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Measuring Vaccine Efficacy for Both Susceptibility to Infection and Reduction in Infectiousness for Prophylactic HIV-1 Vaccines

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Summary: Current Phase III trials are designed to assess only a vaccine candidate's ability to reduce susceptibility to infection or disease, that is, vaccine efficacy for susceptibility (VE_S). Human immunodeficiency virus (HIV) vaccination, however, may reduce the level of infectiousness of vaccinees who become infected, producing an important indirect reduction in HIV transmission even if the vaccine confers only modest protection against infection. We propose two approaches for augmenting the information of a classic trial for estimating protective efficacy that enable the additional estimation of the vaccine's effect on infectiousness, that is, vaccine efficacy for infectiousness (VE_I). In the first augmentation, steady sexual partners of trial participants are recruited but not randomized to vaccine or placebo. Their infection status is monitored throughout the trial. In the second augmentation, the sexual partners are randomized. Through computer simulations and analytic methods, we investigate the feasibility and statistical properties of the augmented designs. Phase III prophylactic HIV-1 vaccines trials are currently being planned. Employment of the augmented designs described in this paper would not only provide estimation of VE_I but also increase the precision of the VE_S estimator and the power to reject the null hypothesis of no vaccine effect. **Key Words:** Clinical trial—Phase III—HIV—Statistics—Vaccines.

Efforts to control the human immunodeficiency (HIV) pandemic have had limited success. The World Health Organization estimates that 18 million people are currently infected (1) and that 40 million will be infected by the year 2000 unless an effective intervention strategy is found. An effective prophylactic HIV vaccine could be an important component of such an intervention strategy. The overall effectiveness of a vaccination program depends not only on the protection conferred on susceptible persons but also on how effectively infected persons are prevented from transmitting agent to others (2). Interventions, such as mass vaccination, need to be evaluated by their effectiveness in all these aspects.

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With the current HIV-1 vaccine candidates, the effect of reduction in infectiousness may be just as important as the protection against infection and disease in reducing the number of new infections. The recombinant envelope protein vaccine candidates glycoprotein (gp)120 and gp160, which have had extensive evaluation in Phase I/II vaccine trials, evoke a good antibody immune response but do not appear to produce sterilizing immune protection against infection (3). A good antibody response, however, might reduce the early viremia during primary infection, which analyses suggest accounts for a large amount of transmission (4). Thus, in Phase III HIV vaccine trials, it will be important to measure a vaccine candidate's ability to reduce infectiousness as well as to protect against infection and disease.

Current plans for Phase III HIV vaccine trials involve assessing only a vaccine candidate's ability to reduce susceptibility to infection or disease (5). This approach is

not designed to obtain information for the overall evaluation of the benefits of the HIV vaccine candidates. In theory, measuring reduction in infectiousness requires comparable individuals to be exposed equally to infected vaccinated and unvaccinated persons. In practice, such a comparison is achieved by comparing the secondary attack rate resulting from exposure to infected vaccinated and unvaccinated persons in specific settings, such as households or sexual partnerships (6–9). Koopman and Little (10) have proposed an HIV vaccine trial design that recruits nonmonogamous steady sexual partnerships rather than just individuals into the trial. Vaccine and placebo are then randomly assigned equally to couples such that the individuals in a couple receive either vaccine or placebo. They show that vaccine efficacy for both susceptibility (VE_S) and infectiousness (VE_I) are estimable. In this paper, we consider feasible alternatives to this idea that preserve the classic Phase III vaccine trial design but augment it in a way that allows estimation of both aspects of vaccine efficacy. In the first approach, steady sexual partners of the randomized primary trial participants are recruited but not randomized to vaccine or placebo. Their infection status is monitored throughout the trial. In the second approach, the steady sexual partners are randomized. Through the use of simulation and analytic methods, we demonstrate how such augmentations allow estimation of the vaccine's effect on both susceptibility and infectiousness.

