

**Full title: CASE-CONTROL VACCINE EFFECTIVENESS STUDIES: PREPARATION, DESIGN, AND ENROLLMENT OF CASES AND CONTROLS**

**Authors:** Jennifer R. Verani<sup>a</sup>, Abdullah H. Baquib, Claire V. Broome<sup>c</sup>, Thomas Cherian<sup>d</sup>, Cheryl Cohene, Jennifer L. Farrar<sup>a</sup>, Daniel R. Feikin<sup>a,f</sup>, Michelle J. Groome<sup>g</sup>, Rana A. Hajjeh<sup>a</sup>, Hope L. Johnson<sup>h</sup>, Shabir A. Madhi<sup>e,g</sup>, Kim Mulholland<sup>i,j</sup>, Katherine L. O'Brien<sup>f</sup>, Umesh D. Parashar<sup>a</sup>, Manish M. Patel<sup>a</sup>, Laura C. Rodrigues<sup>l</sup>, Mathuram Santosham<sup>f</sup>, J. Anthony Scott<sup>h,k</sup>, Peter G. Smith<sup>i</sup>, Halvor Sommerfelt<sup>m,n</sup>, Jacqueline E. Tate<sup>a</sup>, J. Chris Victor<sup>o</sup>, Cynthia G. Whitney<sup>a</sup>, Anita K. Zaidi<sup>p</sup>, Elizabeth R. Zell<sup>a</sup>

**Corresponding Author:** Jennifer R. Verani; email: [jverani@cdc.gov](mailto:jverani@cdc.gov)

**Affiliations:**

---

<sup>a</sup> National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention; 1600 Clifton Rd. Atlanta, GA, USA

<sup>b</sup> International Center for Maternal and Newborn Health, Johns Hopkins Bloomberg School of Public Health; 615 N Wolfe St, Baltimore, MD, USA

<sup>c</sup> Rollins School of Public Health Emory University; 1518 Clifton Rd, Atlanta, GA USA

<sup>d</sup> Department of Immunizations, Vaccines and Biologicals, World Health Organization; 20 Avenue Appia 1211 Geneva, Switzerland

<sup>e</sup> Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases; 1 Modderfontein Road, Sandringham, Johannesburg, South Africa

<sup>f</sup> International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health; 615 N Wolfe St, Baltimore, MD, USA

<sup>g</sup> Respiratory and Meningeal Pathogens Unit, University of Witwatersrand; Richard Ward, 1 Jan Smuts Ave, Braamfontein, Johannesburg, South Africa

<sup>h</sup> Monitoring & Evaluation, Policy & Performance, GAVI Alliance; Chemin des Mines 2, 1202, Geneva, Switzerland

<sup>i</sup> Murdoch Children's Research Institute; Royal Children's Hospital, 50 Flemington Rd, Parkville VIC 3052, Australia

<sup>j</sup> Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine; Keppel St, London WC1E 7HT, UK

<sup>k</sup> KEMRI-Wellcome Trust Research Programme; P.O. Box 230-80108, Kilifi, Kenya

<sup>l</sup> MRC Tropical Epidemiology Group; London School of Tropical Medicine and Hygiene; London, UK

<sup>m</sup> Centre of Intervention Science in Maternal and Child Health and Centre for International Health, University of Bergen; P.O.Box 7800, Bergen, Norway

<sup>n</sup> Department of International Public Health, Norwegian Institute of Public Health, PO Box 4404 Nydalen, Oslo, Norway

<sup>o</sup> PATH; 2201 Westlake Avenue, Seattle, WA USA

<sup>p</sup> Aga Khan University; Stadium Rd, Karachi, Pakistan

1 **Abstract**

2 Case-control studies are commonly used to evaluate effectiveness of licensed vaccines after deployment  
3 in public health programs. Such studies can provide policy-relevant data on vaccine performance under  
4 'real world' conditions, contributing to the evidence base to support and sustain introduction of new  
5 vaccines. However, case-control studies do not measure the impact of vaccine introduction on disease  
6 at a population level, and are subject to bias and confounding, which may lead to inaccurate results that  
7 can misinform policy decisions. In 2012, a group of experts met to review recent experience with case-  
8 control studies evaluating the effectiveness of several vaccines; here we summarize the  
9 recommendations of that group regarding best practices for planning, design and enrollment of cases  
10 and controls. Rigorous planning and preparation should focus on understanding the study context  
11 including healthcare-seeking and vaccination practices. Case-control vaccine effectiveness studies are  
12 best carried out soon after vaccine introduction because high coverage creates strong potential for  
13 confounding. Endpoints specific to the vaccine target are preferable to non-specific clinical syndromes  
14 since the proportion of non-specific outcomes preventable through vaccination may vary over time and  
15 place, leading to potentially confusing results. Controls should be representative of the source  
16 population from which cases arise, and are generally recruited from the community or health facilities  
17 where cases are enrolled. Matching of controls to cases for potential confounding factors is commonly  
18 used, although should be reserved for a limited number of key variables believed to be linked to both  
19 vaccination and disease. Case-control vaccine effectiveness studies can provide information useful to  
20 guide policy decisions and vaccine development, however rigorous preparation and design is essential.

