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Title: CASE-CONTROL VACCINE EFFECTIVENESS STUDIES: DATA COLLECTION, ANALYSIS AND REPORTING RESULTS

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1 **Abstract**

2 The case-control methodology is frequently used to evaluate vaccine effectiveness post-licensure. The
3 results of such studies provide important insight into the level of protection afforded by vaccines in a
4 ‘real world’ context, and are commonly used to guide vaccine policy decisions. However, the potential
5 for bias and confounding are important limitations to this method, and the results of a poorly conducted
6 or incorrectly interpreted case-control study can mislead policies. In 2012, a group of experts met to
7 review recent experience with case-control studies evaluating vaccine effectiveness; we summarize the
8 recommendations of that group regarding best practices for data collection, analysis, and presentation
9 of the results of case-control vaccine effectiveness studies. Vaccination status is the primary exposure of
10 interest, but can be challenging to assess accurately and with minimal bias. Investigators should
11 understand factors associated with vaccination as well as the availability of documented vaccination
12 status in the study context; case-control studies may not be a valid method for evaluating vaccine
13 effectiveness in settings where many children lack a documented immunization history. To avoid bias, it
14 is essential to use the same methods and effort gathering vaccination data from cases and controls.
15 Variables that may confound the association between illness and vaccination are also important to
16 capture as completely as possible, and where relevant, adjust for in the analysis according to the
17 analytic plan. In presenting results from case-control vaccine effectiveness studies, investigators should
18 describe enrollment among eligible cases and controls as well as the proportion with no documented
19 vaccine history. Emphasis should be placed on confidence intervals, rather than point estimates, of
20 vaccine effectiveness. Case-control studies are a useful approach for evaluating vaccine effectiveness;
21 however careful attention must be paid to the collection, analysis and presentation of the data in order
22 to best inform evidence-based vaccine policies.

23 **Key words:** vaccines, case-control studies, evaluation studies

24 **Introduction**

25 New vaccines are licensed based on the results of randomized controlled trials demonstrating
26 safety and efficacy. Yet even after licensure, there are often questions about how well a vaccine protects
27 against disease in a “real world” context because of differences in epidemiologic contexts, host factors
28 affecting immune response, vaccine implementation (e.g. varying dosing schedules), and the potential
29 for waning immunity over time¹ The case-control method is commonly used to estimate effectiveness
30 after a vaccine has been implemented in a public health system; recent examples include evaluations of
31 vaccines against *Haemophilus Influenzae* type B (Hib)²⁻¹³, *Streptococcus pneumoniae*¹⁴⁻²¹, influenza²²,
32 rotavirus²³⁻³⁶, and cholera³⁷⁻³⁹. The results of case-control vaccine effectiveness studies can complement
33 and extend the data generated by clinical trials.

34 However the potential for bias and confounding are important limitations to the case-control
35 method^{40,41}. In 2012, a group of experts met to review recent experience with case-control studies
36 evaluating the effectiveness of several vaccines; here we summarize the recommendations of that group
37 regarding best practices for data collection, analysis and interpretation. (A separate paper provides an
38 overview of the case-control method for evaluating vaccine effectiveness and reviews planning, design,
39 and the identification and enrollment of cases and controls.) While case-control vaccine effectiveness
40 studies have been carried out in countries of all income levels, this review focuses on their
41 implementation in resource-poor settings.

42 ***Assessment of vaccination status***

43 Vaccination status is the primary exposure of interest for case-control vaccine effectiveness
44 studies, but it can be challenging to assess it accurately⁴². Misclassification of vaccination status can
45 affect the VE estimates in various ways. Non-differential misclassification of vaccination status (i.e. cases
46 and controls have similar risks of misclassification) will bias the effectiveness estimate towards the

47 null⁴¹. Differential misclassification (i.e. vaccine classification errors have different probabilities in cases
48 and controls) can bias the effectiveness estimate towards or away from the null, or even result in a
49 negative VE, giving the false impression that vaccinated are at greater risk of the target disease than
50 unvaccinated⁴¹. The same strategies to obtain vaccination history should be used for both cases and
51 controls. Equal, intense effort must be made to obtain vaccination histories from all cases and
52 controls^{40,43}, and those efforts should be clearly documented and reported.

