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Maximizing statistical power in group-randomized vaccine trials

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SUMMARY

Statistical power in group-randomized vaccine trials is complex: group randomization may increase power by capturing more transmission effects but may decrease power as more individuals are affected by a common source of variance. The former effect dominates when most infections arise from within the group and the latter when most arise outside. This process is complicated further when individuals possess partial natural immunity. Vaccine trials typically compare infection frequency (as measured by agent or antibody detection) in vaccinated *vs.* unvaccinated groups. To assess the relative contributions to statistical power by direct agent detection *vs.* serological detection of recent infection, we constructed stochastic compartmental models using differential equations describing all possible discrete states of the group. We contrasted models where natural immunity was absent, altered only the susceptible state, or altered both the susceptible and infected states. We observed the effects of endemic infection levels, the fraction of infection arising from outside the group, infectiousness *vs.* susceptibility vaccine effects and waning rates. There was significant enhancement of statistical power when serological testing separated infected and susceptible classes into subsets by natural immunity status.

INTRODUCTION

Individual-based study designs in epidemiology often work well for non-communicable diseases, since disease in one individual is generally independent of disease occurrence for others in the group. Infectious diseases require a different approach, since infection in one individual may generate a chain of transmission to many others while reduction of infection levels in some members of the community can have large indirect effects to decrease infection risks for others in the same group. Infectious disease transmission within a group, therefore, has an inherent intra-cluster correlation [1]. Vaccines may reduce a person's infectiousness towards others, or may reduce susceptibility to infection. The former effect cannot be distinguished by individually randomized trials [2], but requires group randomization. There is a loss of statistical efficiency in cluster-randomized trials, known as the design effect, $D=1+(n-1)\rho$, where n is the unit size and ρ is the intra-class correlation [3]. Design effect is the factor by which the sample size needs to be increased compared with an individually based randomized trial. Therefore, cluster size and intra-class correlation both influence the design effect. Investigation of transmission dynamics within groups should, therefore, enhance the understanding of the determinants of statistical power in vaccine trials based on group randomization.

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Table 1. *Comparison of three models*

Model	SIS	SIS*	SIS*I*
Number of possible states for an individual	2	3	4
Total number of states for a unit with n individuals	$n+1$	$1/2\ (n+2)\ (n+1)$	$\sum_{k=0}^{k=N} 1/2(n+2)(n+1)$
Parameters	C, λ, γ	C, $C\theta$, λ, $\lambda\theta$, γ, ω	C, $C\theta$, $C\phi$, $C\theta\phi$, λ, $\lambda\theta$, ω, γ, γ_2
	C, contact function	Also θ, ω	Also ϕ, γ_2
	λ, outside force of infection	θ, effect to decrease susceptibility, based on natural immunity	ϕ, effect to decrease infectiousness, based on natural immunity
	γ, recovery rate	ω, waning rate of immunity	γ_2, enhanced recovery from infection, based on natural immunity
Maximum no. terms per system state	6	12	18

In our previous study of vaccine trials for endemic infections using group randomization [4], we demonstrated the importance of the contact function (the relationship between unit size and contact rate) in determining the fraction of infections generated inside the unit and that greater statistical power was obtained when most infections arose from within the unit. We will now show how the strength and duration of natural immunity influence the magnitude of statistical power obtained from vaccine trials based on group randomization. Specifically, we will contrast the power obtainable from trials where the infected and susceptible individuals are each aggregated into one class *vs.* separable into subclasses with or without natural immunity. To accomplish this, we extended our previous stochastic compartmental model of endemic infection (i) without natural immunity to more complex models with (ii) natural immunity involving two susceptible states and (iii) natural immunity that altered both susceptible and infected states.

METHODS

We modified our previous SIS model to include additional states, representing (i) decreased susceptibility (by proportion θ) and (ii) both decreased susceptibility and infectiousness (by proportions θ and ϕ) following a natural infection. Table 1 contrasts these three models, in which the number of states for an individual is 2, 3 and 4 while the number of system states for the entire group is a linear, quadratic and cubic function of unit size, respectively. The maximum number of terms per equation required to describe each of these system states is respectively 6, 12 and 18. The motivation for our previous study [4] was to model transmission of non-typable *Haemophilus influenzae* (NTHi) within day-care centres (DCC). We used unit sizes and prevalence values consistent with that study. In this study, our motivation was to extend the results from that of an endemic infection without natural immunity to a model with both natural immunity and vaccine effects.

SIS* model (Appendix 1)

The total number of states within a unit of size n can be represented by the upper half of a $(n+1)\times(n+1)$ square:

$$\begin{matrix} Y_{0,0} & Y_{1,0} & \dots & Y_{n,0} \\ Y_{1,0} & Y_{1,1} & \dots & \\ \dots & \dots & & \\ Y_{n,0} & & & \end{matrix}$$

Rows are indexed by the number of infected, designated as I and columns by the number of naive susceptible, S. Those with partial immunity are designated as S*. The major diagonal contains all S* = 0, the immediate supradiagonal, S* = 1, etc. to the upper left corner where S* = n. Six processes describe the state transitions in the SIS* model, four that generate infections and one each representing recovery from I→S* and waning immunity from S*→ S:

(i) The outside force of infection acting on a susceptible with no natural immunity at a *per capita* rate, λ, is represented as movement along diagonals from upper right to lower left.

(ii) The outside force of infection acting on a susceptible with natural immunity at a modified

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per capita rate of $\lambda\theta$ is represented by movement down the columns.

(iii) Interaction, based on the term $c\mathrm{IS}/(n-1)$ represents transmission between infected and a susceptible without natural immunity. Movement along the diagonals represents this transition, but the first row makes no contribution, since there are no infected individuals represented in that row.

(iv) Interaction is modified by natural immunity to the term $c\theta\mathrm{IS}^*/(n-1)$. Like the outside force of infection, transition is represented by movement down the columns, but again the first row makes no contribution.

(v) Recovery from the infected state occurs at a *per capita* rate, γ, represented by vertical movement up the columns.

(vi) Waning of natural immunity occurs at a *per capita* rate, ω, represented by a horizontal left to right movement along rows.

The full probability distribution at equilibrium of this stochastic compartmental model was solved by numerically integrating the forward Kolmogorov set of equations [5, 6] (see Appendix 1), using Berkeley Madonna software [7] and running them to equilibrium.

Overview of how the parameters influence the distribution

The waning process directs flow left to right across the rows and is maximized at column 1, row 1. The recovery process directs flow up the columns and is maximized at column 1, last row. The outside force acting on the S class directs flow diagonally to increase I while decreasing S, while the outside force (modified by factor θ) acting on S* directs flow down the columns; the former is maximized at column 1, row 1 and the latter is maximum at the last column, row 1. While waning, recovery and outside force act respectively to increase S, S* and I in a linear fashion, the contact function acts nonlinearly and is at maximum when I equals its median value, in the first column, when infection involves S* and along the major diagonal for S.

SIS*I* model (Appendix 1)

The total number of states within a unit of size n can be represented by a pyramidal structure having n stacked triangular strata as described for the SIS* model, with the additional state I*, which describes an infected individual, but with diminished infectiousness based on a recent infection. At the apex, there is a single system state where all n individuals are in the I* state; in the next stratum $(n-1)$ individuals are in the I* state and there are three possible states (I, S or S*) for the remaining individual, etc. The individual states are designated $\mathrm{Y}_{i,j,k}$, where k denotes the stratum, beginning with the apex. Compared to the SIS* model three additional processes are added, a recovery from I* to S*, and two more contact processes, I* with S, and I* with S*, along with the following modifications:

Processes (ii) and (iv) now involve transition to the next I* stratum.