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

## 22 **Introduction**

23 Many new vaccines have been introduced into public health programs over the past decade and  
24 others are under development. Vaccines are generally licensed based on safety and efficacy as  
25 measured in randomized controlled trials. Once vaccines are introduced into public health programs,  
26 their performance under “real world” conditions also needs assessment<sup>1</sup>, including among populations  
27 with subgroups that may have been excluded from pre-licensure trials (e.g., malnourished or HIV-  
28 infected), with more variable dosing schedules (e.g. age at administration, interval between doses,  
29 number of doses), against outcomes not included in randomized clinical trials (e.g. strain-specific  
30 protection or mortality), and over more extended periods of time

31 Furthermore, some vaccines are licensed based on immunologic correlates of protection<sup>2</sup>, and  
32 post-licensure evaluations provide important information about protection against disease endpoints.  
33 After vaccines have been introduced, conducting placebo-controlled trials is generally not considered  
34 ethical<sup>3</sup>. Observational post-licensure evaluations are important to underpin policy decisions on vaccine  
35 introduction, to optimize the vaccine program implementation, and to provide evidence for sustaining  
36 vaccine use and investment from governments and donors.

37

## 38 **Efficacy, effectiveness and impact**

39 ‘Efficacy’, ‘effectiveness’ and ‘impact’ are sometimes used interchangeably in everyday  
40 language, but in the context of vaccine studies the terms have come to be used with distinctly different  
41 meanings (although not entirely consistently)<sup>4-7</sup>. Their usage in this document is defined below:

42 **Efficacy** is the percentage by which the rate of the target disease among those who are vaccinated  
43 according to the recommended schedule is reduced compared to the rate in similar unvaccinated

44 persons. This is generally measured in the context of a placebo-controlled randomized trial as the “per  
45 protocol” efficacy (i.e. excluding persons who did not receive the recommended schedule), because the  
46 intention is to establish the biologic performance capacity of the product under optimal conditions.

47 **Effectiveness** measures the same percent reduction in the rate of disease as efficacy, but in the context  
48 of routine, real-world use of the vaccine. Vaccine effectiveness may be similar to the efficacy as  
49 measured in clinical trials. However, it often differs in magnitude because in routine use the population  
50 vaccinated includes some who may have a less robust immune response, and program implementation  
51 (e.g. cold-chain maintenance, dosing schedules) is more variable than in clinical trial settings.

52 **Impact** quantifies the reduction in disease at a population level following introduction of the vaccine<sup>7</sup>.  
53 Impact can be expressed as a percentage decline or as an absolute change in the rate of disease. It is  
54 determined by a combination of vaccine effectiveness, vaccine coverage in the population, and any herd  
55 effect (i.e. vaccination of part of the population leading to reduced transmission of the infection in the  
56 community, and thus lowered risk of disease in both vaccinated and unvaccinated persons)<sup>8</sup>.

57 Studies of vaccine efficacy, effectiveness, and impact may use non-disease outcomes such as  
58 colonization as endpoints; however disease endpoints are more commonly used.

#### 59 **Observational methods to assess vaccine effectiveness and impact**

60 Several observational epidemiologic methods are used to assess the impact of vaccination  
61 programs and the effectiveness of vaccines in routine use<sup>4,5,9</sup>. Examination of trends in disease incidence  
62 before and after vaccine introduction measures vaccination program impact. However this approach  
63 requires a stable, unchanged disease surveillance system before and after the introduction of vaccine.  
64 Interpretation of such studies can be challenging because of changes in measured disease incidence or  
65 the true disease incidence unrelated to vaccination. For example, changes in healthcare seeking

66 behaviors can increase or decrease measured disease incidence, concomitant implementation of non-  
67 vaccine interventions can reduce disease risk, and natural temporal variation in disease incidence  
68 unrelated to vaccination can also occur.

69         Vaccine effectiveness is generally measured through either cohort or case-control approaches.  
70 Cohort studies estimate effectiveness by comparing the incidence of disease among vaccinated and  
71 unvaccinated persons. Cohort studies require large samples, may be costly, and accurate data on the  
72 vaccination status and potential confounding variables for an entire population are often not available,  
73 especially in resource-poor settings. The cohort design may not be practical for diseases with low  
74 incidence. Case-control studies assess effectiveness by comparing the odds of antecedent vaccination  
75 among individuals who develop the target disease (cases) and among a group of individuals without the  
76 disease (controls) who are representative of the population from which the cases arise<sup>10,11</sup>. Because  
77 efforts are focused on accurately ascertaining disease status and vaccination history for a relatively  
78 small number of cases and controls (compared to cohort studies), the method can be resource-efficient  
79 and particularly useful for diseases or outcomes that are relatively uncommon. The screening method, in  
80 which the vaccination status of cases is compared to population-level vaccine coverage, is another  
81 approach for assessing vaccine effectiveness<sup>12</sup>; however accurate data on the proportion of the  
82 population vaccinated is often not available in resource-poor settings.