53 Preferred sources of vaccination data are family-held vaccine records, clinic records,
54 immunization registry data, or other written documentation of vaccines received and the dates on
55 which they were administered. Doses not recorded on these documents are assumed to have not been
56 received; although this assumption may be incorrect if recordkeeping is poor. Parent reporting of
57 routine infant immunizations received, without written verification, may be unreliable⁴⁴. However, if
58 parents report receipt of no vaccines of any type or receipt of only birth doses, such a history may be
59 valid even in the absence of written confirmation since unvaccinated children rarely will have family-
60 held records and generally parents are unlikely to state that the child is unvaccinated when in fact he or
61 she did receive vaccines. Because excluding unvaccinated children will lead to bias, children with a
62 parental report of having received no routine vaccines beyond birth doses should be included and
63 considered to have received no doses of the vaccine of interest. All eligible cases and controls should be
64 enrolled regardless of whether a documented vaccination history is available at the time of enrollment.
65 Although those lacking a confirmed vaccination history (other than unvaccinated children) will be
66 excluded from primary analyses because of missing data, the proportion of enrolled children for whom
67 vaccination history could not be obtained should be described in the results, and sensitivity analyses
68 used to assess the impact of missing data on the effectiveness estimates (see Analysis section).

69 Investigators should endeavor to understand factors associated with vaccination card
70 availability and retention in the study setting, and whether those factors may also be linked to risk of
71 disease or likelihood of vaccination⁴⁵. In preparation for the study, efforts can be made to improve
72 availability of cards and/or the quality and completeness of data in the clinic records. If vaccine histories
73 are unavailable for a sizeable proportion of children in the area (e.g. $\geq 5-10\%$), then efforts should be
74 made to assess differences between children with and without documented histories. If important
75 differences exist with regards with risk factors for disease, then a case-control study in that context is
76 likely to yield biased effectiveness estimates. Case-control studies may not be a valid method for
77 evaluating VE in settings where more than a small fraction of children lack a documented immunization
78 history.

79 Abstracting vaccination data from family-held cards or clinic records is not always
80 straightforward and can be a source of bias. Copies of the vaccination data source (e.g. digital photo,
81 photocopies, or scanned images of the card or record) are extremely useful for controlling data quality.
82 Copies can be used for double-abstraction (e.g. by two independent observers), which may improve the
83 quality of data, particularly in settings where interpretation of information in the record may be
84 challenging, for example, where parental-held records have no dedicated space for a new vaccine or for
85 vaccines administered during campaigns. Copies potentially allow for blinding with regard to case or
86 control status for the person abstracting the vaccination data⁴⁰. Vaccine lot numbers, if recorded, can
87 aid in determining which vaccines were received. Dates of all relevant vaccine doses, including the
88 vaccine of interest and other vaccines given on the same or similar schedules, should be carefully
89 recorded.

90 ***Other variables and unmeasured confounding factors***

91 In addition to vaccination status, data should be gathered on other variables that may confound
92 the association between vaccination and the disease of interest^{46,47}. Known or hypothesized
93 confounders should be identified before study initiation, accurately and thoroughly captured during
94 data collection, and adjusted for in the analysis if they confound the association between vaccination
95 and illness. As with all observational studies, some degree of unmeasured confounding often occurs in
96 case-control studies and has the potential to substantially alter the measured VE⁴⁸. Unmeasured
97 confounding may result from failure to collect data on a known confounder, insufficient or inadequate
98 data collection for a known confounder, or lack of data on an unrecognized or unknown confounder.

99 A few strategies to quantify unmeasured confounders have been suggested. The first has been
100 called a “bias-indicator”^{37,39,49} or “sham outcome”⁵⁰ study. This is performed concurrently with a case-
101 control study of vaccine effectiveness, where the effectiveness of the studied vaccine is measured
102 against another disease which is not expected to be prevented by the vaccine^{37,39,49}. As the vaccine
103 should confer no protection against this other disease, any measured vaccine effectiveness would be
104 indicative of unmeasured confounding. A bias-indicator study of oral cholera vaccine in Mozambique
105 evaluated the vaccine’s effectiveness against non-cholera diarrhea, and found an effectiveness of 35%
106 (95% CI -18 to 65%); however after adjustment for known confounders the vaccine effectiveness was
107 0%. This suggests that while there was confounding of the effectiveness results, it was not due to
108 unmeasured confounding³⁷. A limitation of the bias indicator study is the assumption that vaccine
109 effects are specific to the vaccine target, whereas there is increasing evidence that some vaccines may
110 have non-specific effects that could reduce the risk for non-targeted infections⁵¹. Non-infectious
111 illnesses (e.g. accidents or injuries) could be considered as outcomes for bias indicators studies. Another
112 type of study to quantify unmeasured confounding has been dubbed a “sham exposure”⁵⁰ or “sham
113 case-control”⁵² study. Here vaccine effectiveness of another vaccine is measured against the disease of
114 interest. In Kenya, investigators measured the effectiveness of diphtheria-tetanus-pertussis-Hib-

115 Hepatitis B vaccine against rotavirus disease among children prior to the expected introduction of the
116 rotavirus vaccine in 2014 and found no protection⁵². Because sham case-control studies are generally
117 carried out before the introduction of a new vaccine, they require advance planning and resources.
118 When feasible, they can be useful for planning case-control studies, for example by revealing the least
119 biased control group or identifying measurable confounders in the population.

