

Assessment of the Protective Efficacy of Vaccines against Common Diseases Using Case-Control and Cohort Studies

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Case-control and cohort studies may be employed to assess the protective efficacy of vaccines. The appropriate measure of vaccine efficacy is shown to depend upon the mode of action of the vaccination. Two models of vaccine action are considered. In the first, vaccination is assumed to reduce the instantaneous disease-rate in the total vaccinated population by a constant proportion and, in the second, vaccination is assumed to render a constant proportion of individuals totally immune from the disease. The implications of these two models on the behaviour of different measures of vaccine efficacy in cohort studies is explored. It is shown that the design of case-control studies to measure vaccine efficacy is dependent upon which model is considered appropriate. In particular, under the second model, individuals who have already had the disease under study should not be excluded from the control group.

Randomized controlled trials have long been accepted as the best method for assessing the protective efficacy of a vaccine. Participants in such a trial are randomized to receive or not to receive the vaccine (commonly, the comparison group is given an inert placebo or is just left unvaccinated) and the subsequent disease incidence in the two groups is compared.

Controlled trials of this kind may be both costly and difficult to justify ethically if there is prior evidence of some efficacy of the vaccine under study. Also, what is often required is an estimate of the efficacy of the vaccine as given by the routine health services rather than that in the carefully controlled situation of a randomized trial. Whereas in the latter great care is taken, usually, to store, make up and administer a potent vaccine, this may not always be the case for routine vaccination—especially in less developed countries, where the potential benefits of vaccination are greatest but where there are often great difficulties in preserving an adequate cold chain and in maintaining a well qualified cadre of vaccinators. In such circumstances, alternative methods of measuring vaccine efficacy are required that are simple and cheap and that may be used on a routine basis to monitor the

efficacy of vaccination over time or in different regions of a country.

In some circumstances, serological surveys of the population may provide a good measure of the coverage and efficacy of a vaccination programme; but this requires a good laboratory backup and for some vaccines this method is unreliable or inappropriate (eg BCG). Case-control studies¹ or cohort studies provide alternative approaches for assessing vaccine efficacy. The essence of these methods is that the relative incidence of disease is measured in those who have received and those who have not received the vaccine and this enables inferences to be drawn about the possible efficacy of the vaccine. The major limitation of such studies is that the assessment is made by comparing two groups (vaccinated and unvaccinated) which are composed of individuals who were not allocated to one or other of the groups on a 'random' basis. Thus, the two groups may differ not only in their vaccination status but also with respect to other risk factors for the disease under study. To some extent it may be possible to correct for the biases, introduced by the non-random allocation, through careful design and analysis of a study (eg by 'matching' and/or stratifying with respect to potentially confounding variables such as socioeconomic status and area of residence). Nevertheless, some uncertainty may remain as such investigations can never be totally free from potential bias. On the other

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hand, in many circumstances such studies may provide a sufficiently good estimate of the value of a vaccine for operational purposes. For example, if studies of this kind suggest that a vaccine is offering little protection, it may be considered worthwhile, and ethical, to set up a properly designed randomized trial or it may prompt an investigation of the methods used to store, refrigerate and transport the vaccine.

In this paper we discuss how vaccine efficacy may be measured in such studies. In particular we find that assumptions concerning the mechanism of action of vaccination may determine the choice of measures to be used. The issue we discuss with respect to cohort studies is relevant equally to randomized controlled trials (ie what is the appropriate measure of vaccine efficacy). With respect to case-control studies the issue resolves to the appropriate method of selecting the control group.

The choice of a suitable control group in a case-control study is often a matter of some controversy, especially when the study is not population based. In this paper we explore two aspects of this problem: how the controls should be chosen if we are dealing with a common disease, and how this is affected by different assumed mechanisms of action of the risk factor. This topic has been discussed by other authors²⁻⁴ but there seem to be especially interesting issues in this regard when considering the assessment of vaccines.

MEASUREMENT OF VACCINE EFFICACY

Suppose, in a randomized controlled trial, that equal numbers of individuals are allocated to vaccinated and placebo groups and both groups are followed for an equal period of time. Suppose also that there are no losses to follow-up or deaths, that all cases of disease are ascertained and that the time of onset of each case is recorded. We then have the situation as below:

| | Number of persons in group | Number of cases of disease | Person years at risk* |
|------------|----------------------------|----------------------------|-----------------------|
| Vaccinated | N | c ₁ | Y ₁ |
| Placebo | N | c ₀ | Y ₀ |

By convention, the efficacy of the vaccine under consideration (VE) is measured as

$$\frac{(\text{Incidence rate in non-vaccinated}) - (\text{Incidence rate in vaccinated})}{(\text{Incidence rate in non-vaccinated})}$$

$$= 1 - R$$

where $R = (\text{Incidence rate in vaccinated}) / (\text{Incidence rate in non-vaccinated})$.