METHODS

For the classic Phase III vaccine trial, n uninfected participants are randomized in a double blinded fashion to placebo and vaccine. We will refer to such participants as primary participants and consider the case of a single vaccine candidate, where n_0 participants receive placebo and n_1 vaccine. Each participant has an equal chance of receiving vaccine or placebo, that is, $n_0 \approx n_1$. These participants are monitored prospectively for infection status for a fixed time. We let γ be the probability that an unvaccinated trial participant is infected from his or her nonsteady sexual partners over the course of the trial; for example, if $\gamma = 0.1$, then 10% will be infected over the course of the trial. Then the VE_S and γ are jointly estimated. The probability model and statistical methods that we employ (given in the Appendix) were first derived by Longini and Koopman (11) and have been extended specifically for partner studies in a variety of statistical frameworks (10,12, 13). We let AR_0 and AR_1 be the cumulative infection attack rates in the unvaccinated and vaccinated subjects. The estimator of the vaccine efficacy for susceptibility (VE_S) is $VE_S = 1 - (AR_1/AR_0)$. Methods for constructing confidence intervals (CI) for VE_S and the hypothesis test H_0: $VE_S = 0$ can be found in Longini et al. (9) (also see the Appendix). Because the trials are double-blinded, all hypothesis tests are two-sided. The VE_I is not estimable from this design (7). To estimate VE_I, we need information on sexual partners of the primary participants. Thus, we propose augmenting the classic design by adding m_0 and m_1 steady sexual partners of the unvaccinated and vaccinated primary participants, respectively. The partners are monitored for infection status but are not randomized into the trial. We will refer to this augmented design as the *nonrandomized partner augmentation.* For this design, we have m_0 partnerships in which if either participant is infected, his or her partner will be directly exposed to an unvaccinated partner during his or her primary infection. In addition, we have m_1 partnerships in which the steady partner can be exposed to an infected vaccinated primary participant during his or her primary infection. We let β be the probability that an infected, unvaccinated trial participant will infect his or her unvaccinated steady sexual partner over the course of the trial, for example, if $\beta = 0.50$, if an unvaccinated primary participant is infected, there is a 50% chance that the participant will infect his or her unvaccinated steady partner, if he or she has one. Note that β is the steady sexual partner secondary attack rate between unvaccinated partners. This contrast is exploited in the likelihood function through joint estimation of γ, β, VE_S and VE_I. There are no closed forms for the estimators, but the likelihood equations can be solved numerically (see Appendix).

A second form of augmentation is to randomize the steady sexual partners of the primary participants into the trial on an individual level. We refer to this augmented design as the *randomized partner design.* For this design, the composition of the partnerships will be approximately as follows: one fourth with both partners vaccinated, one fourth with both partners unvaccinated, and half with one partner vaccinated and one unvaccinated. These three combinations provide a richer set of contrasts for estimating VE_I than that provided by the nonrandomized design. Again, the resulting likelihood equations are solved numerically (see Appendix). Further statistical details can be found in Datta et al. (14). For all three designs, the parameters are estimated from cumulative infection data over the entire course of the trial (11). Statistical tests are constructed for the separate null hypotheses H_0: $VE_S = 0$, and H_0: $VE_I = 0$, and composite null hypotheses H_0: $VE_S = 0$ and $VE_I = 0$ (see the Appendix). The latter test is for the null hypothesis of no vaccine effect at all.

We employ computer simulations and asymptotic methods to investigate the statistical properties of the estimators based on the different designs. The asymptotic methods are more flexible than the simulations, allowing us to explore a wider range of plausible parameter values. For the classic trial design, primary trial participants do not have steady sexual partners. We assume that $VE_S = 0.2$; that is, the vaccine reduces an exposed vaccinated person's chance of infection by 20% compared with an unvaccinated person. Also, we assume that $VE_I = 0.5$, that is, if a vaccinated person is infected, then his or her level of infectiousness to others is reduced by 50% compared with an unvaccinated infected person.