120 ***Implementation and adherence to protocols***

121 The quality of data on enrollment, vaccination status, and potential confounders depends on
122 writing and implementing clear protocols and Standard Operating Procedures (SOPs) for study conduct.
123 Efforts to recruit cases and controls should be documented using standardized forms such as screening
124 logs or registers; such documentation can be used to monitor the adherence to study procedures and
125 identify lapses as quickly as possible.

126 Because of potential for selection bias in control enrollment for vaccine effectiveness case-
127 control studies, it is particularly important to standardize, document clearly in logs, and regularly
128 monitor at the field level, the process for enrolling controls.⁵³ This should include the number of
129 potential controls screened, number and timing of attempts made to enroll potentially eligible controls,
130 the reasons for non-enrollment of potential controls, the frequency of refusals, and the number and
131 characteristics of the controls who were not enrolled. Some methods for supervision of field staff
132 enrolling controls may include GPS tracking of field staff (to monitor their locations and pace of
133 recruitment and enrollment) and intermittent supervisor monitoring of the homes that were visited.
134 Any departures from the protocol or SOPs must be reported to study lead investigators and
135 documented.

136 ***Analysis***

137 The statistical analysis of a case-control study for the evaluation of vaccine effectiveness should
138 follow directly from the protocol and analysis plan, which should define the outcomes to be examined,
139 as well as the exposures of interest (e.g. complete schedule, 2 or more doses). The “unadjusted”
140 effectiveness from a case-control study is calculated as $(1 - \text{odds ratio for vaccination}) \times 100\%$.

141 For cases, vaccination status is defined based on the number of doses received before becoming
142 ill and usually excludes doses received within the two weeks prior to allow for induction of immune
143 response. For individually matched controls, a reference date should be defined in order to examine the
144 control’s vaccination status before the corresponding case became ill⁴²; the reference date is often
145 based on the case’s date of illness onset, but may be based upon the date of hospitalization or sample
146 collection. Doses received more than two weeks (if this is the period used for the case) before the
147 reference date should be considered in the analysis. For frequency matched controls, the situation in
148 which multiple controls are matched to multiple cases, there are different reference dates (or ages)
149 associated with each of the cases and controls, and the analysis must take account of this. A method for
150 doing this has been described by Keogh et al⁵⁴.

151 The odds ratio is usually calculated from a logistic regression model, using unconditional logistic
152 regression for unmatched or frequency matched studies, and conditional logistic regression for matched
153 studies, with strata defined for each matched case-control set⁵⁵. For simple conditional logistic
154 regression, only discordant strata (e.g. vaccinated cases with at least one non-vaccinated control, or
155 non-vaccinated case with at least one vaccinated control) contribute to the analysis⁵⁵; thus in settings of
156 very high or low vaccine coverage, the power of the analyses will be reduced.

157 While all efforts should be made in the study design phase to minimize confounding (e.g. by
158 matching), it is usually necessary to also control for confounding in the analysis, where potential
159 confounders are included as independent variables in a regression model. Because inclusion of multiple
160 covariates can result in loss of statistical power, it is important to avoid including factors that are not

161 true confounders. There is no formal statistical test for evaluating whether to include a potential
162 confounder in the final analysis⁴⁶. Some researchers approach the inclusion of confounders based on the
163 past literature and include all potential confounders in a full model. Others prefer to evaluate potential
164 confounders based on the data of the current study. A common approach to confounder evaluation is
165 to include both vaccination status and single potential confounders, one at a time, as independent
166 variables in the logistic regression model. If the OR associated with vaccination status changes by a
167 predetermined, albeit arbitrary, percent (e.g. 10%) or more after adjusting for the potential confounder,
168 then that variable is retained in the final multivariable model since it appears to impact the VE⁴¹.
169 Another approach for determining which variables to include in a multivariable model is the use of
170 directed acyclic graphs, which are causal diagrams used to identify a subset of covariates that address
171 confounding while avoiding introduction of bias⁵⁶. Directed acyclic graphs have been used for case-
172 control vaccine effectiveness studies of influenza^{57,58}. While different strategies for identifying
173 important confounding variables are acceptable, the method used should be determined at the stage of
174 developing the analytic plan.