Now, there are two possible measures of incidence rate (see, for example²)

$I_r = c/N$ measures the *risk* (probability) of developing the disease in the follow-up period

$I_f = c/Y$ measures the average *instantaneous incidence rate* of the disease in the follow-up period (ie the average 'force of morbidity' from the disease).

If I_r and I_f are low (ie if we are dealing with a 'rare' disease), these two measures will be approximately equal and it will be immaterial which is used to compute vaccine efficacy. In these circumstances it is common to use I_f , as the 'ideal' study we have postulated (the same follow-up time for all individuals in the study) is not often encountered in practice and the use of person years at risk in the denominator is a convenient method of allowing for different follow-up times. (Alternatively, it would be easy to estimate I_r using actuarial methods.)

If, however, we are considering a relatively common disease, such as measles, which may afflict a high proportion of those in the unvaccinated group, I_r and I_f may be substantially different. In this situation, VE_r (vaccine efficacy as measured by incidences based on 'risk') will be different from VE_f (vaccine efficacy as measured by incidences based on 'instantaneous rate'). Under these circumstances, the appropriate use of VE_r or VE_f as the measure of efficacy may depend on the mode of action we postulate for the vaccine.

POSSIBLE MODELS OF ACTION OF VACCINATION

Consider two possible models of action of a vaccine:

Model 1

Suppose that in some small interval of time ($t, t + \delta t$) the probability of an unvaccinated person contracting the disease is $\lambda_t \delta t$. Further suppose that vaccination reduces this probability to $R\lambda_t \delta t$ (where R is assumed to be constant for all t). For simplicity, and without loss of generality, we will restrict our discussion to the situation in which $\lambda_t = \lambda$ (for all t). This model of action of a vaccine will result in the appearance of disease in

* Person years at risk are computed for each individual as the time from entry into the study to the development of the disease under study, or to the end of the study period for those who do not develop the disease.

the vaccinated and unvaccinated groups as represented in Figure 1a. If we follow those in the unvaccinated and vaccinated groups from the initiation of the trial until time T, the proportions of individuals in each group who would be expected to have developed the disease would be $(1 - e^{-\lambda T})$ and $(1 - e^{-\lambda RT})$ respectively. Thus, if we calculated $VE_r = (1 - (c_1/N)/(c_0/N))$ we obtain

$$VE_r = 1 - [(1 - e^{-\lambda RT}) / (1 - e^{-\lambda T})] \quad (1)$$

This measure has the property of decreasing towards zero as the follow-up time, T, increases (as the model assumes that everyone gets the disease if the follow-up is long enough). Only for small λT will $VE_r \approx 1 - R$.

On the other hand, if we calculate $VE_f = (1 - (c_1/Y_1)/(c_0/Y_0))$ we obtain (see Appendix 1)

$$VE_f = 1 - R \quad (2)$$

This measure is independent of T.

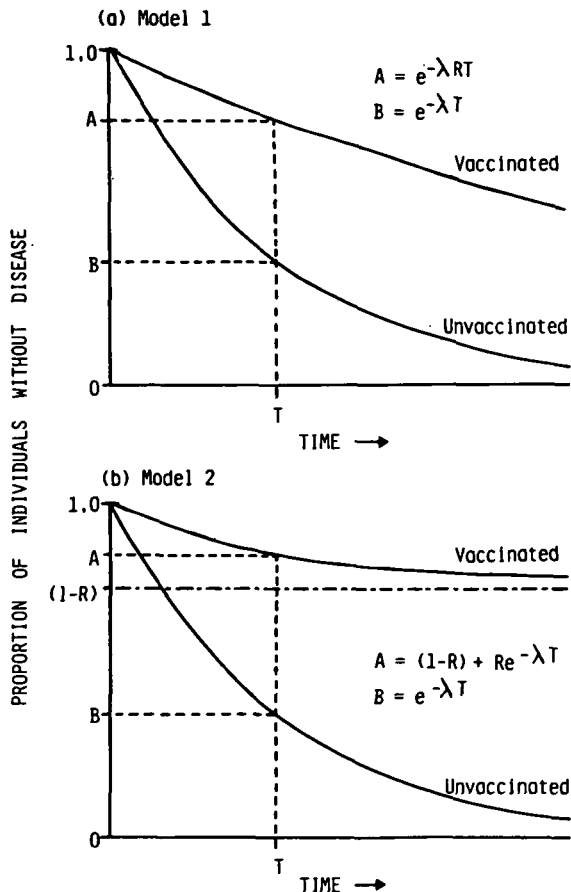


FIGURE 1 Proportion of individuals without disease by time since start of trial under two models of vaccine action.