83         In recent years, case-control studies have been conducted to evaluate the effectiveness of  
84 *Haemophilus influenzae* (Hib)<sup>13-24</sup>, pneumococcal<sup>25-32</sup>, influenza<sup>33</sup>, rotavirus<sup>34-47</sup>, and cholera<sup>48-50</sup> vaccines.  
85 Despite being widely used to evaluate vaccine performance, the case-control methodology is susceptible  
86 to bias and confounding<sup>51,52</sup>. Because vaccine effectiveness estimates often impact policy decisions and  
87 donor support for vaccines their validity is important. In November 2012, a group of experts met to  
88 review recent experience with case-control studies evaluating effectiveness of several vaccines. We

89 summarize the recommendations from that group regarding best practices for the preparation and  
90 design of such studies, as well as the enrollment of cases and controls. (Data collection, vaccine status  
91 ascertainment, analysis and reporting of results are discussed in a separate paper [insert reference for  
92 paired manuscript].) While discussions of case-control methodology in general can be found  
93 elsewhere<sup>52,53</sup>, here we focus on the application of these methods to evaluate vaccine effectiveness in  
94 resource-constrained settings.

95

## 96 **Methodological aspects of case-control vaccine effectiveness studies**

### 97 ***Preparation for case-control vaccine effectiveness studies***

98         Although data collection for case-control vaccine effectiveness studies begins after vaccine  
99 implementation, rigorous study planning and preparation, focused on understanding the local study  
100 context, should begin well before cases and controls are recruited, ideally a year or more beforehand. In  
101 the preparatory period, it is important to assess factors that may affect case ascertainment, such as  
102 healthcare-seeking behavior, barriers to care, determinants of hospitalization and diagnostic capacities.  
103 Different potential sources of control groups should be considered to identify the group least likely to  
104 lead to bias; for example, if cases are identified from a source population that includes large slum areas  
105 and controls are recruited only from more wealthy areas, the controls may be very different from cases  
106 in ways that could bias effectiveness estimation. Preparation should also include assessing vaccine  
107 coverage, factors associated with non-vaccination, and the ability to obtain valid, complete data on  
108 vaccination status among the intended study population. Identifying key potential confounders and the  
109 most accurate ways to measure them are also essential components of study preparation.

110 Prior studies of the outcome of interest in the local study context may inform case definitions  
111 and strategies for recruitment. For example, a “vaccine-probe” study in South Africa found that a widely  
112 used case definition for likely bacterial pneumonia, based on standardized interpretations of pediatric  
113 chest radiographs, underestimated the burden of pneumonia that could be prevented with the  
114 pneumococcal conjugate vaccine<sup>54</sup>; therefore a subsequent case-control vaccine effectiveness study  
115 used a modified case definition aimed at better capturing probable pneumococcal pneumonia cases in  
116 that setting<sup>32</sup>. Health care utilization studies provide important information on where cases might be  
117 identified for a case-control vaccine effectiveness study, as well as cases that may be missed by health  
118 facility-based studies<sup>55-57</sup>. Vaccine coverage surveys or analysis of immunization data from Demographic  
119 and Health Surveys or Multiple Indicator Cluster Surveys can offer insight on the completeness and  
120 timeliness of routine immunization in the intended study population, the availability of documented  
121 vaccine histories, and factors associated with non-vaccination that may be important confounders for a  
122 vaccine effectiveness study<sup>58</sup>. In the context of a Hib vaccine study in the Ukraine it was noted that  
123 providers considered underlying immunocompromising conditions to be a contraindication for receiving  
124 the vaccine; thus children at increased risk for Hib disease were less likely to receive the vaccine,  
125 potentially leading to an overestimation of the actual effectiveness in the full population<sup>23</sup>. Identifying  
126 important factors that influence likelihood of vaccination during the planning phase can help avoid bias  
127 during study implementation.

### 128 ***Sample size and feasibility***

129 During the preparatory phase, the feasibility of achieving adequate enrollment during the  
130 planned study timeline must be assessed. The desired study size is determined by the expected  
131 effectiveness (with lower effectiveness requiring larger sample sizes), anticipated vaccine coverage in  
132 the study population, and the number of controls enrolled per case<sup>9</sup>. Study size may be based on

133 statistical “power” (i.e. testing the hypothesis that the vaccine is significantly protective) or precision-  
134 based (i.e. targeting a certain width of confidence interval)<sup>59</sup>. Sample size calculations should allow for  
135 missing data, adjustment for confounding, and the expected prevalence of incomplete vaccination (e.g.  
136 one or two doses of a three-dose schedule). Once the desired sample size is determined, an assessment  
137 of the ability to enroll that target number must take into account the potential for declining incidence of  
138 disease over time following vaccine rollout, refusals, age-eligibility for vaccination, and ability to collect  
139 vaccination histories. Thus, simple sample size calculations should be considered as the minimum  
140 necessary number needed to assess the primary outcome, but enrollment beyond that minimum is likely  
141 required for a robust analysis and the ability to address secondary objectives (e.g. effectiveness in  
142 subgroups, effectiveness of incomplete schedule, and strain-specific effectiveness).

143           Several planned case-control studies of Hib vaccine effectiveness were not completed because  
144 of lower than anticipated enrollment attributable to rapid declines in invasive Hib disease burden  
145 following vaccine introduction (R. Hajjeh, personal communication, November 16, 2012). Case-control  
146 studies may have limited power if the number of available cases is small, which can occur following  
147 introduction of highly efficacious vaccines, in settings that achieve rapid, high coverage and significant  
148 herd effects.

