentifiability problems (35). Our practical recommendation is to fit several different models to the time to event data and to compare the results and interpretations. Hougaard et al. (39) fit several frailty models to nephropathy data. Biologic information from other sources, such as phase I and II studies, could help in interpreting the different efficacy estimates, in choosing among models, and in improving estimation. The application of Bayesian and empirical Bayesian methods to combine such information in the estimation and interpretation (1) or imputing exposure to infection data (7) are promising areas to pursue.

Our goal is to develop meaningful and interpretable estimates of the protection conferred by prophylactic vaccines in the field. The overall public health effectiveness (27, 28) of a vaccination program is also sensitive to the distribution of protection conferred by the vaccine (1), so such estimates are important for planning long-term vaccination strategies. The interpretation of vaccine efficacy estimates depend on the data available for estimation, the parameters estimated, the distributions of susceptibility and exposure to infection, and the distribution of protection conferred by the vaccine. These aspects and assumptions of an efficacy measure should be included when reporting vaccine efficacy.

**ACKNOWLEDGMENTS**

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REFERENCES


APPENDIX

Following Hougaard (18, 19, 22) and Aalen (20, 21), Longini and Halloran (17) developed the population level survival functions in the vaccinated and unvaccinated groups as

\[ S_0(t) = E[\exp(-Z_0\Lambda_0(t))] = L_2[\Lambda_0(t)], \quad (16) \]

where \( \Lambda_0(t) = \int_{-\infty}^{t} c(t)p(\tau)d\tau, \quad \Lambda_1(t) = \theta\Lambda_0(t), \quad (17) \)

and \( L_2(\cdot) \) is the Laplace transform. For a mixing distribution with point mass at 0 with probability \( \alpha_0 \), the Laplace transform of \( Z_0 \) is

\[ \Lambda_0(t) = \pi \int_{0}^{t} c(t)p(\tau)d\tau, \quad \Lambda_1(t) = \theta\Lambda_0(t), \quad (17) \]
\[ L_Z(s) = \alpha_v + (1 - \alpha_v)L_{X_v}(s). \] (18)

Longini and Halloran (17) developed the situation that \( X_v \) follows a gamma distribution in the susceptible portion of the population. For the estimation problem described, however, the mean is not identifiable without further constraint. Thus, they let \( f_v(t) \) be from a two-parameter family, but with \( E(X_v) = 1 \), so that \( E(Z_v) = 1 - \alpha_v \). From the condition that \( \text{Var}(X_v) = \delta_v \) then \( \text{Var}(Z_v) = (1 - \alpha_v)(\delta_v + \alpha_v) \). Under these constraints, the gamma distribution of \( X_v \) has both scale and shape parameters equal to \( 1/\delta_v \) and

\[ S_v(t) = \alpha_v + (1 - \alpha_v)\left[ \frac{1}{1 + \Lambda_v(t)\delta_v} \right]^{1/\delta_v}. \] (19)