Model 2

Suppose the effect of vaccination is to render a proportion $(1 - R)$ of the vaccinated group completely immune from the disease. We will assume, as before, that the probability of an unvaccinated person contracting the disease in the interval $(t, t + \delta t)$ is $\lambda_t \delta t$ and, again for simplicity and without loss of generality, that $\lambda_t = \lambda$, for all t . Persons who are vaccinated but in whom the vaccine does not produce immunity (a proportion R of the vaccinated) will be assumed, similarly, to have a probability of contracting the disease in the interval $(t, t + \delta t)$ equal to $\lambda \delta t$. This model of action of a vaccine will result in the appearance of disease in vaccinated and unvaccinated groups as represented in Figure 1b. If we follow those in the unvaccinated and vaccinated groups from the initiation of the trial until time T, the proportions of persons in each group who would be expected to have developed the disease would be $(1 - e^{-\lambda T})$ and $(1 - (1 - R) - Re^{-\lambda T} = R(1 - e^{-\lambda T}))$, respectively. It is straightforward (see Appendix 1) to show that the measures of vaccine efficacy, VE_r and VE_f will be

$$VE_r = 1 - R \quad (3)$$

$$\text{and } VE_f = 1 / [1 + R(1 - e^{-\lambda T}) / T\lambda(1 - R)] \quad (4)$$

$$(\approx 1 - R \text{ for small } \lambda T).$$

Thus, if this model is appropriate, the time invariate measure of vaccine efficacy is given by VE_r and, in the limit, as T increases, VE_f will tend to unity (as all those in the unvaccinated group will have developed the disease and all those in the vaccinated group will either have had the disease or be immune through the vaccination).

An example of the calculation of protective efficacy under Models 1 and 2 is given in Appendix 2. Also noted in this Appendix are examples of published trials in which the different methods of measuring efficacies have been employed.

IMPLICATIONS FOR COHORT AND CASE-CONTROL STUDIES

In a randomized trial we may measure vaccine efficacy from the start of the trial or in successive time intervals as the trial progresses. If VE_r falls with time but VE_f remains constant this would suggest a Model 1 type mechanism. Alternatively, if VE_r remains constant whereas VE_f rises with time, this would suggest the Model 2 mechanism. It must be emphasized, however, that this may be too simplistic a view as the 'true' efficacy of a vaccine may wane with the passage of time (ie R may increase with time) and this would

further complicate the interpretation of observed results.

The problems of measurement in a cohort study (in which vaccine allocation is non-random) are exactly the same as those in a randomized trial (which is just a special kind of cohort study). On the other hand, the implications for case-control studies are of some theoretical and practical interest.

Under Model 1 the appropriate method of selecting controls would be to choose one or more controls for each case, from among those individuals who had not yet contracted the disease under study *at the time the case developed the disease*. Thus it is possible, and likely for a common disease, that a substantial proportion of 'controls' would become 'cases' later in the study and, in the analysis they would appear in both case and control groups but at different time points. In a study designed in this way we obtain a direct estimate of the ratio of the instantaneous disease rates in vaccinated and unvaccinated individuals.²⁻⁴ Thus the cross product estimate of relative risk (stratified by time in the analysis) would estimate $1 - VE_f$ and would be a more complicated function of VE_r (which would also involve λ and T).

Under Model 2 the appropriate method of selecting controls would be to choose one or more controls for each case from among other individuals in the population *irrespective of whether or not they had already had the disease under study*. Thus the control group is used to estimate the proportion of the total population that has been vaccinated, whereas under Model 1 the control group is used to estimate the proportion of unvaccinated individuals in those remaining unafflicted by the disease at the time each case arises. The cross product, with controls selected as under Model 2, would be a direct measure of $(1 - VE_r)$ and would be a more complicated function of VE_f (which would also involve λ and T).