Simulations

In the simulations, we set $\gamma = 0.10$ and $\beta = 0.50$. For each type of trial, we carry out 500 simulations, finding the maximum likelihood estimates of the parameters for each simulation. We then conduct the statistical analyses, described in the Appendix, based on the empirical distribution of the maximum likelihood parameter estimates. This provides the means and standard deviations (SD) of the estimates, 95% CI on the parameters, and the power of hypothesis tests. Although the simulation approach provides a full set of sample statistics, it is an impractical approach for exploring the full range of parameter values.

Asymptotic Methods

In this approach, we analytically approximate the distribution of the maximum likelihood estimates through first-order Taylor series expan-

sions of the Jacobian vector of the log-likelihood function (see Section 12.2.1 in Agresti [15] and Datta et al. [14]). This is an analytic method that provides approximated SD of the estimates and approximate 95% CI on the parameters but does not allow for power calculations. For the asymptotic methods, we consider a range of plausible values for the infection and partnership secondary attack rates, respectively: γ = 0.05–0.25 and β = 0.10–0.50.

RESULTS

Table 1 gives the results of the simulations for the classic design with $n_0 = n_1 = 2{,}000$ primary trial participants in the vaccinated group and the placebo group, and when the classic design is augmented so that $m_0 = m_1 = 500$ primary participants in each trial arm have steady sexual partners. For the classic design, the point estimate of VE_S is 0.198 with a SD of 0.083 and a 95% CI of 0.022–0.346, which just misses covering 0. The power to reject H_0: $VE_S = 0$ is low at 0.668. Thus, if the actual VE_S is $\geq$0.20, we will fail to conclude that it is different from zero about 33% of the time. Of course, VE_I is not estimable with the classic design. By adding the partnerships in the nonrandomized partner design, the power to reject H_0: $VE_S = 0$ is increased to 0.784. The increased precision of the VE_S estimator is indicated by the decrease in its SD from 0.083 for the classic design to 0.072 for the nonrandomized partner design. The increased precision is also reflected by the tighter 95% CI, from 0.022–0.346 for the classic design to 0.049–0.317 for the nonrandomized partner design. This gain in power and precision is due to the increase in infection risk for those primary participants who have steady sexual partners and to the increase in the number of study participants. With respect to the latter effect, we simulate the power to reject H_0: $VE_S = 0$ for the classic trial design with an equal number of participants as the nonrandomized design described above, that is, $n_0 = 3{,}000$ and $n_1 = 2{,}000$. This power is 0.768 (not shown in Table 1), compared with 0.784 for the nonrandomized design.

The VE_I is also estimable for the nonrandomized design and is estimated in Table 1 as 0.501 with a 95% CI of 0.005–0.952, but the power to reject H_0: $VE_I = 0$ is only 0.570; however, the power to reject the null hypothesis of no vaccine effect on either susceptibility or infectiousness is increased to 0.856. When we go to the randomized partner design, there is a significant gain in precision and power, especially with respect to VE_I. The 95% CI on the VE_I is now 0.111–0.778, and the power to reject H_0: $VE_I = 0$ is increased to 0.864 compared with 0.570 for the nonrandomized partner design. This increase in power and precision is due to the increased number of contacts between vaccinated partners available for the estimation of VE_I. With respect to VE_S, the power to reject H_0: $VE_S = 0$ is now 0.846. If we conducted a trial using the classic design in an equivalently sized population, that is, $n_0 = 2{,}500$ and $n_1 = 2{,}500$, this power is simulated to 0.786 (not shown in Table 1).