(vii) Recovery from the infected state I* occurs at a *per capita* rate, γ_2, represented by movement from higher to lower strata as I* decreases and S* increases.

(viii) Transmission between I* and S, is expressed by the term $c\phi\mathrm{I}^*\mathrm{S}/(n-1)$. Diagonal movement within a stratum yields a net decrease in S and increases in I. The lowest stratum makes no contribution, since there are no I* infected individuals.

(ix) Transmission between I* and S*, is expressed by the term $c\theta\phi(\mathrm{I}^*)(\mathrm{S}^*)/(n-1)$. Transitions occur to the next stratum, with a net decrease in S* and an increase in I*; again the lowest stratum makes no contribution.

Probability matrix

For each model, the matrix was evaluated to derive the probability distributions for the equilibrium values for the individual S, I, S* and I* states. In the SIS* model, the row subtotals represent the probability that there are $(0, \ldots, n)$ infected, the column subtotals represent the probability that there are $(0, \ldots, n)$ naive susceptible and the diagonal subtotals represent the probability that there are $(0, \ldots, n)$ susceptible with partial natural immunity. Infection prevalence is a weighted sum of the number of infected multiplied by the corresponding marginal row probability. In the SIS*I* model, the strata represent sets of equal I* values, while the row and column totals are summed across strata to arrive at the probability distributions for the I, S and S* states.

Prevalence attributable from inside vs. outside the unit

In the SIS* model, the outside force of infection, λ, acts on n columns $(1, \ldots, n)$ to produce infections at the rate $=\lambda \cdot j \cdot S_j$ and acts on the diagonals (except for

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the major diagonal) to produce infections at the rate $=\lambda\cdot\theta\cdot(n-I-j)\cdot S_{i,j}$. The recovery rate, γ, is constant and was set to 1, therefore, the mean duration of infection is $(1/\gamma)$ or one time unit; since the mean duration of infection is 1, the prevalence of infection numerically equals the incidence. The fraction of infections generated from outside the unit is calculated by summing the infections generated via λ acting on the naive susceptible and $\lambda\cdot\theta$ acting on those with natural immunity *vs.* total prevalence of infection within the unit. For the SIS*I* model, the terms are summed across strata to arrive at the total contribution from the outside force of infection and infection prevalence was calculated for both total infection prevalence and separately for I and I* states.

Model analysis

Our primary outcome was equilibrium probability distributions for the number in the S, I, and S* and I* states. In the SIS* model, without loss of generality, we set $\gamma=1$, so that contact, λ, ω, and θ would determine prevalence and the fraction of infections arising from outside the unit. Among the vaccinated, the susceptibility effect, σ, modifies transmission rates of all susceptible (both inside and outside forces); the infectiousness effect, κ, modifies transmission inside the unit. We adjusted the values of contact and λ that would maintain constant prevalence for the unvaccinated (20 and 40%) as both natural immunity levels and rates of waning immunity were varied. From the I distribution, we calculated vaccine efficacy (VE) or $1-\text{Prevalence}(I_{vac})/\text{Prevalence}(I_{unvac})$; the power to detect a vaccine effect along a range of fraction of infections arising from outside the unit (0·10, 0·50, 0·90) compared all three distributions in vaccinated *vs.* unvaccinated units.

In the SIS*I* model, two additional parameters are introduced (ϕ decreases infectiousness and γ_2 alters the recovery rate) of the I* state. The analysis can be structured as outlined for the SIS* model, but now we need to assess across values for ϕ, γ_2 as well as θ and ω. The outcome is the distribution of S, I, S* and I*, from which infection prevalence can be calculated separately for I, I* or for an aggregated infected state while VE was calculated based on all infected (VE) or based only on the infected with natural immunity (VE*). Similarly, power was calculated based on I, S, S* or I* states, as well as by aggregating the infected into one class.

We chose to maintain the prevalence among the unvaccinated at a constant level and to examine power and VE at various proportions of infections generated from outside the unit since the investigator would know the endemic level of infection and could estimate how much transmission occurred from inside *vs.* outside the unit. This approach made us adjust the values of the model parameters to fit the conditions of prevalence and fraction of infections generated externally; the investigator would probably not have exact estimates for all the model parameters.

The solution when there is no outside force of infection

In the SIS model, it can be shown that when there is no outside force of infection, eventually no one in the unit is infected [4]. When there is no outside force of infection in the SIS* model, the only transition involving the first row (I = 0) is the flow of recovered from the second row (I = 1) and flow along the first row by the process of waning immunity. That is, there is a net flow from the first row to the second row, so eventually there are no infections within the unit when the outside force of infection is zero. When there is no outside force of infection in the SIS*I* model, similar transitions occur within each stratum to its first row and recovery (γ_2) yields a net flow to the lowest stratum. Again, eventually there are no infections within the unit.

Calculation of power in vaccine trials

In a vaccine trial using group randomization, we expect that vaccination will decrease the number of infected and increase the number of susceptible individuals in the group. The null hypothesis is that there is no difference in the distributions from vaccinated groups *vs.* unvaccinated groups. This is an important distinction from the usual hypothesis testing, in that we are not testing an individual biological effect, such as susceptibility, but rather we are evaluating the total group effect from altering each individual's susceptibility. After determining the 5th percentile for the number of infected individuals in the unvaccinated group as a threshold, we measure statistical power as the cumulative probability less than that threshold among the infected, vaccinated individuals. We also estimated statistical power by comparing the probability distributions of the susceptible state for the unvaccinated *vs.* the vaccinated, by using the 95th percentile for the unvaccinated S distribution compared with the

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Table 2. *Power analysis for three models*

Model	SIS	SIS*	SIS*I*
Infectious agent based (current infection)	I	I	I, I* or I-all
Immune based (past infection)	n.a.	S*	S*, I*
Either current or past infection	n.a.	I∪S*, which is equivalent to S	I∪I*∪S*, which is equivalent to S

cumulative probability distribution for the vaccinated S to the right of the same threshold. More generally, the format for power determination was to designate the unvaccinated as the control group and to use the left tail ($\alpha < 0{\cdot}05$) when the vaccinated group showed a decrease and the right tail ($\alpha > 0{\cdot}95$) when the vaccinated group showed an increase. We compared four replications of $n = 12$. Assuming independence for the replications, we used the probability distribution from one trial to calculate the expected distribution of four replications by expanding the initial distribution to the fourth power (Appendix 2). Table 2 summarizes the approach for the three models.

RESULTS

No natural immunity

In the endemic SIS model, power based on the susceptible class contains the same information as power based on the infected class, since each probability distribution completely determines the other, e.g. the probability that three are infected in a group of 12 is the same as the probability that there are nine susceptibles in the group, or more generally, $P[i]_{\mathrm{Inf}} = P[n-i]_{\mathrm{Sus}}$. In the SIS model, power is greater when most infections are generated from inside the unit, when the vaccine effect is on susceptibility and for a higher endemic prevalence. VE is also higher when most infections are generated from inside the unit and when the vaccine effect is on susceptibility, but decreases as endemic prevalence levels rise (Table 3).

