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Estimation of Vaccine Effectiveness Using the Screening Method

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The screening method provides a simple and rapid way of estimating vaccine effectiveness. The paper discusses the validity of the screening method with particular reference to bias and precision. Methods for correcting confounding, adjusting for covariates and over-dispersion, and deriving confidence limits are discussed in a modelling framework. The methods are illustrated using data on measles and pertussis vaccines.

Evaluating the effectiveness of vaccines in the field is an important aspect of monitoring immunization programmes.[1] A variety of methodologies have been described for this purpose.[2,3] The most commonly used are case-control or cohort studies, which require detailed information on non-cases as well as cases. For the purposes of routine monitoring or in circumstances where denominator data on individuals are unavailable the screening method[2–7] is particularly attractive, as it requires data on individuals for cases only. Similarly to other retrospective methods, the screening method is based on a comparison of the proportion vaccinated among the cases and the population. However it differs from other methods in that control is achieved by external standardization, using an estimate of vaccine coverage which is derived from sources external to the study. Clearly, the method depends entirely for its validity on the accuracy of this external estimate. Nevertheless its use as a tool for routine monitoring of vaccine effectiveness is likely to increase in the UK with the spread of district-based computerized vaccination records.[8] These enable notified cases to be linked to vaccination records to estimate the proportion of cases vaccinated. Although full denominator information on the population at risk is not generally available, vaccine coverage statistics available for each annual birth cohort may be used as a proxy. The screening method is the appropriate methodology in this context.

External standardization is commonly used in environmental and chronic disease epidemiology.[9,10] Its use in estimating vaccine effectiveness has met with some scepticism,[11] in part due to shortcomings in its implementation, in particular with regard to controlling confounding. The aim of the present paper is to cast the method in a methodological framework which will facilitate the calculation of confidence intervals (CI), the control of confounding, the incorporation of covariates in the analysis, and sample size calculations. Since the emphasis is on the measurement of vaccine effectiveness in the field, rather than efficacy as measured in a clinical trial under controlled conditions, the term 'vaccine effectiveness' is used throughout.

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THE SCREENING METHOD

Suppose that all or a random sample of cases of disease arising over a given period in a defined population are available, from which the proportion vaccinated PCV is estimated. Suppose also that the proportion of the population vaccinated, PPV, is known. The vaccine effectiveness VE is then given by the following expression:

$$VE = 1 - \frac{PCV}{1-PCV} \cdot \frac{1-PPV}{PPV} \qquad (1)$$

multiplication by 100 giving vaccine effectiveness as a percentage. The relative risk of disease, 1–VE, is equal to the odds ratio of vaccination in cases and the population. This is a particular instance of a general relationship between relative risks and odds ratios, when controls are chosen irrespective of the risk factor (in this case, vaccination) under consideration. Such studies are referred to as case-cohort or case-base studies.[12,13] For the screening method, instead of selec-

ting a random sample of the population and estimating PPV from it, the (assumed) true value of PPV is used. The screening odds ratio is similar to the mortality odds ratio (MOR) proposed by Miettinen and Wang[10] in a different context. Table 1 shows the relationship between sampling schemes, vaccination odds ratios, and disease relative risks for a variety of study designs.

As for other study designs, confounding may bias the screening method, as shown by the following example. Suppose that cases arise in two cohorts of equal size, A and B. In cohort A there are 100 cases, 50 of whom are vaccinated and the value of PPV for cohort A is 0.9. In cohort B there are 10 cases, one of whom is vaccinated and the value of PPV for cohort B is 0.5. The screening estimate of VE is 89% in each cohort. However if the cohorts are combined, then there are 110 cases, 51 of whom are vaccinated, while the combined value of PPV is 0.7. This produces an aggregate estimate of VE of only 63%. Clearly, effectiveness is confounded by cohort. This example underlines the need for stratification by possible confounding variables, such as age and location.