Table 1 also gives the results of the simulations when the classic design is augmented so that $m_0 = m_1 = 1{,}000$

TABLE 1. *Estimated parameters and hypothesis tests for the classic design with 2,000 primary participant per arm and augmented designs when 500 and 1,000 steady sexual partners are added per arm*[a]

Design	Parameter	Estimate	SD	95% CI	Power
Classic	VE_S	0.198	0.083	0.022–0.346	0.668[b]
$m_0 = m_1 = 500$					
Nonrandomized	VE_S	0.198	0.072	0.049–0.317	0.784[b]
partner	VE_I	0.501	0.238	0.005–0.952	0.570[c]
	VE_S and VE_I				0.856[d]
Randomized	VE_S	0.200	0.067	0.057–0.323	0.846[b]
partner	VE_I	0.484	0.161	0.111–0.778	0.864[c]
	VE_S and VE_I				0.964[d]
$m_0 = m_1 = 1{,}000$					
Nonrandomized	VE_S	0.196	0.066	0.067–0.317	0.822[b]
partner	VE_I	0.502	0.163	0.176–0.808	0.870[c]
	VE_S and VE_I				0.966[d]
Randomized	VE_S	0.198	0.057	0.083–0.306	0.932[b]
partner	VE_I	0.499	0.116	0.259–0.700	0.988[c]
	VE_S and VE_I				0.996[d]

VE_S, vaccine efficacy for susceptibility; VE_I, vaccine efficacy for infectiousness; CI, confidence interval.

[a] γ = 0.1, β = 0.5, VE_S = 0.2, and VE_I = 0.5.

[b] Power to reject H_0: $VE_S = 0$.

[c] Power to reject H_0: $VE_I = 0$.

[d] Power to reject H_0: $VE_S = 0$ and $VE_I = 0$.

primary participants in each arm of the trial have steady sexual partners. Precision and power are further increased. For the randomized partner design, the SD of the VE_I estimator decreases from 0.161 to 0.116 when going from 500 to 1,000 steady sexual partners per arm, and the power to reject H_0: $VE_I = 0$ increases from 0.864 to 0.988. With 1,000 steady sexual partners added, the power to reject the null hypothesis of no vaccine effect is nearly 1 (i.e., 0.996).

Figure 1 gives the results of the asymptotic SD for the estimators of VE_S and VE_I when the classic design is augmented so that $m_0 = m_1 = 1{,}000$ primary participants in each arm have steady sexual partners and when $VE_S = 0.2$ and $VE_I = 0.5$. Note that for both the nonrandomized and randomized partner design, we have decreasing SD (i.e., increased precision) with increasing β and γ. The SD of the VE_S estimator decreases dramatically with increases in γ. For example, for the nonrandomized partner design, when $\gamma = 0.05$ and $\beta = 0.2$, the SD of the estimate of the VE_S is about 0.10, but it decreases to 0.04 when $\gamma = 0.25$ and $\beta = 0.2$. The SD of the VE_S estimator decreases slightly with increasing β because the number of infection events increases with β. The light horizontal line at SD = 0.10 indicates that value of the SD above which an approximate 95% CI on $VE_S = 0.20$ would cover zero; that is, we would not reject H_0: $VE_S = 0$. Thus, in a nonrandomized partner design with $\gamma = 0.05$, the 95% CI on VE_I would cover zero for $\beta \leq 0.16$, but for the randomized partner design, it would not cover zero for $\beta \geq 0.10$. Thus, for the sample sizes given, we would have adequate power to reject H_0: $VE_S = 0$ for virtually the whole range of plausible values of γ and β given here.

Figure 1 also gives plots for the SD of the VE_I estimator. Again, for both designs, we have decreasing SD with increasing β and γ. The light horizontal line at SD = 0.26 indicates that value of the SD above which an approximate 95% CI on $VE_I = 0.50$ would cover zero; that is, we would not reject H_0: $VE_I = 0$. Thus, in a nonrandomized partner design with $\gamma = 0.05$, the 95% CI on VE_I would cover zero for $\beta \leq 0.45$, but for the randomized partner design, it would cover zero for $\beta \leq 0.27$. If $\gamma = 0.25$, then this cutoff is decreased to $\beta \leq 0.23$ and $\beta \leq 0.15$ for the nonrandomized and random-