Natural immunity affecting susceptibility alone

Probability distributions

The three classes in the SIS* model are also interrelated, in that $P[i]_{\mathrm{Inf}}$ = the sum of all $P[j]_{\mathrm{Sus}}$ and $P[k]_{\mathrm{Sus*}}$, conditional on $[n = i + j + k]$. Figure 1 illustrates the bivariate probability distributions from four repetitions with units of size 12, while maintaining 40% endemic prevalence, a small fraction of infections arising externally and as the waning rate was varied from 1·0 to 0·01. As waning slows, more individuals within an unvaccinated group are likely to be in the immune state, concentrating the probability distribution along the first row (note the change in scale across waning rates). Regardless of waning rate, vaccination decreases the probability of infection and increases the probability of being susceptible. Under slower waning, vaccination has less effect to increase the probability of being susceptible. Figure 2 separates the cumulative probability distributions of the I, S and S* classes under the rapid waning rate scenario shown in Figure 1, but contrasts low *vs.* high external generation of infection. When most infections are generated inside the unit, the variance within I and S class is higher, but vaccination has both direct and indirect effects to decrease transmission, resulting in a stronger total effect. Figure 3 shows the cumulative probability distributions for the immune state in vaccinated *vs.* unvaccinated groups as the waning rate is varied. As shown earlier in Figure 1, vaccination decreases the probability of being immune when waning is rapid, increases this probability when waning is slow and has minimal effect at an intermediate waning rate.

Table 3. *Statistical power and vaccine efficacy for the SIS model at 40 and 20% prevalence*

	Proportion of infections from outside the unit					
	Susceptibility effect (σ) = 0·50			Infectiousness effect (κ) = 0·50		
	0·10	0·50	0·90	0·10	0·50	0·90
Prevalence (40%)						
Power [Agent]	0·921	0·816	0·735	0·696	0·221	0·066
Vaccine efficacy	0·758	0·499	0·393	0·593	0·202	0·031
Prevalence (20%)						
Power [Agent]	0·611	0·470	0·414	0·335	0·092	0·036
Vaccine efficacy	0·839	0·593	0·468	0·698	0·264	0·041

Power [Agent] is based on comparison of distributions of infected individuals, I.
Vaccine efficacy (VE) = 1 − prevalence of infected (vac)/prevalence of infected (unvac).

Power based on direct agent detection

The power to detect vaccine effects is summarized in Table 4, in which direct agent-based detection is

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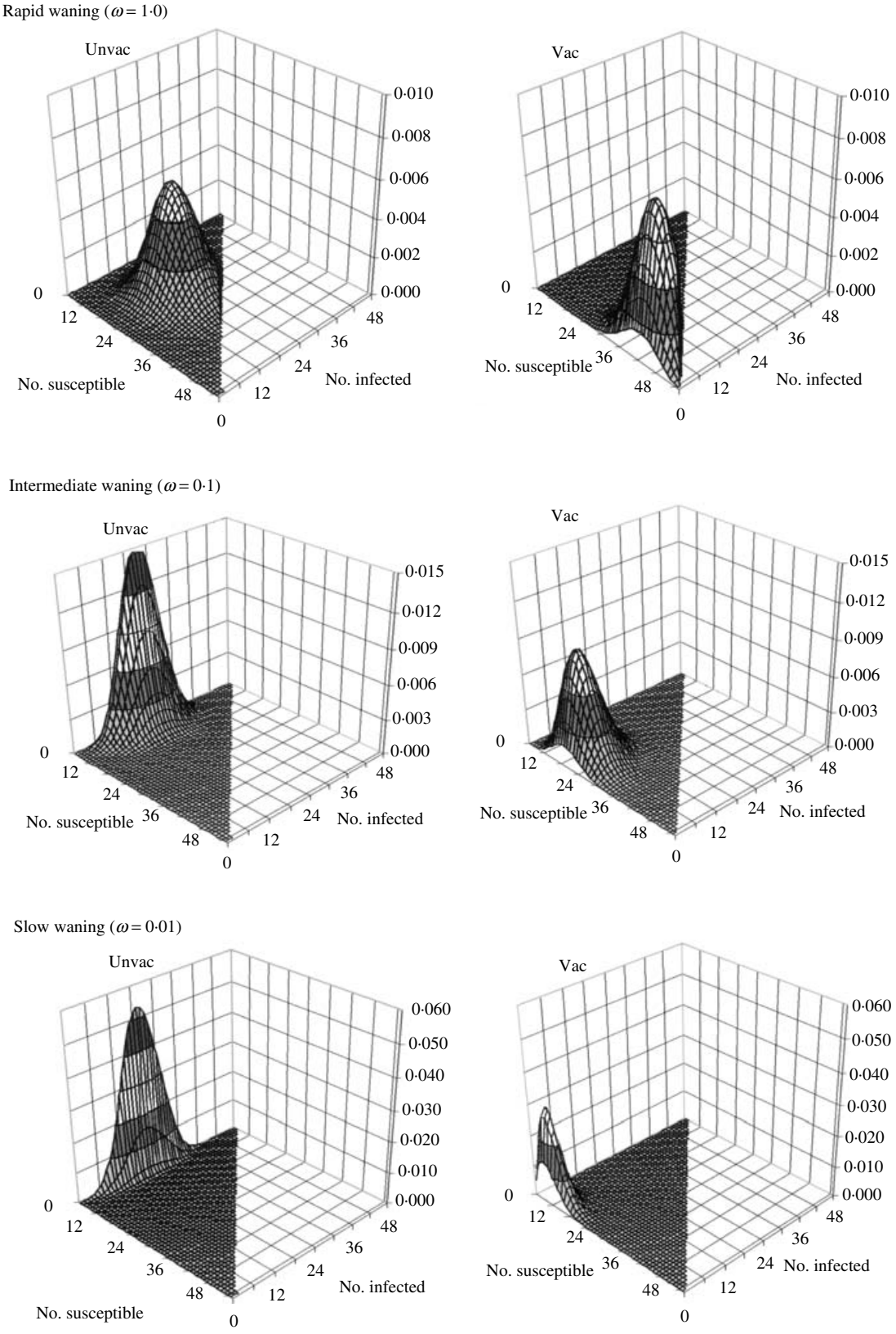

Fig. 1. Probability distributions for the SIS* model with a susceptibility vaccine effect at slow, intermediate and rapid waning rates for the S* state. Each scenario has endemic prevalence of 40% with 10% of infections arising from outside the unit. (Note the change in scale for probability.)

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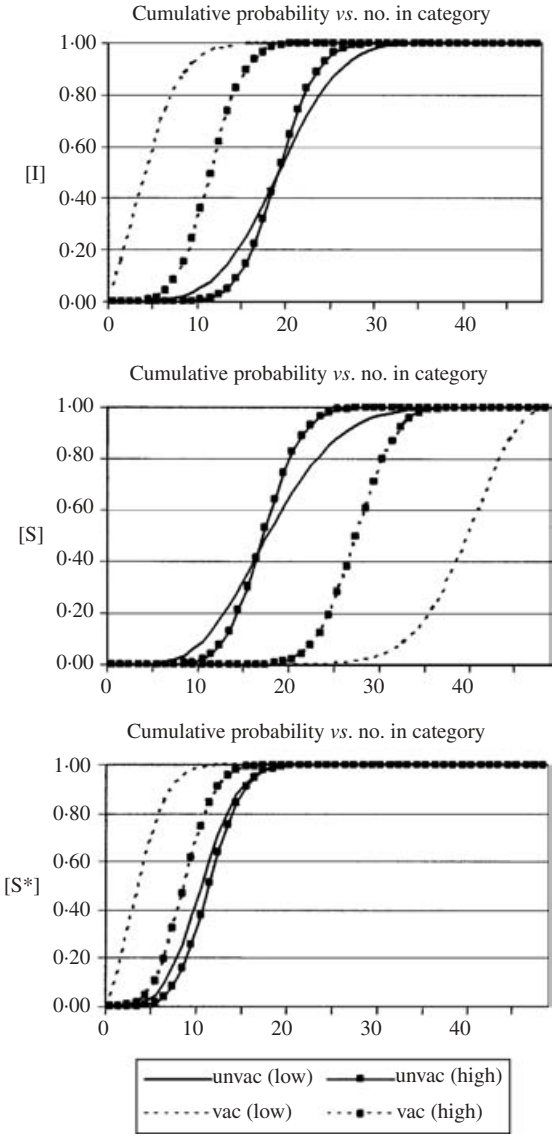

Fig. 2. Cumulative probability distributions for I, S and S*, given 40% prevalence, natural immunity ($\theta = 0{\cdot}50$) with rapid waning and a vaccine effect to reduce susceptibility by 50%. High outside force (90% of infections generated externally) is shown with squares, low outside force (10% of infections generated externally) without; solid lines represent the unvaccinated, dotted lines the vaccinated. Although the variance is greater when the outside force of infection is low, power is greater because vaccination has both direct and indirect effects.