TABLE 1 *The relationship between relative risk of disease (RR) and odds ratio of vaccination (OR) for different sampling schemes*

Study design	Sampling scheme	Outcome measure
Cohort	disease status sampled in vaccinated and unvaccinated cohorts	RR in vaccinated relative to unvaccinated cohorts
Case-control	vaccination status sampled in cases and well controls	OR in cases relative to well controls
Case-base	vaccination status sampled in cases and population controls	OR in cases relative to population controls and OR = RR
Screening	vaccination status sampled in cases only	OR in cases relative to population standard and OR = RR

A MODELLING APPROACH

Little has appeared in the literature on the methodological aspects of the screening method. Clarkson and Fine[3] apply age stratification and quote CI, but do not give details of the methods used. Since PPV is regarded as determinate, the analysis for the screening method is considerably simpler than for other retrospective designs.

Conditioning on the total number of cases N, the number of vaccinated cases may be regarded as binomial with parameter PCV and index N. This is valid provided that cases arise in a Poisson process, an assumption which will later be relaxed. Suppose that the quantities PCV and PPV are available for each of n strata, indexed by i = 1, . . . ,n. Denote PCV and PPV by θ_i and π_i, respectively. Let R_i denote the corresponding relative risks of disease in vaccinated relative to unvaccinated individuals, that is 1−VE for each stratum. Suppose that k covariates on each stratum are also available, the value of the jth covariate in the ith stratum being denoted by x_{ij}, j = 1, . . . ,k. The following linear model may then be formulated:

$$\text{Ln}[R_i] = a + b_1x_{i1} + \ldots + b_kx_{ik} \qquad (2)$$

In this model the coefficients b_j parameterize the variation in the relative risk, and hence the variation in vaccine effectiveness, over the variables x_{ij} describing the strata. Confounding is controlled by stratifying the data according to the confounding variables.

Since the relative risk of disease equals the odds ratio of vaccination, equation (2) may be rewritten as:

$$\text{Logit}\,[\theta_i] = \text{Logit}\,[\pi_i] + a + b_1x_{i1} + \ldots b_kx_{ik} \quad (3)$$

This model is easily fitted by logistic regression using GLIM,[14] with the number of vaccinated cases as the dependent variable, a binomial error structure with index equal to the number of cases, and the vector logit $[\pi_i]$ as offset. The fitting procedure produces standard errors for the parameters which may be used to calculate CI.

In some applications, the binomial model may be inappropriate. Especially with data collected in an observational study rather than a controlled clinical trial, one may expect additional variability. This may arise due to heterogeneity in disease incidence caused by variations in population density or herd immunity, or due to heterogeneity in vaccine effectiveness caused by pockets of vaccine failures arising from mishandling of the vaccine. In addition, random errors in the external values of PPV used in the screening method may introduce further variability. These additional sources of variability may most simply be allowed for by rescaling the model.[15] This is demonstrated in the Appendix in the case of extra-Poisson variability in disease incidence.

DESIGN CONSIDERATIONS

The screening method does not require all cases of disease to be analysed, only a random sample. The aim of this section is to indicate how to choose the sample size to achieve a stated precision.

Suppose first that it is required to choose a sample size N of cases to guarantee a high probability that the lower 95% confidence limit of vaccine effectiveness is above a specified threshold. The investigator is required to specify the following parameters: the anticipated true effectiveness V_T, the lower threshold effectiveness value V_L (so that $V_L < V_T$), the proportion of the population vaccinated PPV = π, and the power $1-\beta$ and confidence coefficient $1-\alpha$. Using the direct correspondence between VE and PCV the required sample size may be derived using standard arguments.[16] Thus:

$$N = \frac{(Z_{\alpha/2} + Z_{1-\beta})^2 (1-\pi V_L)^2 (1-V_T)}{\pi (1-\pi) [V_T - V_L]^2} \quad (4)$$