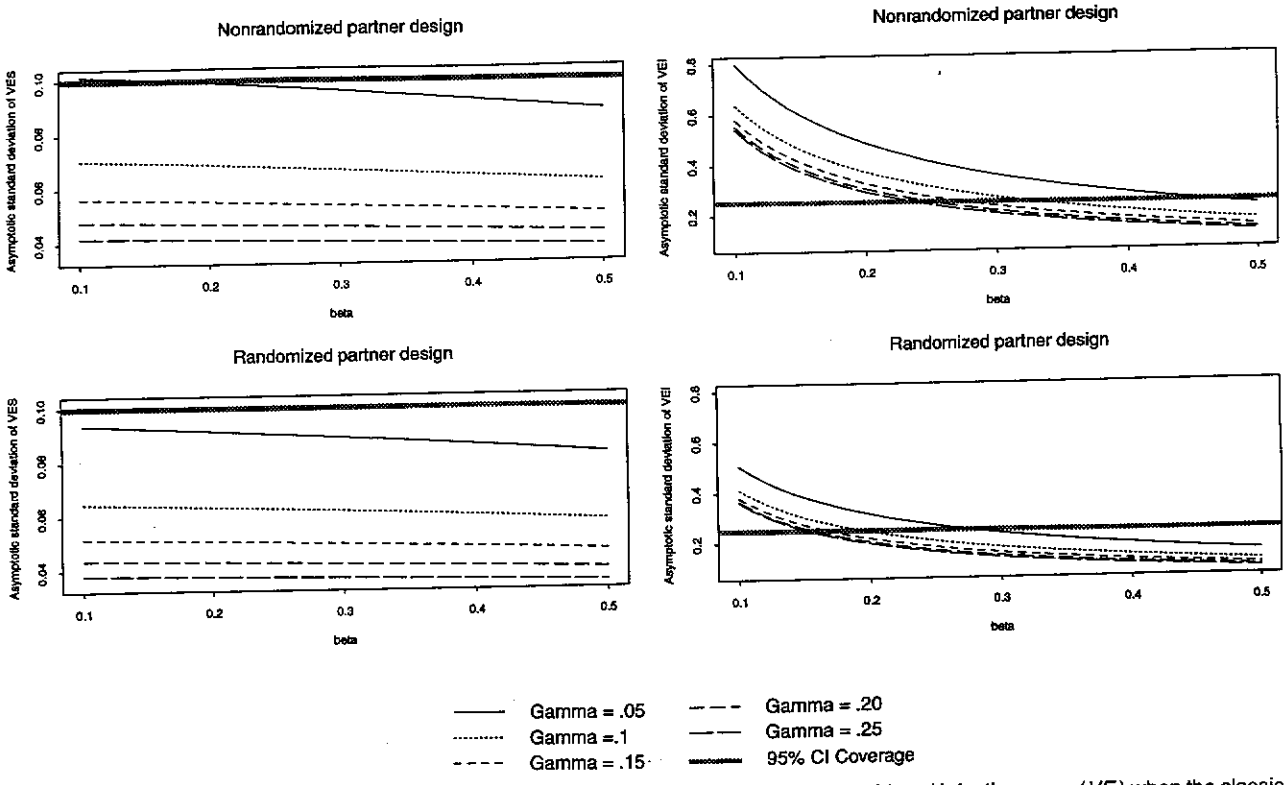

FIG. 1. Plots of the asymptotic SD for the estimators of vaccine efficacy for susceptibility (VE_S) and infectiousness (VE_I) when the classic design is augmented so that $m_0 = m_1 = 1{,}000$ primary participants in each arm have steady sexual partners. The VE values are set at $VE_S = 0.2$ and $VE_I = 0.5$. Points on the curves above the light horizontal line (95% confidence interval coverage) indicate those values of γ and β for which the 95% confidence interval on the VE parameters would cover zero; that is, we would not reject hypothesis test H_0: $VE_S = 0$ or H_0: $VE_I = 0$.

ized partner designs, respectively. The negative relationship between the SD of the estimator of VE_I and β is stronger than that between the SD of the estimator of VE_S and β. Thus, for the nonrandomized design, we would have adequate power to reject H_0: $VE_I = 0$, when the true value of $VE_I = 0.5$, only when the incidence is above $\gamma = 0.10$ and the partnership secondary attack rate is above around $\beta = 0.30$. For the randomized partner design, we need the partnership secondary attack rate above about $\beta = 0.20$ when $\gamma \geq 0.10$.