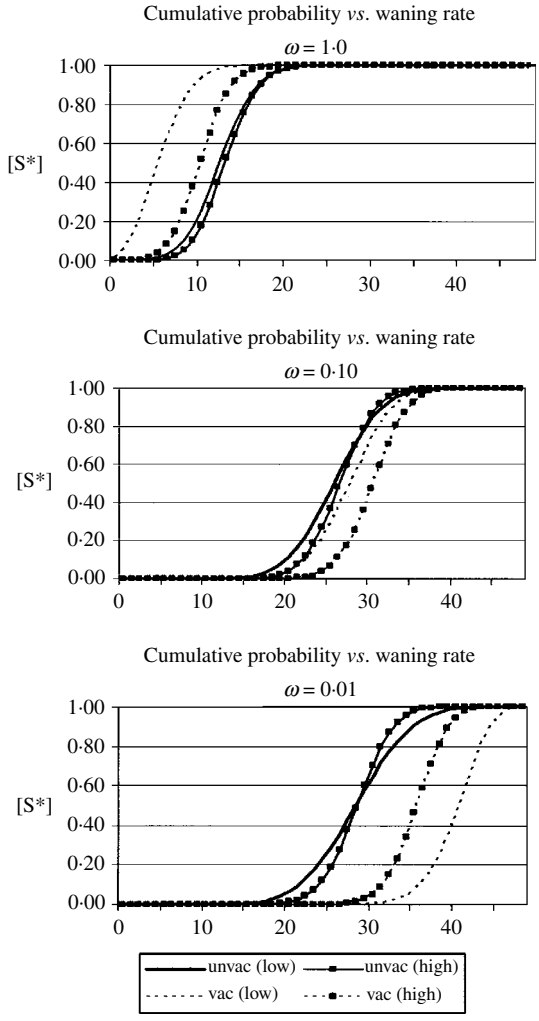

Fig. 3. Cumulative probability distributions for S*, given 40% prevalence, natural immunity ($\theta = 0{\cdot}50$), vaccine susceptibility ($\sigma = 0{\cdot}50$) effect and variable waning rates. High outside force (90% of infections generated externally) is shown with squares, low outside force (10% of infections generated externally) without; solid lines represent the unvaccinated, dotted lines the vaccinated. Vaccination decreases S* when the waning rate is fast, while S* increases when the waning rate is slow. Maximum power to detect vaccine effect based on S* distributions depends on the interaction between the strength and duration of natural immunity.

measured via distributions of the I state, immune-based detection of recent infection is determined via the S* state and the S distribution represents the individuals with neither current nor recent infection. (The latter is equivalent to the distribution of those individuals with either current or recent infection, in that the 5th percentile of one is the 95th percentile of the other.) As in the no natural immunity model, power based on direct agent detection is greater for susceptibility than infectiousness effects, greater when most infections are generated inside the group and when endemic infection levels are higher. Stronger natural immunity acts to decrease statistical power, but this is modified by the waning rate. As waning slows, the power first decreases then increases.

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Table 4. *Statistical power and vaccine efficacy for SIS* model at 40 and 20% prevalence*

	Proportion of infections from outside the unit					
	0·10	0·50	0·90	0·10	0·50	0·90
	Susceptibility effect (σ) = 0·50			Infectiousness effect (κ) = 0·50		
Prevalence = 40%						
No natural immunity						
Power [Agent]	0·921	0·816	0·735	0·696	0·221	0·066
Power [Immune]	0·757	0·348	0·197	0·416	0·084	0·042
Power [Either]	0·974	0·938	0·873	0·811	0·330	0·055
Vaccine efficacy	0·758	0·499	0·393	0·593	0·202	0·031
Natural immunity (θ = 0·50) fast waning (ω = 1·0)						
Power [Agent]	0·848	0·681	0·617	0·590	0·169	0·061
Power [Immune]	0·619	0·265	0·151	0·291	0·057	0·058
Power [Either]	0·944	0·894	0·830	0·736	0·240	0·052
Vaccine efficacy	0·655	0·426	0·341	0·490	0·167	0·025
Natural immunity (θ = 0·50) intermediate waning (ω = 0·17)						
Power [Agent]	0·847	0·727	0·668	0·642	0·193	0·065
Power [Immune]	0·084	0·232	0·294	0·189	0·106	0·050
Power [Either]	0·910	0·637	0·407	0·603	0·119	0·040
Vaccine efficacy	0·654	0·449	0·363	0·517	0·185	0·029
Natural immunity (θ = 0·50) slow waning (ω = 0·01)						
Power [Agent]	0·900	0·804	0·727	0·673	0·217	0·066
Power [Immune]	0·839	0·736	0·662	0·658	0·188	0·058
Power [Either]	0·670	0·178	0·108	0·323	0·048	0·023
Vaccine efficacy	0·738	0·492	0·390	0·581	0·200	0·031
Prevalence = 20%						
No natural immunity						
Power [Agent]	0·611	0·470	0·414	0·335	0·092	0·036
Power [Immune]	0·617	0·531	0·320	0·329	0·059	0·048
Power [Either]	0·755	0·759	0·744	0·442	0·163	0·061
Vaccine efficacy	0·839	0·593	0·468	0·698	0·264	0·041
Natural immunity (θ = 0·50) fast waning (ω = 1·0)						
Power [Agent]	0·523	0·408	0·368	0·255	0·077	0·035
Power [Immune]	0·511	0·431	0·246	0·229	0·096	0·039
Power [Either]	0·737	0·764	0·653	0·416	0·175	0·049
Vaccine efficacy	0·795	0·556	0·439	0·632	0·238	0·037
Natural immunity (θ = 0·50) intermediate waning (ω = 0·10)						
Power [Agent]	0·430	0·338	0·332	0·216	0·072	0·035
Power [Immune]	0·636	0·310	0·136	0·208	0·053	0·051
Power [Either]	0·892	0·825	0·680	0·527	0·155	0·071
Vaccine efficacy	0·729	0·509	0·409	0·588	0·225	0·036
Natural immunity (θ = 0·50) slow waning (ω = 0·01)						
Power [Agent]	0·538	0·441	0·397	0·297	0·087	0·036
Power [Immune]	0·060	0·229	0·289	0·100	0·090	0·070
Power [Either]	0·755	0·223	0·256	0·366	0·040	0·040
Vaccine efficacy	0·804	0·576	0·457	0·672	0·258	0·041

Power [Agent] compares infected individuals, I; Power [Immune] compares individuals with evidence of recent infection, S*; Power [Either] compares individuals with either current infection or evidence of recent infection, which is equivalent to comparison of S; Vaccine efficacy (VE) = 1 − prevalence infected (vac)/prevalence infected (unvac).