In most cases, rather than requiring a high power of exceeding a specified threshold value, it is required to estimate VE with a specified precision, or equivalently a specified expected half-width of the 95% CI. In this case $V_T - V_L$ represents the desired lower half-width of the 95% CI. The sample size required is given by expression (4) with $z_{\alpha/2} = 1.96$ and $Z_{1-\beta} = 0$. Table 2 gives sample sizes N for various values of vaccine effectiveness V_T and proportion of the population vaccinated π, for given lower half-widths $V_T - V_L = 0.05$, 0.10 and 0.15. The sample size required decreases as vaccine effectiveness increases; thus for a given sample size, the precision increases with VE. The relationship with PPV is more complex, maximum precision occurring at an intermediate value of PPV which is dependent upon VE.

EXAMPLES

The methods of the paper will be illustrated with two examples. The first is from a study of measles vaccine effectiveness.[4] Vaccination histories of 940 measles cases born in 1980–1986 and notified in Leeds in 1987–1988 were obtained, together with vaccine coverage statistics for each birth cohort (Table 3). The published effectiveness estimate of 0.946 was based on the aggregate data for the seven annual birth cohorts: equation (1) was applied to this data using the weighted average (weighted by cohort size) of the cohort coverage figures.

In order to correct for its possible confounding effect the data should be stratified by birth cohort. Fitting the model Ln[R] = a to the stratified data yields a = −3.013 (SE 0.0884). The age-corrected vaccine effectiveness is thus 1−exp (a) = 0.951 with approximate 95% CI of 0.942–0.959. Clearly, confounding by birth cohort is not a problem. The variation in vaccine effectiveness between birth cohorts may be investi-

TABLE 2 *Numbers of cases required for a given lower half-width of the 95% confidence interval on vaccine effectiveness (VE)*

PPV[a] (%)	VE (%)				
	50	60	70	80	90
50	1846	1292	840	480	203
	492	346	226	130	55
	232	164	108	62	27
60	1706	1150	715	387	154
	462	314	197	108	43
	222	152	96	53	22
70	1717	1107	652	330	120
	474	309	185	95	35
	232	153	92	48	18
80	1967	1205	664	307	98
	555	346	195	93	31
	277	175	100	49	17
90	3022	1742	882	361	94
	874	516	271	117	33
	445	269	145	65	20

[a] Proportion of the population vaccinated.
Values quoted are those required for the expected value of the lower 95% confidence limit to lie 5% (first line in each cell), 10% (second line) or 15% (3rd line) below VE.

TABLE 3 *Measles notifications, numbers vaccinated and vaccine coverage in two Leeds districts 1980–1986*

Birth cohort	Cases No.	Vaccinated No.	Vaccine coverage (%)
1980	82	5	70.0
1981	98	9	70.9
1982	180	28	76.0
1983	177	37	81.0
1984	112	22	83.7
1985	140	27	84.5
1986	151	27	83.1
1980–1986	940	155	78.4

Data source: ref. 4.

TABLE 4 *UK whooping cough notifications, vaccine effectiveness (VE) and vaccine coverage by age in two study periods*

Age	Epidemic period		Non-epidemic period		Vaccine cover (%)
	vaccinated/total	VE (%)	vaccinated/total	VE (%)	
1	25/129	95	28/137	94	82
2	42/148	87	41/183	91	76
3	48/173	86	31/157	91	73
4	40/164	86	25/178	93	70
5	23/191	94	39/207	89	68
6	24/124	87	14/128	93	65
7	17/79	85	7/63	93	64
8	9/48	83	9/61	87	58
9	10/40	69	6/47	86	52

gated further by fitting the birth cohort variable as a seven-level factor and examining the corresponding parameters. None of these are significant and neither is the factor as a whole ($\chi^2_6 = 4.74$, $P = 0.6$). Thus there is no evidence that effectiveness varies between birth cohorts.