#### 149 ***Timing of study and vaccine coverage***

150           Case-control studies are most likely to be useful when the vaccine coverage is between 20-80%<sup>9</sup>.  
151 At either very low or very high coverage, unvaccinated persons are likely to differ from the general  
152 population in ways that may be associated with increased or decreased risk of disease, independent of  
153 vaccination. These differences may be more pronounced where coverage levels are driven by individual  
154 factors (e.g. lack of access to care, mistrust of medical system) rather than programmatic factors (e.g.  
155 vaccine stock-outs). Results of several rotavirus case-control studies were difficult to interpret due to



156 high coverage (>90%) soon after vaccine introduction<sup>43,60</sup>. Settings with high vaccine coverage (e.g.  
157 greater than 85 to 90%) are not suitable for case-control vaccine effectiveness studies because of the  
158 strong potential for confounding. High coverage also increases sample size requirements because more  
159 observations are required to detect a significant difference in vaccination between cases and controls.  
160 Furthermore, high coverage can lead to a rapid decline in cases of the disease of interest if vaccine  
161 efficacy is high. Thus, in contexts where the coverage is expected to increase quickly following vaccine  
162 introduction, it may be preferable to conduct a study in a short time period after introduction rather  
163 than a prolonged study with a slower rate of enrolment.

#### 164 ***Study endpoints***

165           Endpoints for case-control vaccine effectiveness studies range from highly specific for the  
166 vaccine target (e.g. invasive pneumococcal disease caused by a serotype included in the vaccine or  
167 rotavirus diarrhea) to non-specific (e.g. clinical syndromes such as pneumonia or acute gastroenteritis).  
168 Pathogen-specific endpoints have precise case definitions that are generally not open to interpretation  
169 or variability in the field application. Non-specific outcomes, however, may be of greater interest from a  
170 policy perspective because of the larger associated burden of disease, albeit the fraction of that disease  
171 preventable by the vaccine may be low. Yet effectiveness estimates from case-control studies of non-  
172 specific outcomes can be confusing or misleading. For example, a systematic review of Hib vaccine  
173 effectiveness noted that case-control studies using radiologically confirmed pneumonia endpoints may  
174 have overestimated effectiveness (compared to clinical trial estimates of efficacy against that same  
175 endpoint), although the reason for the high point estimates is unclear<sup>61</sup>.

176           Protection against a non-specific endpoint depends on the proportion of the endpoint that is  
177 attributable to the pathogen targeted by the vaccine; this may vary over time or seasonally, be higher or  
178 lower in certain sub-groups (e.g. young infants, malnourished children) or be affected by outbreaks of

179 other pathogens with overlapping clinical symptoms. Such variability can result in inconsistent estimates  
180 of effectiveness against non-specific endpoints between studies. For vaccines that lead to herd effect  
181 (e.g. Hib or pneumococcal conjugate vaccine), the proportion of a non-specific endpoint (e.g.  
182 pneumonia) attributable to the vaccine-preventable pathogen decreases among both vaccinated and  
183 non-vaccinated populations; thus as herd effects increase, effectiveness estimates for non-specific  
184 endpoints will decline. The risk for developing non-specific clinical syndromes such as all-cause  
185 pneumonia or diarrhea may also be strongly affected by individual-level non-vaccine risk factors (e.g.  
186 poverty, maternal education, crowding); such factors are difficult to measure well and may be  
187 associated with vaccination status. Furthermore, non-specific endpoints require enrolling larger  
188 numbers of participants, since effectiveness against non-specific endpoints is lower than that against  
189 specific endpoints<sup>10</sup>. Because of variability in the vaccine-preventable portion and the strong potential  
190 for bias, case-control vaccine effectiveness studies using non-specific endpoints must be interpreted  
191 with care, and are best conducted only when accompanied by analyses of disease trends over time or by  
192 a nested or parallel evaluation of a more specific endpoint in the same study setting.

### 193 ***Identification and enrollment of cases***

194         Once the study endpoint is decided, the endpoint case definition must be clearly defined to  
195 avoid variable inclusion of cases during study implementation. It is not necessary to enroll all individuals  
196 who develop the disease in a given area or time period for a case-control study<sup>10</sup>. However, studies  
197 should report the proportion of eligible cases enrolled, since low enrollment may result in selection bias.  
198 Some vaccine effectiveness studies focus on a specific subset of cases because the effectiveness of the  
199 vaccine against the outcome is of particular public health interest (e.g. hospitalized or severe cases). The  
200 generalizability of the vaccine effectiveness will be limited to the types of cases included, and such  
201 restrictions must be taken into account in the interpretation of study findings<sup>51</sup>. Whenever possible and

202 culturally acceptable, cases among children who have died should be included in case-control vaccine  
203 effectiveness studies, since they represent the most severe spectrum of disease and failing to include  
204 them could bias the effectiveness estimate if their likelihood of vaccination differs than that of cases  
205 who survive.

## 206 ***Sources of controls***

207 In all case-control studies, controls should be representative of the source population from  
208 which the cases are selected<sup>51,62-64</sup>. A way of exploring this is to ask “If this control had developed the  
209 disease of interest, would he or she have been identified and included in this study as a case?” If the  
210 answer is no, then the control selection method is probably not appropriate. This question should be  
211 asked at the study design phase, when the source of potential controls is being determined.