Power using immune-based detection

Power based on immune-based detection was similar to that based on direct agent detection *vs.* type of vaccine effect, strength of natural immunity, the unvaccinated prevalence level and fraction of infections arising from outside the unit. Immune-based power showed the same biphasic response *vs.* the waning rate as that based on direct agent detection;

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when the immune class dominated, power based on serological detection exceeded the other methods. Power based on the naive susceptible class often resulted in the greatest statistical power to detect vaccine effects; it was more robust for detection of a vaccine susceptibility effect as the fraction of infections arising from outside the unit was varied. Power based on the susceptible class was poor only when the waning rate was very slow and the immune class dominated. For a vaccine effect on infectiousness, power based on the susceptible state was often greater than that based on direct agent detection, although both were very weak when most infections were generated from outside the unit.

Vaccine efficacy

As in the SIS model, VE is higher when most infections are generated from inside the unit and when the vaccine effect is on susceptibility, but decreases as endemic prevalence levels rise (Table 4). VE is higher when natural immunity is weak (we are comparing groups with the same endemic prevalence among the unvaccinated). As the waning rate of natural immunity slows, VE first decreases then increases, i.e. the same biphasic response exhibited by power based on direct agent detection across waning rates.

Natural immunity affecting susceptibility and infectiousness

Probability distributions

The four states in the SIS*I* model are also constrained in that any three determine the fourth, since the grand total must equal the group size. Figure 4 illustrates the bivariate probability distribution in the same scenario as described for Figure 1, as the waning rate was varied. The axes represent (i) the number of infected who lack any immunity and (ii) the number of infected who had partial immunity based on evidence of a recent infection. As waning slows, more individuals within an unvaccinated group will be infected and have partial immunity, i.e. concentrated along the first column. Regardless of the waning rate, vaccination will decrease the probability of being infected, but the distribution is more concentrated among infected who lack immunity when the waning rate is rapid.

Power based on separation of infected classes

Figure 5 shows the cumulative probability distributions for each of the direct agent-based designations, I, I* and I-all (the latter is represented by the diagonal elements in Fig. 4) for fast *vs.* slow waning rates, using the same scenario as Figure 4. Power based on direct agent detection and partial immunity, the I* state, was generally greater than that based on either direct agent without immunity, the I state or their aggregated infected state, I-all (Table 5). The difference between the I* and I-all distributions decreased at slower waning rates, so the power determinations became equivalent.

Vaccine efficacy

When the full SIS*I* model is considered, VE can now be calculated based on the I* class as VE* or based on an aggregated infected class as the usual VE. As in the previous models, VE is higher when most infections are generated from inside the unit, when natural immunity is weak and when the vaccine effect is on susceptibility, but decreases as endemic prevalence levels rise. As the waning rate of natural immunity slows, VE first decreases then increases, i.e. the same biphasic response exhibited by power based on the infected state across waning rates. The magnitude of VE* is higher than VE, except when the waning rate is very slow and two become equivalent (Fig. 6).

Power using immune-based detection

Power based on immune-based detection was similar to that found with the SIS* model; the same biphasic response *vs.* the waning rate was again documented. Power using immune-based detection worked best when the immune class dominated at slow waning rates. Power based on the naive susceptible class (which was equivalent to enumeration of all the other classes) usually resulted in the greatest statistical power to detect vaccine effects. It was more robust for detection of a vaccine susceptibility effect as the fraction of infections arising from outside the unit was varied and provided greater power for detection of infectiousness effects. Power based on the naive susceptible class was poor only when the waning rate was very slow and the immune class dominated.

DISCUSSION

Vaccine trials typically compare the frequency of agent or antibody detection in vaccinated *vs.* unvaccinated groups, while statistical power in such trials compares their distributions. In our endemic

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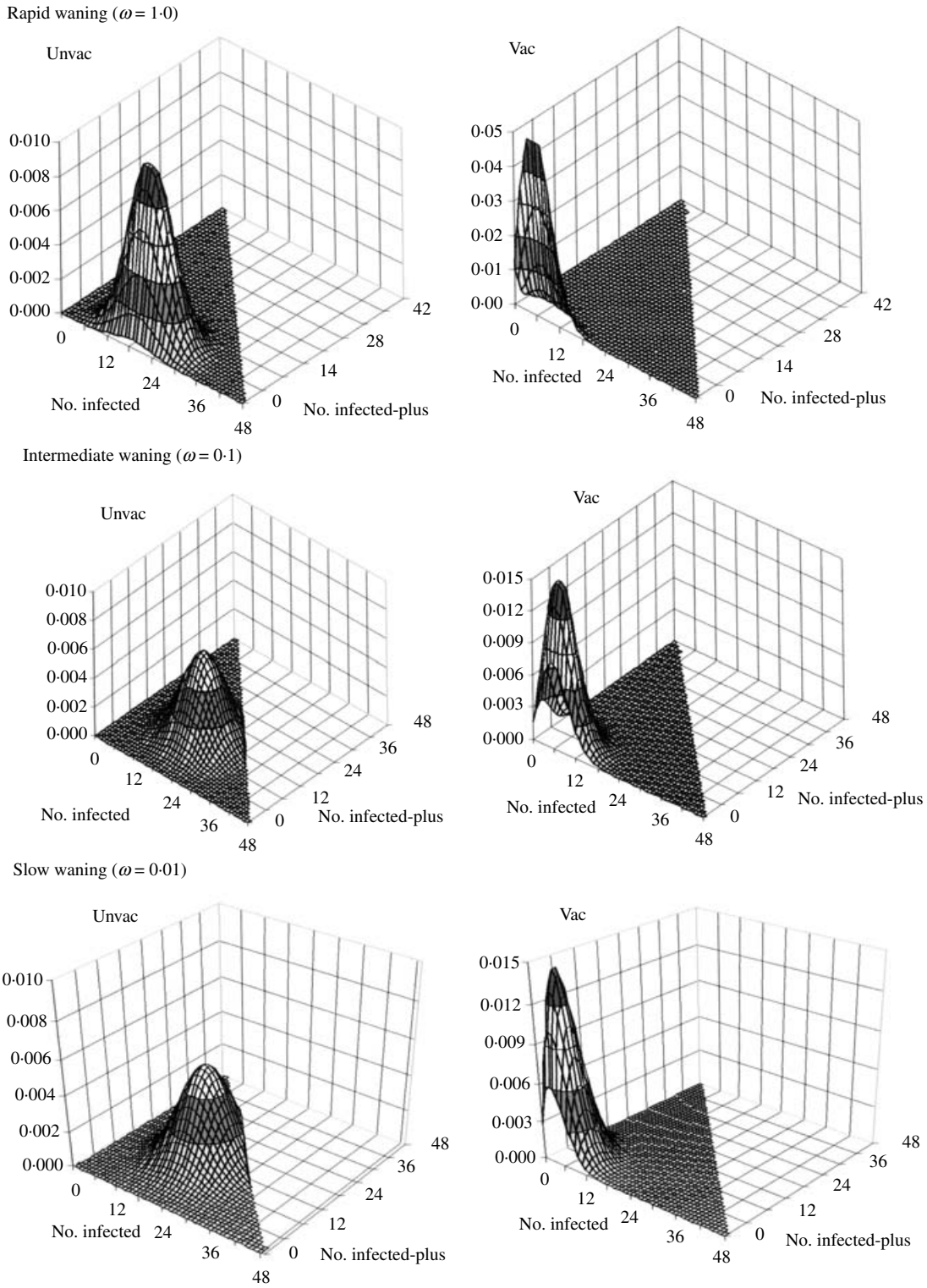