Table A3 illustrates the estimation of vaccine efficacy in a case-control study in which controls are selected either excluding, or not excluding, persons who have previously suffered from the disease under study.

DISCUSSION

We have considered two interrelated issues relevant to assessing vaccines: their mode of action and the appropriate method of measuring efficacy in epidemiological studies.

Most of the current literature on the mechanism of vaccine action is immunological, emphasizing vaccine effects on parameters of either humoral or cellular immunity (eg antibody levels or assays of T-cell

function). On the other hand, in most of the current literature on the field assessment of vaccines, use is made of one or other of the measures of vaccine efficacy we have discussed (see Appendix 2), but without distinguishing between the measures and their possibly different implications. For 'rare' diseases (eg tuberculosis in most communities) the distinction is academic as both types of measures—those calculated from 'risks' and those calculated from 'instantaneous rates'—will give closely similar estimates of efficacy. But, for diseases which may affect a substantial proportion of the population, the two measures have different properties and the choice of the 'correct' measure depends upon the postulated mode of action of the vaccine.

We have proposed two simple models. In the first, the probability of disease in any small interval of time following vaccination is reduced by a factor R in vaccinated as compared to unvaccinated individuals (sometimes called the 'proportional hazards' model⁵). In the second, a proportion, $1 - R$, of vaccinated individuals is assumed to be made totally immune from the disease, whereas the remaining proportion, R , is not affected at all by the vaccination. Which of these models, if either, may be closer to the true situation is unclear. Furthermore, we recognize that other models may be proposed—for example that protection (perhaps defined according to one of the two basic models above) wanes with time. Indeed different vaccines may have different modes of action and each of the models discussed may be appropriate for different vaccines or diseases.

The two models we have proposed predict different behaviour in vaccine efficacy over time since vaccination according to the measure employed. In simplest terms, under Model 1 the apparent vaccine efficacy, using the initial populations as the denominators of the incidence rates, will fall with time; whereas, if person years at risk are used in the denominators, the apparent efficacy will remain constant with time. In contrast, under Model 2, the first measure of vaccine efficacy (population denominators) will remain constant with time and the second measure (person years at risk denominators) will increase with time. It is of interest to note, in this respect, that in the Medical Research Council's trial of measles vaccination⁶ a method of calculating vaccine efficacy was used that approximated using person years at risk in the denominators. It was found that the apparent efficacy of the vaccine increased slightly with time since vaccination. This suggests that Model 2 might be appropriate for measles vaccination.

The use of case-control methods for assessing

vaccine efficacy has several advantages over cohort studies, primarily in terms of speed and simplicity of design and avoidance of ethical constraints to withholding vaccines from a control group. Such studies should provide an effective means for monitoring the efficacy of ongoing vaccination programmes. Case-control studies, however, raise particular problems in the context of vaccination studies. One problem concerns the appropriate method to estimate 'relative risk' given the high incidence rate of many immunizable diseases and a second concerns the method of selecting the controls when dealing with common diseases.

In case-control studies of chronic disease it is generally the practice to exclude from the control group persons who have previously had the disease under study (often necessitated by their death!). It has been pointed out that if controls are chosen for each case on this basis at the time each case develops the disease a valid estimate of the 'relative rate'—that is the ratio of the instantaneous disease rates in exposed and non-exposed groups—may be derived if the appropriate analysis is conducted (ie stratified by time) and that in these circumstances the 'rare disease assumption' is unnecessary.²⁻⁴ This is true, however, only if we assume a disease model of the form illustrated by Model 1 (ie that the ratio of the instantaneous disease rates in the 'exposed' and 'non-exposed' groups remains constant with time). For studies of vaccine efficacy it is not clear to us that Model 1 is appropriate. Furthermore, although it is likely that neither model is a completely correct representation of the true biological situation, there would seem to be quite strong arguments in favour of a model which is closer to our Model 2, in particular for live virus vaccines.

The implications of these two models are interesting in that to obtain a good measure of vaccine efficacy under Model 2 it is necessary to not exclude from the control group persons who have already had the disease under study. In practical terms this is quite a useful result. Medical records in less developed countries are often incomplete and it may be difficult to determine whether or not a child has suffered previously from a specific disease (as a parent's history of such an illness may also be unreliable—especially so for diseases with a variable course).

It is true, of course, that the measured efficacy of a vaccine will be affected by the proportion of children who had already been infected at the time the vaccine was given but this is a different issue.