## 212 **Community controls**

213 In many contexts, it is good practice to seek controls in the community in which the case  
214 resides, since those living in the community are most reflective of those who *would be identified as*  
215 cases if they were to fall ill<sup>62</sup>. The community from which the cases are derived from can be defined in  
216 various ways, depending on the study context and the available options for identifying controls.  
217 Population-based lists, such as birth registries or population-based databases in which the cases are  
218 included, can be used to randomly select potential controls<sup>65</sup>. For example, in studies of the  
219 pneumococcal conjugate vaccine in the US<sup>17</sup> and Brazil<sup>66</sup>, birth registries were used to select potential  
220 controls, and in a study in Canada, controls were selected from a health insurance registry that included  
221 all residents in a province<sup>27</sup>. Such lists should be comprehensive and inclusive, since selecting children  
222 from an incomplete list may limit generalizability<sup>62</sup>. The basis for the list must not be associated with  
223 receipt of vaccines (e.g. immunization registries that include only vaccinated children). Lists with the  
224 appropriate characteristics often do not exist or are incomplete in many resource-poor settings,

225 obviating this method for control selection. If such a list is used to identify controls, then cases not  
226 appearing in the list should be excluded.

227           Alternatively, community controls may be sought geographically, for example, around a case's  
228 place of residence. Children from the same geographic area often tend to be comparable with respect to  
229 underlying risk of disease and access to vaccination, and it is possible to match on, or adjust for, distance  
230 to healthcare facilities if there is concern about differential access to care. Matching by neighborhood  
231 can also help control for a variety of potential confounding factors that may be difficult to measure, such  
232 as socio-economic status or other barriers to vaccination<sup>65</sup>. Geo-mapping of the population in an area  
233 can provide a sample frame from which to select geographically-matched controls, as was done for a Hib  
234 vaccine case-control study in Bangladesh<sup>67</sup>. A less sophisticated, but more commonly employed, strategy  
235 is to identify the household of the case, and then walk in a random direction (e.g. by spinning a bottle)  
236 from that residence, seeking a suitable control from the nearest neighboring house. This method is  
237 based on the approach developed for vaccine coverage surveys<sup>15,21,58</sup>. Having standardized procedures  
238 for visiting potential control households is essential for reducing selection bias<sup>62</sup>. Procedures should  
239 include the requirement to visit non-responsive households multiple times and at different times of day  
240 before excluding their residents as potential controls, since children whose parents are not at home  
241 might be more or less likely to be vaccinated than children whose parents are at home. Enrolling  
242 community controls can be logistically challenging and resource-intensive, particularly when tight age-  
243 matching criteria are used. Security concerns can also interfere with recruitment of community controls;  
244 investigators of Hib vaccine effectiveness in Colombia and Pakistan had to alter control recruitment  
245 strategies due to the safety risks associated with seeking neighborhood controls.<sup>24,68</sup> Conducting control  
246 recruitment in locations that are safer or more convenient can induce substantial biases in the vaccine  
247 effectiveness measure if residence in those areas is associated with higher likelihood of vaccination.

248 **Hospital or clinic controls**

249 Another common source of controls for case-control vaccine effectiveness studies are children  
250 hospitalized with illnesses other than the outcome of interest<sup>62</sup>. The specific inclusion criteria for  
251 hospitalized children to serve as controls must be carefully considered in the design phase of each study  
252 since the local conditions influence the risk of bias. Children who are hospitalized, particularly those with  
253 frequent or prolonged hospitalization, may differ in important ways, including vaccination history, from  
254 the general population; recruiting from among recently admitted children may avoid overenrolling  
255 children with severe prolonged illness as controls. Children hospitalized with vaccine-preventable  
256 diseases should be excluded as controls, as they are probably less likely to be vaccinated in general,  
257 including with the vaccine under study<sup>51,62</sup>. Where vaccines that protect against the most common  
258 childhood illnesses (e.g. gastroenteritis, pneumonia) are in routine use, and therefore children  
259 hospitalized with these illnesses cannot serve as controls, it may be challenging to identify enough  
260 eligible hospital controls<sup>31</sup>. In settings where access to health care is limited or hospitalization is largely  
261 restricted to certain subsets of children (e.g. children with malnutrition), then hospital controls may  
262 have the advantage of being relatively comparable to hospitalized cases with regards to access to care<sup>62</sup>.  
263 However, results of a study in such a context are only generalizable to children who would be  
264 hospitalized when ill.

265 Controls can also be identified in out-patient clinics that cases would attend if ill<sup>65</sup>, an approach  
266 used for Hib vaccine effectiveness studies in Colombia<sup>68</sup> and Ukraine<sup>23</sup>. However, if immunizations are  
267 delivered at the clinic, then controls attending the clinic would be more likely to be vaccinated than the  
268 general population, as was found in a study of tuberculosis vaccination in Brazil<sup>69</sup>. Thus, if outpatient  
269 clinics are to be used as a source of controls, they should be clinics where immunizations are not  
270 routinely provided.