Fig. 4. Probability distributions for the SIS*I* model showing vaccination susceptibility effect = 0·50 under slow, intermediate and rapid waning rates. Each scenario has endemic prevalence of 40 % with 10 % of infections arising from outside the unit. (Note the change in scale for probability.)

model without natural immunity, individuals are either infected or susceptible, so the distribution of the number of infected inside a unit completely determines the distribution of the number of susceptible, making their power determinations equivalent. When there are two susceptible classes, separable by

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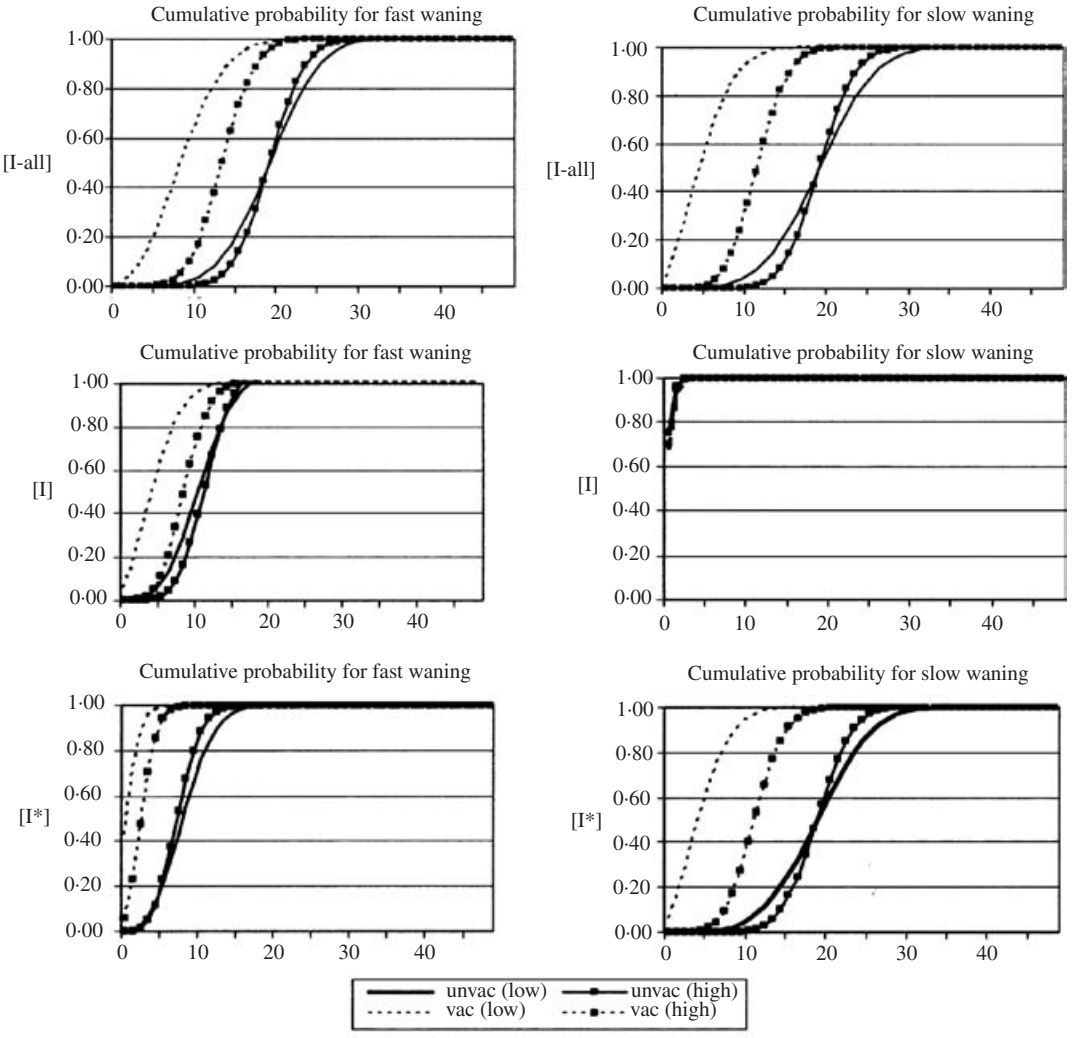

Fig. 5. Cumulative probability distributions for the infected classes I, I* and their aggregate, I-all, for 40 % prevalence among the unvaccinated and a slow *vs*. fast waning rate. High outside force (90 % of infections generated externally), is shown with squares, low outside force (10 % of infections generated externally) without squares. Solid lines represent the unvaccinated, dotted lines the vaccinated. Power based on the I* class is greater than that for the aggregated infected class, but when waning is slow, the I class is almost zero and there is almost no difference between I* and I-all classes.

serological detection of natural immunity, then power based on analysis of the susceptible without natural immunity was superior to that based on agent detection in the range of prevalence examined, across degrees of natural immunity, becoming poor only when waning was very slow. In this SIS* model, the distribution of the I state is equivalent to that based on aggregating both susceptible states, while the distribution of the S state is the complement of those individuals with either current or recent infections. Power based on the latter was generally more robust as the strength of natural immunity or the fraction of infections arising from outside the unit was varied. When the waning rate was very slow and the recently immune state became dominant, then power was greater using the direct agent or immune distributions.

When natural immunity affected both the susceptible and the infected classes (SIS*I* model), then power based on analysis of the I* state was superior to that based on the I state when natural immunity reduced either susceptibility or infectiousness, for either type of vaccine effect and across a wide range of waning rates. The interaction of natural immunity and the vaccine effect created a stronger protective effect for the I* class.

Statistical power to detect an effect is enhanced by decreasing the group variance or by amplifying the

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Table 5. *Statistical power for SIS*I* model at 40% prevalence*