In practice, if there is doubt as to whether Model 1 or Model 2 is appropriate it may be necessary to examine both measures of vaccine efficacy (VE_r and

VE_f) in a cohort study or a randomized trial. Similarly, in case-control studies it may be necessary to use two control groups, one including past cases of disease and one not so doing, to assess which, if either, model is most appropriate.

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APPENDIX 1

DURATION OF PERSON YEARS AT RISK

Let N = number of persons in vaccinated group

Let $E(c)$ = expected number of cases in the vaccinated group in the interval (O, T)

Let $E(Y)$ = expected number of person years at risk in the unvaccinated group in the interval (O, T)

Thus we have

$$\begin{aligned} \text{Model 1:} \quad E(c) &= N(1 - e^{-\lambda RT}) \\ E(Y) &= N \int_0^T e^{-\lambda R t} dt \\ &= N(1 - e^{-\lambda RT}) / \lambda R \end{aligned}$$

$$\begin{aligned} \text{Model 2:} \quad E(c) &= NR(1 - e^{-\lambda T}) \\ E(Y) &= N \int_0^T [(1 - R) + R e^{-\lambda t}] dt \\ &= N[T(1 - R) + R(1 - e^{-\lambda T}) / \lambda] \end{aligned}$$

Using these results (1) to (4), in text, are easily derived.

APPENDIX 2

EXAMPLE OF PROTECTIVE EFFICACIES CALCULATED UNDER MODELS 1 AND 2

Consider a disease for which the instantaneous incidence rate is 0.2/person/year in the unvaccinated group and suppose the protective efficacy (ie $1 - R$ in the two models described) imparted by the vaccine is 75%.

Under Model 1, the instantaneous incidence rate in the vaccinated group would be 0.05/person/year.

Under Model 2, 75% of the vaccinated group would be completely protected and the other 25% would suffer an instantaneous incidence rate of 0.2/person/year.

Suppose, in a randomized trial, 1000 persons are

TABLE A1 Cases and person years at risk under Models 1 and 2 by time since start of trial.

| Year (i) | Models 1 and 2 | | | Model 1 | | | Model 2 | | |
|----------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | Unvaccinated | | | Vaccinated | | | Vaccinated | | |
| | N _i | c _i | Y _i | N _i | c _i | Y _i | N _i | c _i | Y _i |
| 1 | 1000 | 181 | 906 | 1000 | 49 | 975 | 1000 | 45 | 977 |
| 2 | 819 | 149 | 742 | 951 | 46 | 928 | 955 | 37 | 936 |
| 3 | 670 | 121 | 608 | 905 | 44 | 883 | 918 | 31 | 902 |
| 4 | 549 | 100 | 497 | 861 | 42 | 840 | 887 | 25 | 874 |
| 5 | 449 | 81 | 407 | 819 | 40 | 799 | 862 | 20 | 852 |
| 6 | 368 | 67 | 333 | 779 | 38 | 760 | 842 | 17 | 833 |

N_i = number 'at risk' (ie unaffected by disease) at start of year i.

c_i = number of cases of diseases expected in year i.

Y_i = person years at risk in year i.

TABLE A2 Vaccine efficacy under Models 1 and 2 by time since start of trial measured by different methods.

| Year | Model 1 | | | | | Model 2 | | | | |
|------|-----------------|-----------------|------------------|------------------|------------------|-----------------|-----------------|------------------|------------------|------------------|
| | VE _r | VE _f | VE' _r | VE' _f | VE' _k | VE _r | VE _f | VE' _r | VE' _f | VE' _k |
| 1 | 73* | 75 | 73 | 75 | 73 | 75 | 77 | 75 | 77 | 75 |
| 2 | 71 | 75 | 69 | 75 | 73 | 75 | 79 | 75 | 80 | 79 |
| 3 | 69 | 75 | 64 | 75 | 73 | 75 | 80 | 74 | 83 | 81 |
| 4 | 67 | 75 | 58 | 75 | 73 | 75 | 81 | 75 | 86 | 85 |
| 5 | 65 | 75 | 51 | 75 | 73 | 75 | 83 | 75 | 88 | 87 |
| 6 | 63 | 75 | 43 | 75 | 73 | 75 | 84 | 75 | 90 | 89 |

* all vaccine efficacies are shown as percentages.

VE_r = vaccine efficacy measured in each year with denominators for rates based on populations at start of trial
eg year 4 under Model 1: $VE'_r = 1 - [(42/1000)/(100/1000)]$.