271 **Controls with same clinical syndrome who are ‘test-negative’ for the pathogen of interest**

272 Another potential source of controls is children who become ill with the same clinical syndrome  
273 as those with the outcome of interest, but whose illness is shown to have an etiologic pathogen not  
274 targeted by the vaccine under evaluation<sup>70-72</sup>. Examples of this approach include: rotavirus-negative  
275 gastroenteritis as controls for cases of rotavirus<sup>36,41,43</sup>, influenza-negative respiratory infection for cases  
276 of influenza<sup>71</sup>, pneumococcal or non-purulent/Hib-negative meningitis as controls for Hib meningitis  
277 cases<sup>18,20</sup>, and non-vaccine serotype invasive pneumococcal disease for cases of vaccine-type invasive  
278 disease (also known as the ‘indirect cohort’ or ‘Broome’ method)<sup>73-77</sup>. This approach requires accurate  
279 diagnostic testing and sample collection at an appropriate time to diagnose the pathogen of interest in  
280 order to avoid misclassification. Imperfect test sensitivity and specificity leads to an underestimation of  
281 effectiveness using test-negative controls<sup>78</sup>. Some tests, such as culture of blood or cerebrospinal fluid,  
282 are too insensitive to reliably identify test-negative controls; however when such tests detect an  
283 etiology that is not preventable by vaccines included in the national schedule (e.g. pneumococcal  
284 meningitis for evaluation of Hib vaccine [before introduction of pneumococcal vaccine], or non-vaccine-  
285 type pneumococcal bacteremia for evaluation of pneumococcal conjugate vaccine), such individuals can  
286 serve as controls. The validity of using test-negative controls has been demonstrated by re-analyses of  
287 data from randomized clinical trials of influenza<sup>70</sup> and rotavirus<sup>79</sup> vaccines that yielded effectiveness  
288 estimates very similar to the efficacy measured by the original trials.

289 One major advantage of the test-negative approach is a high degree of comparability between  
290 cases and controls, since controls would have been enrolled as cases if they had the vaccine-preventable  
291 outcome of interest. It also offers logistical and cost advantages, since cases and controls can be  
292 recruited from within a single surveillance system. Also, since test results are often not available at the  
293 time of recruitment, bias in ascertainment of vaccination through knowledge of case-control status is

294 less likely. A limitation to this method is that it assumes the vaccine being evaluated has no effect on the  
295 incidence of test-negative cases who will serve as controls. For pneumococcal conjugate vaccines, this  
296 assumption may not be valid, since their widespread use has been associated with increases in non-  
297 vaccine type pneumococcal carriage and disease incidence<sup>80</sup>. However, modeling work conducted in  
298 conjunction with indirect cohort analyses indicates that while increases in non-vaccine type disease (and  
299 carriage) among vaccinated individuals compared with the non-vaccinated can lead to overestimates of  
300 VE, the magnitude of the overestimation is relatively small, particularly if conducted before vaccine  
301 coverage is very high<sup>74,76</sup>. For influenza vaccine, models have similarly shown that even if influenza  
302 infection is presumed to provide transient non-specific immunity to all respiratory infections (and thus  
303 individuals vaccinated against influenza, who would not benefit from this immunity, would be over-  
304 represented among non-influenza respiratory infection cases) the impact on effectiveness estimates  
305 derived from case-control studies using the test-negative design is minor<sup>72,81</sup>.

### 306 **Multiple control groups**

307 In some case-control vaccine effectiveness studies two or more types of control group are  
308 enrolled<sup>17,19,40,42</sup>. However, when the estimates of effectiveness differ by the control group used, the  
309 disparate results are difficult to interpret and communicate<sup>63</sup>. Multiple control groups may be useful for  
310 evaluation of study methods and identifying bias in different groups. In general, however, it is preferable  
311 to understand the study context well, to consider carefully the best control group before conducting the  
312 study, and then to use one source of controls<sup>62</sup>.

### 313 ***Matching***

314 Matching of cases and controls is often used in vaccine effectiveness studies to increase the  
315 statistical efficiency of the analysis and to attempt to control for unmeasured confounders<sup>64,65,82</sup>.  
316 However, overmatching, which occurs when the matching variable is strongly associated with

317 vaccination but not (or only weakly) with the illness, results in a loss of statistical power<sup>83</sup>. Matching  
318 also greatly increases the operational complexity of enrolling controls. Matching in case-control vaccine  
319 effectiveness studies is most commonly done at an individual level, where each enrolled control is  
320 matched to a specific case based on certain criteria (e.g. date of birth or geographic region). An  
321 alternative approach is ‘frequency’ or ‘stratum’ matching, in which the group of controls is enrolled  
322 based on the frequency of certain characteristics among all cases (e.g. if 20% of cases are from a certain  
323 neighborhood, then controls are enrolled so that 20% are from that same neighborhood)<sup>10</sup>. Matching, if  
324 used, should be reserved for a limited number of important variables believed to be linked to both  
325 vaccination and disease (i.e. confounding), since unnecessary matching can lead to reduced efficiency in  
326 the analysis and substantially increases the complexity of study implementation<sup>65,82,84</sup>.