	Proportion of infections from outside the unit					
	0·10	0·50	0·90	0·10	0·50	0·90
	Susceptibility effect (σ) = 0·50			Infectiousness effect (κ) = 0·50		
No natural immunity						
Power [I]	0·634	0·239	0·210	0·313	0·046	0·074
Power [I*]	0·942	0·700	0·707	0·792	0·142	0·065
Power [I-all]	0·921	0·816	0·735	0·696	0·221	0·067
Power [Immune]	0·757	0·348	0·197	0·416	0·084	0·042
Power [Either]	0·974	0·938	0·873	0·811	0·330	0·055
Natural immunity (θ = 0·50) fast waning (ω = 1·0)						
Power [I]	0·510	0·296	0·166	0·131	0·069	0·060
Power [I*]	0·810	0·535	0·374	0·573	0·116	0·030
Power [I-all]	0·848	0·681	0·617	0·590	0·169	0·061
Power [Immune]	0·619	0·265	0·151	0·291	0·057	0·058
Power [Either]	0·944	0·894	0·830	0·736	0·240	0·052
Natural immunity (θ = 0·50) intermediate waning (ω = 0·10)						
Power [I]	0·050	0·095	0·085	0·050	0·071	0·050
Power [I*]	0·942	0·772	0·696	0·776	0·167	0·050
Power [I-all]	0·847	0·727	0·668	0·642	0·193	0·065
Power [Immune]	0·084	0·232	0·294	0·189	0·106	0·050
Power [Either]	0·910	0·637	0·407	0·603	0·119	0·040
Natural immunity (θ = 0·50) slow waning (ω = 0·01)						
Power [I]	0·070	0·060	0·050	0·070	0·060	0·040
Power [I*]	0·926	0·755	0·658	0·713	0·162	0·040
Power [I-all]	0·900	0·804	0·727	0·673	0·217	0·066
Power [Immune]	0·839	0·736	0·662	0·658	0·188	0·058
Power [Either]	0·670	0·178	0·108	0·323	0·048	0·023
Natural immunity (ϕ = 0·50) fast waning (ω = 1·0)						
Power [I]	0·529	0·221	0·209	0·251	0·046	0·040
Power [I*]	0·882	0·838	0·703	0·682	0·124	0·065
Power [I-all]	0·850	0·700	0·640	0·588	0·143	0·040
Power [Immune]	0·656	0·328	0·205	0·334	0·083	0·065
Power [Either]	0·931	0·992	0·887	0·700	0·270	0·065
Natural immunity (ϕ = 0·50) intermediate waning (ω = 0·10)						
Power [I]	0·035	0·068	0·059	0·131	0·056	0·041
Power [I*]	0·932	0·871	0·726	0·748	0·251	0·042
Power [I-all]	0·807	0·772	0·729	0·562	0·209	0·066
Power [Immune]	0·063	0·132	0·140	0·063	0·100	0·056
Power [Either]	0·934	0·828	0·646	0·664	0·209	0·060
Natural immunity (ϕ = 0·50) slow waning (ω = 0·01)						
Power [I]	0·070	0·060	0·060	0·064	0·050	0·040
Power [I*]	0·924	0·759	0·666	0·711	0·161	0·040
Power [I-all]	0·897	0·866	0·734	0·671	0·217	0·066
Power [Immune]	0·696	0·662	0·603	0·560	0·164	0·051
Power [Either]	0·714	0·191	0·101	0·356	0·040	0·020

Power [Agent] compares infected individuals as I*, I or total infected, I-all; Power [Immune] compares individuals with evidence of recent infection S*; Power [Either] compares individuals with either current infection or evidence of recent infection, which is equivalent to comparison of S.

effect. Although the variance in the number of infected was lower when most infections were generated from outside the unit, the statistical power was less when such units were compared in vaccine trials [4]. That is, despite the larger variance in the number of infected when most infections arose from

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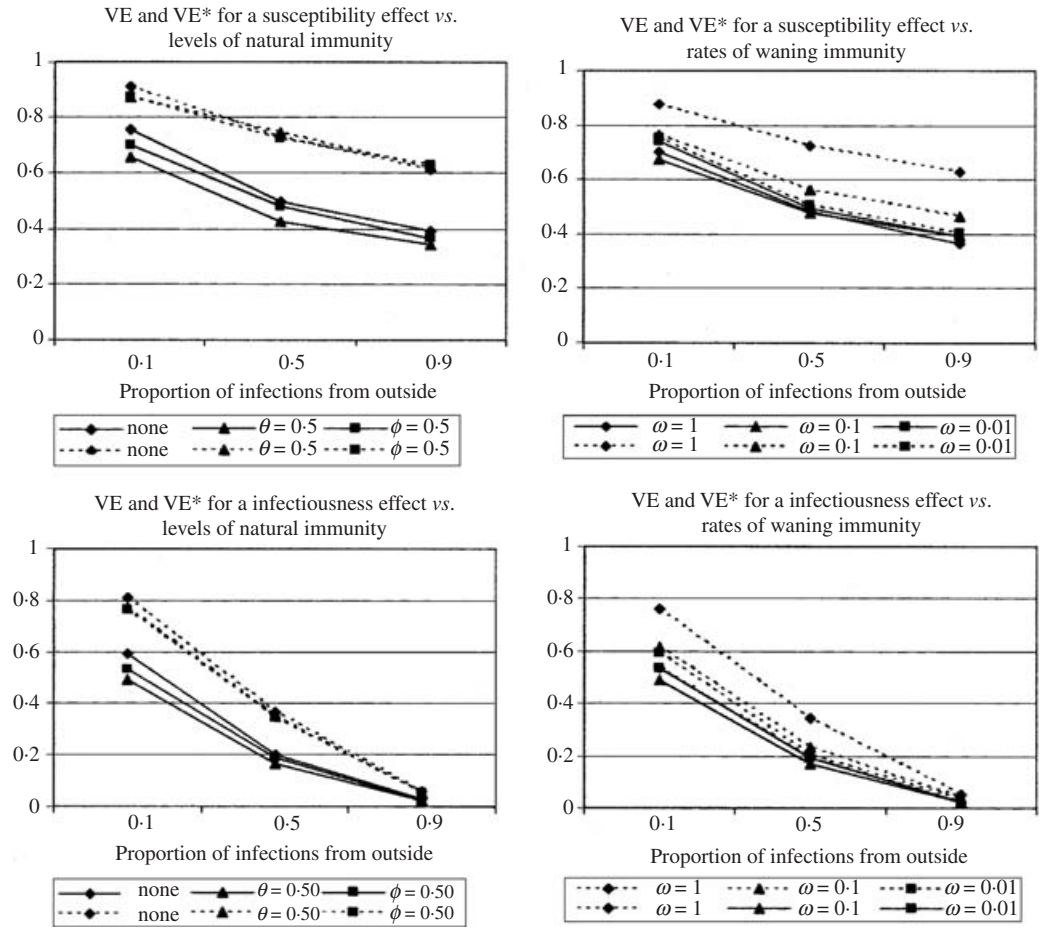

Fig. 6. Vaccine efficacy, based on all infected individuals (VE) is shown with solid lines, while vaccine efficacy, based only on those infected who had recovered from a recent infection (VE*) is shown with dotted lines (prevalence among the unvaccinated is constant at 40%). The left panels contrast levels of natural immunity, while the right panels contrast waning rates. The upper panels show vaccine susceptibility effects, the lower panels show infectiousness effects. VE* is greater than VE, both are higher when low outside force of infection dominates and susceptibility effects have a greater magnitude than infectiousness effects. At very slow waning rates, there is little difference between the magnitude of VE and VE*, since almost all infected are in the [I*] class.

inside the unit, vaccination of such groups produced strong indirect as well as direct effects, so greater separation of the distributions was obtained. The same phenomenon of increased variance in the number of infected (and the number of susceptible) when most infections arose from inside the unit was observed in the SIS* and the SIS*I* models. Nonlinearity of the contact process generated this variance *vs.* when most infections arose from outside the unit and a more homogeneous distribution developed. For both the SIS* and SIS*I* models, when most infections arose inside the unit, there were strong indirect and direct effects that resulted in much greater separation between the vaccinated and the unvaccinated groups and hence greater power.

Exposure to other children, either through attendance at a DCC or via household contacts, is an important source of transmission for both NTHi and *S. pneumoniae* [8–10]. Greater size of the DCC increases the transmission; the odds ratio (OR) for otitis media increased (compared to no day care) from 1·5, 2·0, 3·0 and 3·8 as the number of children in the unit rose from 1–3, 4–6, 7–12, and >12 [11]. Among households, the proportion of infections acquired within a household increased with its size [9]. Carriage rates of *S. pneumoniae* in young children increased with household size (OR 3), comparable to the increased odds found with lower socio-economic status or attendance at a DCC [12]. Groups therefore differ with regard to likelihood of internal *vs.* external transmission; our models suggest that characterizing the proportion of

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infection generated from inside the unit strongly influences both the power to detect vaccine effects and magnitude of VE.