The second example is drawn from a study of whooping cough notifications in the UK.[7] The vaccination status of children aged 1–9 years in whom whooping cough was notified was obtained during a non-epidemic and an epidemic period in 1989. UK vaccine coverage figures for the relevant birth cohorts were used as proxy for the proportions of vaccinated 1–9 year olds. For children aged 1–4 years these were obtained from the COVER scheme,[17] and for children aged 5–9 years from Department of Health statistics (Table 4).

The effectiveness estimates display considerable variability with age and study period. The effectiveness is generally (though not always) higher in the non-epidemic than in the epidemic period. This may reflect a greater awareness of whooping cough when incidence is high, resulting in improved diagnoses in vaccinated children. Vaccine effectiveness remained high at all ages with the exception of one outlier corresponding to 9 year olds in the epidemic period, for whom effectiveness was only 69% though with wide CI of 35–87%.

Logistic regression applied to the 18 strata with a two-level factor for study period and a nine-level factor for age gave a deviance of 15.3 on 8 degrees of freedom. This suggests a mild degree of over-dispersion. The rescaled model is therefore used as a basis for inferences about age and period effects.

A plot of the logarithm of the relative risk Ln (1–VE) against age for each study period suggests a broadly linear trend, with considerable scatter. The nine-level age factor in the model did not significantly improve the fit over that obtained with a linear age trend. The final model (deviance 17.3, 15 df) includes a marginally significant period effect ($P = 0.05$) and a significant linear age effect ($P = 0.02$). The relative risk of reported whooping cough (vaccinated relative to unvaccinated) in the non-epidemic period is 0.75 times the relative risk in the epidemic period (95% CI : 0.56–1.00), and the relative risk increases with age by a factor of 1.08 per year (95% CI : 1.01–1.16).

The age-specific vaccine effectiveness estimates are not adjusted for prior cases. As previously demonstrated[18] a broadly increasing log-linear relationship between the age-specific relative risk and age may thus be expected even if vaccine-induced immunity does not wane with time since vaccination.

CONCLUSION

The screening method for estimating vaccine effectiveness provides a simple, rapid and cheap surveillance tool. The effectiveness estimates should be age stratified and should be quoted with CI, calculated so as to take into account any extra variability present in the data. Population vaccination statistics in the UK are currently available through the COVER scheme[17] by sex, birth cohort and health district, thus providing some scope for correcting the estimates for the major confounders.

The screening method suffers from two major shortcomings. The first is that the accuracy of the external estimates of the proportion of the population vaccinated cannot usually be tested. If substantial biases are believed to arise, the screening method is clearly inappropriate. The second shortcoming is that detailed analysis of risk factors for low vaccine effectiveness may not be possible due to unavailability of vaccine coverage statistics stratified according to these risk factors. Other methodologies, such as case-control

studies, are thus required for this purpose. However for routine monitoring the screening method offers substantial advantages over more complex and costly alternatives.

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APPENDIX

Suppose that the incidence of disease in the population has a variance proportional to the mean, rather than equal to the mean as required by the Poisson assumption. Specifically, in a given stratum in the population, let ν_1 and ν_2 denote the incidence in the unvaccinated and vaccinated, respectively, and assume that these are independent random variables with means μ_1 and μ_2 and variances $\phi\mu_1$ and $\phi\mu_2$ respectively. The parameter ϕ is assumed not to vary between strata. The total number of cases N in the stratum then has mean $\mu_1+\mu_2$ and variance $\phi(\mu_1+\mu_2)$. Let $\theta = \mu_2/(\mu_1+\mu_2)$. Letting r denote the number of vaccinated cases in this stratum, $E[V(r \mid N)] = V(r)-V[E(r \mid N)]$. Now $V(r) = \phi\mu_2$ and $V[E(r \mid N)] = V(\theta N) = \theta^2\phi(\mu_1+\mu_2)$. Thus $E[V(r \mid N)] = \phi\, E(N)\, \theta(1-\theta)$. In large samples therefore $V(r \mid N) = \phi\, N\, \theta(1-\theta)$. Hence the extra-Poisson variability in the population may be allowed for by rescaling the binomial model specified by equation (3).