DISCUSSION

We propose two types of augmentations to the classic Phase III vaccine trial that permit the assessment of the role of vaccine in reducing infectiousness of infected vaccinated persons. The nonrandomized partner design would be easy to implement as an addition to the classic trial design at very little additional cost. Not only does it allow investigators to estimate VE_I but it increases the precision of the VE_S estimator and the power to reject the null hypothesis of no vaccine effect. The randomized partner design is somewhat more difficult to implement as an addition to the classic trial design, but it results in a further increase in precision and power in the estimation of the vaccine's effect on susceptibility.

In proposing the augmented designs, we have in mind the recombinant envelope protein vaccines gp120 and gp160 and the canarypox vector vaccine, which may express core proteins such as *gag* p24, as well as envelope proteins. The envelope vaccines have gone through Phase I/II trials in more than 1,600 healthy, non-HIV-infected adults. They are currently ready to undergo Phase III trials, possibly in Thailand (16). The canarypox vaccine is now entering Phase I trials. The next vaccine concept could possibly be primary vaccination with the canarypox vaccine followed by boosting with one of the envelope vaccines (17). This prime-boost vaccine concept could enter Phase III trials by 1998. The U.S. National Institutes of Health is maintaining both domestic and international vaccine trial sites through its HIV Network of Prevention Trials (HIVNET). Phase III HIV vaccine trials involving the envelope vaccines are being contemplated for cohorts of intravenous drug users, military conscripts, and heterosexual populations in Thailand. Yearly heterosexual HIV incidence has recently been estimated at 3.2% among men and 3.6% among women attending sexually transmitted diseases clinics in northern Thailand (18). At sexually transmitted disease clinics at another HIVNET site in Pune, India, yearly HIV incidence has been estimated to be 9.5% in men, 14.2% in women, and 27.8% in female commercial sex workers (19). With regard to β, Duerr et al. (20) estimated the male-to-female partnership secondary attack rate in Northern Thailand to be 43%. Mastro et al. (21) report an average estimated male-to-female partnership secondary attack rate in the United States and Europe to be 23.4% compared with 12.1% for female-to-male transmission. Although investigators are exploring the numbers of steady sexual partnerships in some of the HIV vaccine trial study populations, the estimated HIV incidence and partnership secondary attack rates should be sufficient to conduct 2-year-long Phase III HIV vaccine trials with the sample sizes explored in this study.

Many vaccines, such as those for chickenpox, pertussis, and polio, and transmission-blocking malaria vaccines do not completely prevent infection but may reduce the infectiousness of the vaccinated person who does become infected. For example, the highly effective oral polio vaccine may not always prevent infection by wild polio virus but prevents paralytic disease and reduces both intestinal and nasopharyngeal viral shedding of wild polio virus (22). In animal studies, when cynomolgus monkeys were vaccinated with live attenuated HIV-2 vaccine and subsequently challenged with pathogenic simian immunodeficiency virus, viral replication was reduced and survival was prolonged for vaccinated compared with unvaccinated monkeys (23,24). Current HIV vaccine candidates could have similar effects in humans; thus, estimation of VE_I is important.

To understand the possible overall benefits of a vaccine as part of an intervention strategy, it is important to evaluate not only how it protects against infection but also how it prevents new infections by reducing infectiousness as well as other characteristics, such as duration of protection and whether it is sensitive to boosting (25). If these other characteristics are not evaluated, the vaccine licensure decision could become difficult. A case in point is the chickenpox vaccine recently licensed in the United States. Field trials were not designed to evaluate reduced infectiousness of breakthrough cases and boosting of protection. It became necessary to convene an expert panel to give its opinion in place of the missing data and to incorporate these opinions into the examination of the overall health benefits of the vaccine (2). As we gain a greater understanding of the overall effects of vaccines in populations, it is important to expand our concept of what is important to measure in vaccine field trials. With HIV vaccines, it will be especially important to understand how the combined reduction in susceptibility and infectiousness might counterbalance any increased sexual activity that would occur because vaccinated persons believe themselves to be protected (26–28).