VE is a proportion used to quantify the degree of protection afforded by vaccination. It can manifest as a reduction in susceptibility or infectiousness; Longini et al. [13] denote these as VE_S and VE_I respectively. The protection offered by a vaccine can reduce the probability of acquiring infection by a constant factor for all recipients, or a certain proportion of vaccinees may be completely protected, while the remainder have limited or no protection [14]. In this study, we modelled susceptibility and infectiousness effects separately and as a reduction in transmission, rather than as a complete immunity, so that the joint effect of natural immunity and vaccination could be examined. Natural immunity and vaccine effects were modelled as a multiplicative interaction. We found that vaccine efficacy (VE*) derived from a separate analysis of those with natural immunity showed a greater protective effect than that based on aggregating all infected into one class. The interaction of natural immunity and the vaccine effect magnified VE for the [I*] class. Halloran et al. [15] described the use of validation sets for estimation of VE, in vaccine field studies where the initial estimates of disease are made based on a clinical case definition, but later refined by studying a subset with a more definitive test, e.g. culture confirmation. Although in our model all infected subjects have the same disease, a subset with natural immunity might only be distinguishable by measuring antibody titres, etc.; analysis of this subset both increases the estimate of VE and offers greater statistical power. Haber et al. [16] analysed the effect of a disease prior to an outbreak on estimates of VE following the outbreak; in their model, natural immunity would provide complete protection from an infection, while only a proportion of vaccinees would be completely immune. They pointed out the problem of identifying individuals based on case history alone *vs.* testing for pre-existing immunity and the potential bias introduced into estimates of VE when vaccinees and non-vaccinees had different levels of immunity from natural disease.

In *Design and analysis of group-randomized trials* by Murray [17], multiple steps are outlined for proper analysis of statistical power in group-randomized trials. Included among the steps are specifying the form and magnitude of the intervention effect and determining the distribution and variance of the outcome. From the models we developed for an infectious disease, it is clear that the relative value of the internal *vs.* external force of infection in the group is an important determinant of the intra-class correlation, the magnitude of the intervention effect and hence the statistical power. The baseline prevalence among the unvaccinated group is insufficient to predict the statistical power of the trial; one needs an understanding of the group transmission dynamics to predict the vaccine effect. The ability to discriminate a subset possessing natural immunity within infected and susceptible classes enhanced the statistical power to detect a vaccine effect and increased VE. In the range of prevalence we examined [S] or [S*] classes represented a majority or a plurality in the unit. When the naive susceptible could be differentiated from the others, statistical power based on a vaccine effect to increase their number was frequently superior to power based on decreasing the infected.

Our analysis suggests that assessing the outcome of a vaccine trial should include information beyond the risk of infection among the unvaccinated *vs.* the vaccinees. When there is natural immunity that decreases the probability of acquiring and/or transmitting an infection and some means (e.g. serological) of identifying individuals possessing those characteristics, then greater statistical power is possible by separate analysis of those individual classes. In the case of highly recurrent agents where natural immunity rapidly wanes, power may be maximized by analysis of the S class, i.e. those individuals lacking any residual natural immunity. When the natural infection provides long-lasting immunity, then power estimates using immune-based detection or power based on separation of the infected that have prior evidence of a natural infection may provide maximum power. When immunity wanes very slowly, then power may be maximized by analysis of the immune state. However, the duration of the vaccine trial may be too short for the vaccine effects to come to equilibrium in the latter situation. Vaccine trials that are based on group randomization should also include information about the nature of transmission within the groups, since the proportion of infections generated from within has a strong influence on both vaccine efficacy and the power to detect vaccine effects.

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APPENDIX 1. Summary of equations used for the SIS* and SIS*I* models

SIS* model

1st column ($Y_{i,0}$)

$$\mathrm{d}/\mathrm{d}t(Y_{0,0}) = -\omega n Y_{0,0} - n\lambda\theta Y_{0,0} + \gamma Y_{1,0}, \tag{1}$$

$$\begin{aligned}\mathrm{d}/\mathrm{d}t(Y_{1,\ldots,n-1,0}) = &-\omega(n-i)Y_{i,0} + \lambda Y_{i-1,1} + \lambda\theta((n+1-i)Y_{i-1,0} - (n-i)Y_{i,0}) + c(i-1)Y_{i-1,1} \\ &+ c\theta((n+1-i)(i-1)Y_{i-1,0} - (n-i)iY_{i,0}) + \gamma(i+1)Y_{i+1,0} - \gamma i Y_{i,0},\end{aligned} \tag{2}$$

$$\mathrm{d}/\mathrm{d}t(Y_{n,0}) = \lambda Y_{n-1,1} + \lambda\theta Y_{n-1,0} + c(n-1)Y_{n-1,1} + c\theta(n-1)Y_{n-1,0} - n\gamma Y_{n,0}. \tag{3}$$

2nd column ($Y_{i,1}$)

$$\mathrm{d}/\mathrm{d}t(Y_{0,1}) = \omega(nY_{0,0} - (n-1)Y_{0,1}) - \lambda(1+\theta\,(n-1))Y_{0,1} + \gamma Y_{1,1}, \text{ etc.} \tag{4}$$

Each of the $Y_{i,j}$ entries represent the probability of the system being at that state, when equilibrium is reached.

The equations for the SIS*I* model are summarized as follows.

I(n) stratum*

$$\mathrm{d}/\mathrm{d}t(Y_{0,0,0}) = -n\gamma_2 Y_{0,0,0} + \lambda\theta Y_{0,0,1} + (n-1)c\theta\phi(1/(n-1))Y_{0,0,1}.$$

I(n−1) stratum*

$$\mathrm{d}/\mathrm{d}t(Y_{0,0,1}) = +n\gamma_2 Y_{0,0,0} - (\lambda\theta + \omega + (n-1)(\gamma_2 + c\theta\phi))Y_{0,0,1} + \gamma_1 Y_{1,0,1} + 2\theta(\lambda + (n-2)c\phi/(n-1))Y_{0,0,2},$$

$$\mathrm{d}/\mathrm{d}t(Y_{1,0,1}) = -(\gamma_1 + (n-1)\gamma_2)Y_{1,0,1} + (\lambda + c\phi)Y_{0,1,1} + (c\theta/(n-1))(\phi(n-2)+1)Y_{1,0,2},$$

$$\mathrm{d}/\mathrm{d}t(Y_{0,1,1}) = +\omega Y_{0,0,1} - (\lambda + (n-1)\gamma_2 - c\phi)Y_{0,1,1} + \theta(\lambda + c\phi(n-2)/(n-1))Y_{1,1,2}, \text{ etc.}$$

APPENDIX 2. Multinomial expansion

An example of expansion of probability distribution from a group of size 12 to arrive at probability distributions for four independent replications:

Let $P[0]$, $P[1]$, …, $P[12]$ be the probability that 0, 1, …, 12 are infected within the unit:

Then the probability that 0 are infected among $48 = P[0]^4$.
The probability that 1 is infected among $48 = 4 \cdot P[1] \cdot P[0]^3$.
The probability that 2 are infected among $48 = 4 \cdot P[2] \cdot P[0]^3 + 6\ P[1]^2 \cdot P[0]^2$.

Or generally, the probability that k are infected among four replications is

$$\sum (4 \cdot P[k] \cdot P[0]^3 + C^4_{2,1,1} \cdot P[k-1] \cdot P[1] \cdot P[0]^2 + \ldots),$$

i.e. across all combinations of probabilities that total k infected, where each probability $P[i]$, is raised to the power of the number of repeats and where the C notation represents all possible combinations of four items, given the number of repeats.

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