175 Before deciding on a final model, some investigators prefer to examine whether the odds ratio
176 (and thereby the VE) differ between strata of potential confounders (i.e. effect modification). This may
177 be formally tested using appropriate interaction terms in the regression models. If such interaction is
178 meaningful and statistically significant, stratum-specific VEs might be reported⁵⁹. For example, in a
179 study of the 7-valent pneumococcal conjugate vaccine in the United States, the effectiveness against
180 vaccine-type and non-vaccine type invasive pneumococcal disease was presented for healthy children
181 and those with comorbidities, since this variable was found to have significant interaction with
182 vaccination status¹⁴.

183 Missing vaccination data present a problem in a vaccine effectiveness case-control study, since
184 those with missing data likely differ from those with a documented vaccination history in ways that

185 could bias effectiveness estimates. One approach to handling missing vaccination histories is to conduct
186 a sensitivity analysis. The simplest sensitivity analysis assumes those with a missing vaccination history
187 are either all unvaccinated or all completely vaccinated, providing two estimates of effectiveness under
188 two different assumptions. A study of the Hib vaccine conducted in the Dominican Republic used this
189 approach and found very little impact on the results, suggesting that the findings of the primary analysis
190 were not substantially biased by the missing vaccination history data⁶⁰. Sensitivity analysis could also be
191 conducted to examine the impact of low (and potentially biased) enrollment of controls on effectiveness
192 estimates by assuming a range of vaccine coverage for individuals who were eligible but not enrolled.
193 Methodological approaches to dealing with missing data have been advancing rapidly, and although
194 there has been little work in vaccine effectiveness studies evaluating the usefulness of multiple
195 imputation for missing vaccination histories for enrolled participants (or non-enrolled participants, as
196 mentioned above), this approach warrants exploration⁶¹. Nonetheless, all possible efforts should be
197 made to obtain as complete information as possible on vaccination status of cases and controls; no
198 sensitivity analysis or imputation can fully compensate for data completeness and validity.

199 ***Reporting study results***

200 The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines
201 for reporting on case-control studies are an excellent reference for determining the key pieces of
202 information to record for a vaccine effectiveness study⁶². For case-control vaccine effectiveness studies,
203 it is crucial to provide a clear and explicit description of the recruitment strategy for cases and controls,
204 and to carefully document non-enrollment as well as enrollment. Readers should be given a clear
205 understanding of how many potential cases and controls were screened to achieve the number of
206 enrolled participants and the primary reasons for non-enrollment (e.g. not eligible, unable to contact,
207 refused participation). The number of cases and controls with no documented vaccination history

208 should also be stated in the results. Relevant differences between included and not included cases and
209 controls, as well as between those with and without reliable vaccination history, should be documented.

210 In interpreting the study findings, investigators should focus on the confidence intervals of
211 effectiveness estimates. Although readers or policy makers may be naturally drawn to point estimates,
212 confidence intervals add crucial information on the precision of these estimates. Reports of case-control
213 vaccine effectiveness studies should also include a discussion of the limitations and potential sources of
214 bias, taking into consideration the inherent limitations of the study design.

215 **Conclusions**

216 The case-control methodology is frequently used to evaluate the effectiveness of new vaccines,
217 providing important data on the ‘real-world’ performance of vaccines that guide decisions about vaccine
218 introduction and sustained use^{63,64}. However, the potential for bias and confounding is high, and can
219 threaten the validity of the findings. Studies aimed at better understanding bias in case-control studies,
220 such as a simulation model estimating potential biases in influenza vaccine effectiveness studies⁶⁵, can
221 advance the field and provide more specific guidance regarding circumstances in which the case-control
222 approach is likely to yield reliable results.

223 High quality vaccination data collected using the methods for cases and controls is crucial for
224 vaccine effectiveness studies; in settings where documented vaccination histories are difficult to obtain,
225 case-control vaccine effectiveness studies are unlikely to be useful. Variables that confound the
226 association between vaccination and disease should be carefully measured and adjusted for in the
227 analysis. In reporting the results of a case-control vaccine effectiveness study, it is important to include
228 information that provides insight into the degree of possible bias in enrollment and data collection, such
229 as the number of potential controls screened or the proportion of cases and controls with documented
230 vaccine history. Vaccine effectiveness estimates should be presented with emphasis on the confidence

231 interval rather than the point estimate. In order for case-control studies to accurately guide vaccine
232 policy decisions, data collection must be thorough and with careful attention to minimize bias, the
233 analysis performed per the analytic plan with attention to potential confounding, and the results
234 carefully interpreted and presented.

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258 JAS: Conceptualization, Methodology, Writing; Review and editing
259 PGS: Conceptualization, Methodology, Writing: Review and editing
260 HS: Conceptualization, Methodology, Writing: Review and editing
261 JET: Conceptualization, Writing: Review and editing
262 JCV: Conceptualization, Writing: Review and editing
263 CGW: Conceptualization, Methodology, Writing: Review and editing, Supervision
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275
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