VE_f = vaccine efficacy measured in each year with denominators for rates based on person years at risk during year
eg year 4 under Model 2: $VE'_f = 1 - [(25/874)/(100/497)]$.

VE_k = vaccine efficacy measured in each year with denominators for rates based on disease free population up to the start of the year
eg year 4 under Model 2: $VE'_k = 1 - [(25/887)/(100/549)]$.

allocated to each of the vaccinated and unvaccinated groups. The results expected, year by year, in the first six years under each model are shown in Table A1.

Various measures of protective efficacy that could be obtained in these trials are shown in Table A2.

Under Model 1, VE_f remains constant but VE_r decreases with time whereas under Model 2, VE_r remains constant but VE_f increases with time. Also shown in Table A2 are measures denoted by VE'_r and VE'_f which are VE_r and VE_f calculated year by year. Thus, for example, if we consider only year 6, there are 67 cases of disease in the unvaccinated group and, under Model 1, 38 in the vaccinated group. VE'_r for year 6 is calculated by relating the numbers of cases in the year to the initial sizes of the vaccinated and unvaccinated groups (ie $1 - (38/1000)/(67/1000) = 43%$). In contrast, VE'_f is calculated by relating the numbers of cases in the year to the person years at risk in the vaccinated and unvaccinated groups in year 6 (ie

$1 - (38/760)/(67/333) = 75%$). Under Model 2, in year 6, VE'_r is 75% and VE'_f is 90%. In addition to these two measures, a measure VE'_k is shown. This is the measure of vaccine efficacy obtained when the numbers of cases in each year are related to the numbers of persons who have not yet developed the disease by the start of that year (eg in year 6 under Model 2, $VE'_k = 1 - (17/842)/(67/368)$). In general VE'_k will give a measure of efficacy close to VE'_f as, if the number of cases in a time interval is small relative to the total size of the disease free population at the start of the interval, the person years at risk in the interval may be approximated by the starting population multiplied by the length, in years, of the interval.

All of the measures illustrated above have been employed, in different trials, to calculate protective efficacies. VE_r has been used to measure the efficacy of hepatitis vaccine;⁷ VE_f and VE'_f to assess the effect

TABLE A3 Vaccine efficacy under Models 1 and 2 as measured in case-control studies.

| | | Cases | Not yet cases | VE' _k | Total population | VE' _t |
|----------------|----------------|--------------------|--------------------|------------------|---------------------|------------------|
| MODEL 1 | | | | | | |
| Year 3 | Vaccinated | 44 f ₁ | 905 f ₂ | 73% | 1000 f ₂ | 64% |
| | Not vaccinated | 121 f ₁ | 670 f ₂ | | 1000 f ₂ | |
| Year 6 | Vaccinated | 38 f ₁ | 779 f ₂ | 73% | 1000 f ₂ | 43% |
| | Not vaccinated | 67 f ₁ | 368 f ₂ | | 1000 f ₂ | |
| MODEL 2 | | | | | | |
| Year 3 | Vaccinated | 31 f ₁ | 918 f ₂ | 81% | 1000 f ₂ | 74% |
| | Not vaccinated | 121 f ₁ | 670 f ₂ | | 1000 f ₂ | |
| Year 6 | Vaccinated | 17 f ₁ | 842 f ₂ | 89% | 1000 f ₂ | 75% |
| | Not vaccinated | 67 f ₁ | 368 f ₂ | | 1000 f ₂ | |

f₁ = sampling fraction for cases.

f₂ = sampling fraction for controls.

VE'_k = vaccine efficacy calculated with 'not yet cases' as controls.

VE'_t = vaccine efficacy calculated with 'total population' as controls.

of BCG against tuberculosis;⁸ VE'_t to evaluate pertussis vaccine;⁹ and VE'_k to calculate the efficacy of measles vaccine.⁶

Table A3 illustrates the outcomes that would be expected in case-control studies under Models 1 and 2 depending on whether or not individuals who had previously had the disease under study were included in the control group. For simplicity we have shown, in columns 2 and 3, the results that would be obtained if controls were selected from among those who had not developed the disease at the start of the time interval under consideration, rather than assuming controls to be selected for each case at the time the case developed the disease. Thus we will be estimating VE'_k rather than VE'_t but, if the number of cases in the interval is small, relative to the disease free population at the start of the interval, this will be close to VE'_t, as discussed above.

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