We have presented here the simplest variant of a design and analysis of a Phase III HIV vaccine trial for estimating vaccine efficacy for both susceptibility and infectiousness. Using previously developed techniques, one can extend the statistical method in a number of ways. Because trial participants will be monitored for infection status periodically (usually every 6 months), the analysis can be extended to handle interval-censored infection and illness data (29,30). Other extensions include more flexible and dynamic partner formation patterns and partner types (e.g., monogamous, nonmonogamous, male, female) (31), risk of infection based on number and types of sexual contacts (29,30), and stage of infection of infected sexual partners (29).

The current design for HIV vaccine field trials does not allow estimation of the various vaccine effects needed for the overall evaluation of the benefits of the HIV vaccine candidates. If a vaccine does not protect well against infection or disease but produces a substantial reduction in infectiousness, and thereby reduces the number of cases in the population substantially, it may be worthwhile to approve and recommend its use. We argue that Phase III HIV-1 trials can and should be implemented to evaluate changes in infectiousness as well as susceptibility.

APPENDIX

We parameterize the VE as $VE_S = 1 - \theta$ and $VE_I = 1 - \phi$. Our goal is to find maximum likelihood estimates of θ and ϕ and, thus, VE_S and VE_I. We define the vaccination status index for the primary participant as $\nu = 0$ for unvaccinated and $\nu = 1$ for vaccinated. If there is a steady partner, his or her vaccination index is $\mu = (0,1)$. The infection status index for the primary participant is $i = 0$ for not infected over the course of the trial and $i = 1$ for infected at any time during the trial. If there is a steady partner, his or her infection status index is $j = (0,1)$.

Probability Model for Primary Participants Without Steady Sexual Partners

We let π_ν^i be the probability of infection outcome i when the vaccination status is ν; for example, π_1^1 is the probability that a vaccinated primary participant is infected. For unvaccinated primary participants, the probabilities of the possible outcomes are

$$\pi_0^0 = 1 - \gamma, \qquad \pi_0^1 = \gamma \tag{1}$$

For vaccinated primary participants, the probabilities of the possible outcomes are

$$\pi_1^0 = 1 - \theta\gamma, \qquad \pi_1^1 = \theta\gamma \tag{2}$$

Probability Model for Sexual Partnerships

We let $\pi_{\nu\mu}^{ij}$ be the probability of infection outcomes i and j, when vaccination status is ν and μ; for example π_{10}^{10} is the probability, in a partnership in which the primary partner is vaccinated and the steady sexual partner is unvaccinated, that the primary participant gets infected and the partner escapes infection. When both partners are unvaccinated, the probabilities of the possible outcomes are

$$\begin{aligned} \pi_{00}^{00} &= (1-\gamma)^2 \\ \pi_{00}^{10} &= \pi_{00}^{01} = \gamma(1-\beta)(1-\gamma) \\ \pi_{00}^{11} &= \gamma^2 + 2\gamma(1-\gamma)\beta \end{aligned} \tag{3}$$

When one of the partners is vaccinated and the other is unvaccinated, the probabilities of the possible outcomes are

$$\begin{aligned} \pi_{10}^{00} &= \pi_{01}^{00} = (1-\gamma)(1-\theta\gamma) \\ \pi_{10}^{10} &= \pi_{01}^{01} = \theta\gamma(1-\phi\beta)(1-\gamma) \\ \pi_{10}^{01} &= \pi_{01}^{10} = \gamma(1-\theta\beta)(1-\theta\gamma) \\ \pi_{10}^{11} &= \pi_{01}^{11} = \theta\gamma^2 + \theta\gamma(1-\gamma)\phi\beta + \gamma(1-\theta\gamma)\theta\beta \end{aligned} \tag{4}$$