### 327 ***Control to case ratio***

328         The preferred ratio of controls to cases depends upon the relative ease (and cost) of enrolling  
329 cases and controls. The statistically most efficient approach is equal numbers of cases and controls, if  
330 they are equally easy to enroll. If the number of cases is limited, increasing the number of controls per  
331 case will increase statistical power, but generally little additional power is gained by enrolling more than  
332 four controls per case<sup>62</sup>. However, for studies using individual matching in contexts where vaccine  
333 coverage is very high or very low, more than four controls per case should be considered, since case-  
334 control sets in which all cases and controls have the same vaccination status will not contribute to the  
335 estimates of effectiveness. In contexts where controls are easy to enroll, for example from a population-  
336 based registry<sup>29</sup>, then a higher control to case ratio may be used.

### 337 ***Timing of control enrollment***

338         For individually matched case-control vaccine effectiveness studies, controls should be enrolled  
339 concurrently (i.e. for each incident case enrolled, one or more new matched controls are enrolled from



340 the population at-risk). Rapid enrollment of matched controls can reduce recall bias, minimize difficulty  
341 obtaining compatible vaccination histories for cases and controls, and help ensure comparability  
342 between cases and controls with respect to unmeasured temporal factors that may affect the risk of  
343 developing the outcome of interest (e.g. outbreaks of viral respiratory infections increasing the risk for  
344 pneumococcal pneumonia). However, rapid enrollment of matched controls is not always feasible and  
345 risks regarding vaccine history can be mitigated if there is written documentation, with dates of  
346 administration, of vaccination status so that only doses received before the corresponding case became  
347 ill are considered.

### 348 **Conclusions**

349 Evidence of the protection afforded by new vaccines in the context of real-world immunization  
350 programs is important for accelerating and sustaining their uptake globally<sup>85,86</sup>. Case-control vaccine  
351 effectiveness studies, if carefully conducted, can provide such evidence, complementing data from  
352 randomized controlled trials as well as findings from other observational approaches, such as analyses  
353 of trends in disease incidence over time or cohort studies. Relative to other observational methods for  
354 vaccine evaluation, case-control studies have some advantages. They do not require a stable baseline of  
355 disease surveillance data prior to vaccine introduction and are often considerably less expensive to  
356 perform than cohort studies. Case-control vaccine effectiveness studies do not measure the actual  
357 impact of vaccine introduction on disease at a population level. However, when combined with data on  
358 pre-vaccine burden of disease and vaccine coverage, they can be used to provide insight into the public  
359 health impact of vaccines.

360 The belief that case-control studies are quick and easy to carry out is misplaced. Case-control  
361 vaccine effectiveness studies are complex and require rigorous planning and implementation. They are  
362 susceptible to various types of bias and, if not conducted rigorously and with careful planning, can

363 produce invalid and potentially misleading results. It is imperative that investigators understand the  
364 study context well to minimize bias and correctly interpret results. Case-control vaccine effectiveness  
365 studies are most likely to provide reliable information when assessing outcomes specific to the vaccine  
366 being evaluated (e.g. Hib meningitis rather than all clinical meningitis). Studies using nonspecific  
367 outcomes are particularly challenging and prone to misleading results; such studies should not be  
368 undertaken unless the investigators ensure a high level of rigor and complementary data assessing other  
369 more specific outcomes are available from the same or comparable population. Selection of an  
370 appropriate control group and close attention to potential sources of bias during control enrollment are  
371 crucial. While case-control studies can provide useful information to guide vaccine policy decisions and  
372 vaccine development, they must be thoughtfully planned and rigorously conducted.

### 373 **Acknowledgements**

374 The authors would like to acknowledge Claudia DaSilva for organizing the meeting which formed the  
375 basis for this paper. We would also like to thank Dr. Jill Ferdinand and Tamara Pilishvili for their  
376 contributions to the scientific content of the meeting and subsequent discussions.

### 377 **Author contributions**

378 JRV: Conceptualization, Methodology, Writing: Original draft preparation Writing: Review and editing,  
379 Project administration, Supervision

380 AHB: Conceptualization, Writing: Review and editing

381 CVB: Conceptualization, Writing: Review and editing

382 TC: Conceptualization, Writing: Review and editing

383 CC: Conceptualization, Methodology, Writing: Review and editing

384 JLF: Writing: Review and editing, Project administration

385 DRF: Conceptualization, Writing: Original draft preparation, Writing: Review and editing

386 MG: Conceptualization, Writing: Review and editing

387 RAH: Conceptualization, Methodology, Writing: Review and editing, Funding acquisition

388 HLJ: Conceptualization, Writing: Review and editing

389 SAM: Conceptualization, Writing: Review and editing

390 KM: Conceptualization, Writing: Review and editing

391 KLO: Conceptualization, Methodology, Writing: Review and editing, Supervision

392 UDP: Conceptualization, Writing: Original draft preparation, Writing: Review and editing

393 MMP: Conceptualization, Writing: Original draft preparation, Writing: Review and editing

394 LCR: Conceptualization, Writing: Review and editing

395 MS: Conceptualization, Writing: Review and editing

396 JAS: Conceptualization, Methodology, Writing; Review and editing

397 PGS: Conceptualization, Methodology, Writing: Review and editing

398 HS: Conceptualization, Methodology, Writing: Review and editing

399 JET: Conceptualization, Writing: Review and editing

400 JCV: Conceptualization, Writing: Review and editing

401 CGW: Conceptualization, Methodology, Writing: Review and editing, Supervision

402 AKZ: Conceptualization, Writing: Review and editing

403 ERZ: Conceptualization, Writing: Review and editing

404

405 **Funding:** Funds from the GAVI Alliance covered the cost of an expert meeting held in November, 2012 to

406 discuss the case-control method for evaluating vaccine effectiveness.