When both partners are vaccinated, the probabilities of the possible outcomes are

$$\begin{aligned} \pi_{11}^{00} &= (1-\theta\gamma)^2 \\ \pi_{11}^{10} &= \pi_{11}^{01} = \theta\gamma(1-\theta\phi\beta)(1-\theta\gamma) \\ \pi_{11}^{11} &= (\theta\gamma)^2 + 2\theta\gamma(1-\theta\gamma)\theta\phi\beta \end{aligned} \tag{5}$$

Inference on the Classic Design

Let m_ν^i be the observed frequencies of the π_ν^i given in Eqs. 1 and 2. Then the likelihood function for estimating γ and θ is

$$L(\gamma,\theta) \propto \prod_{i=0}^{1}\prod_{\nu=0}^{1} (\pi_\nu^i)^{m_\nu^i} \tag{6}$$

The values of γ and ϕ that maximize Eq. 6, that is, the maximum likelihood estimates, MLEs, are

$$\hat{\gamma} = \frac{m_0^1}{m_0^0 + m_0^1} \tag{7}$$

and

$$\hat{\theta} = \frac{m_1^1/(m_1^0 + m_1^1)}{\hat{\gamma}} \tag{8}$$

We let the cumulative infection attack rate (AR) in the unvaccinated and vaccinated be AR_0 and AR_1, respectively. Then, in terms of the data we have

$$AR_\nu = \frac{m_\nu^1}{m_\nu^0 + m_\nu^1}, \nu = 0, 1 \tag{9}$$

Substituting Eq. 9 into Eqs. 7 and 8 yields the standard estimator for VE_S,

$$\widehat{VE}_S = 1 - \hat{\theta} = 1 - \frac{AR_1}{AR_0}$$

We point out that an estimate of γ is also available. The asymptotic estimated standard error (SE) of $\widehat{VE}_S$, i.e., $SE(\widehat{VE}_S)$ is easily found. This is used to construct a confidence interval on VE_S. The one-degree-of-freedom hypothesis test H_0: $VE_S = 0$, is performed using the Wald statistic:

$$Z = \frac{\widehat{VE}_S}{SE(\widehat{VE}_S)}.$$

Inference on Nonrandomized and Randomized Partner Designs

Let $m^{ij}_{\nu\mu}$ be the observed frequencies of $\pi^{ij}_{\nu\mu}$ given in Eqs. 1–5. Then the likelihood function for estimating γ, β, θ, and ϕ is

$$L(\gamma, \beta, \theta, \phi) \propto \prod_{i=0}^{1}\prod_{\nu=0}^{1} (\pi^{i}_{\nu})^{m^{i}_{\nu}} \prod_{j=0}^{1}\prod_{\mu=0}^{1} (\pi^{ij}_{\nu\mu})^{m^{ij}_{\nu\mu}} \qquad (10)$$

For the nonrandomized partner design, we always have $\mu = 0$ in the likelihood function (Eq. 10), while for the randomized partner design $\mu = 0, 1$. There are no closed forms for the MLEs, but they are found using standard methods to maximize the natural logarithm of Eq. 10. The *VE* estimates are $VE_S = 1 - \hat{\theta}$ and $\widehat{VE}_I = 1 - \hat{\phi}$. The one-degree-of-freedom hypothesis tests H_0: $VE_S = 0$ and H_0: $VE_I = 0$ are performed using the Wald statistics $Z = \widehat{VE}_S/SE(\widehat{VE}_S)$ and $Z = \widehat{VE}_I/SE(\widehat{VE}_I)$, respectively. The two-degree-of-freedom hypothesis test H_0: $VE_S = 0$, $VE_I = 0$ can be performed using the approximate chi-square test statistic $\chi^2 \approx -2\,[\ln L(\hat{\gamma}, \hat{\beta}, 1, 1) - \ln L(\hat{\gamma}, \hat{\beta}, \hat{\theta}, \hat{\phi})]$, which is based on the likelihood ratio statistic. We point out that estimates of γ and β are also available.

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