407

408 **Disclaimers:** The findings and conclusions in this report are those of the authors and do not necessarily

409 represent the official position of the Centers for Disease Control and Prevention. Thomas Cherian is a

410 staff member of the World Health Organization. He alone is responsible for the views expressed in this  
411 publication, which may not necessarily represent the decisions or the policies of the World Health  
412 Organization

413

414 **Author disclosures of potential conflict of interest:** CC reports having received grant funds from Sanofi  
415 Pasteur that were awarded to the National Institute for Communicable Diseases, South Africa

416

#### 417 **References**

- 418 1. Clemens J, Brenner R, Rao M, Tafari N, Lowe C. Evaluating new vaccines for developing  
419 countries. Efficacy or effectiveness? *JAMA* 1996;**275**(5):390-7.
- 420 2. World Health Organization DoI, Vaccines and Biologicals. Correlates of vaccine-induced  
421 protection: methods and implications. Geneva: World Health Organization, 2013.
- 422 3. Rid A, Saxena A, Baqui AH, Bhan A, Bines J, Bouesseau MC, Caplan A, Colgrove J, Dhali A, Gomez-  
423 Diaz R, Green SK, Kang G, Lagos R, Loh P, London AJ, Mulholland K, Neels P, Pitisuttithum P, Sarr  
424 SC, Selgelid M, Sheehan M, Smith PG. Placebo use in vaccine trials: Recommendations of a WHO  
425 expert panel. *Vaccine* 2014.
- 426 4. Orenstein WA, Bernier RH, Dondero TJ, Hinman AR, Marks JS, Bart KJ, Sirotkin B. Field evaluation  
427 of vaccine efficacy. *Bulletin of the World Health Organization* 1985;**63**(6):1055-1068.
- 428 5. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field. Further  
429 observations. *Epidemiol Rev* 1988;**10**:212-41.
- 430 6. Fedson DS. Measuring protection: efficacy versus effectiveness. *Dev Biol Stand* 1998;**95**:195-201.
- 431 7. Hanquet G, Valenciano M, Simondon F, Moren A. Vaccine effects and impact of vaccination  
432 programmes in post-licensure studies. *Vaccine* 2013;**31**(48):5634-42.
- 433 8. Fine PE. Herd immunity: history, theory, practice. *Epidemiol Rev* 1993;**15**(2):265-302.
- 434 9. Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate  
435 vaccination. Department of Immunization, Vaccines and Biologicals, World Health Organization,  
436 2012.
- 437 10. Rodrigues LC, Smith PG. Use of the case-control approach in vaccine evaluation: efficacy and  
438 adverse effects. *Epidemiologic reviews* 1999;**21**(1):56-72.
- 439 11. Smith PG. Retrospective assessment of the effectiveness of BCG vaccination against tuberculosis  
440 using the case-control method. *Tubercle* 1982;**63**(1):23-35.
- 441 12. Farrington CP. Estimation of vaccine effectiveness using the screening method. *International*  
442 *Journal of Epidemiology* 1993;**22**(4):742-746.
- 443 13. de Andrade ALSS, de-Andrade Jo, Martelli CMT, e Silva SA, de-Oliveira R, Costa MSN, Laval C,  
444 Ribeiro LHV, Di Fabio J. Effectiveness of *Haemophilus influenzae* b conjugate vaccine on  
445 childhood pneumonia: a case-control study in Brazil. *International Journal of Epidemiology*  
446 2004;**33**(1):173-181.
- 447 14. de la Hoz F, Higuera A, Di Fabio J, Luna M, Naranjo A, de la Luz Valencia MÂa, Pastor D, Hall A.  
448 Effectiveness of *Haemophilus influenzae* type b vaccination against bacterial pneumonia in  
449 Colombia. *Vaccine* 2004;**23**(1):36-42.

- 450 15. Adegbola R, Secka O, Lahai G, Lloyd Evans N, Njie A, Usen S, Oluwalana C, Obaro S, Weber M,  
451 Corrah T, Mulholland K, McAdam K, Greenwood B, Milligan PJM. Elimination of Haemophilus  
452 influenzae type b (Hib) disease from The Gambia after the introduction of routine immunisation  
453 with a Hib conjugate vaccine: a prospective study. *Lancet (London, England)*  
454 2005;**366**(9480):144-150.
- 455 16. Daza P, Banda R, Misoya K, Katsulukuta A, Gessner B, Katsande R, Mhlanga B, Mueller J, Nelson  
456 C, Phiri A, Molyneux E, Molyneux M. The impact of routine infant immunization with  
457 Haemophilus influenzae type b conjugate vaccine in Malawi, a country with high human  
458 immunodeficiency virus prevalence. *Vaccine* 2006;**24**(37-39):6232-6239.
- 459 17. Baqui A, El Arifeen S, Saha S, Persson Lk, Zaman K, Gessner B, Moulton L, Black R, Santosham M.  
460 Effectiveness of Haemophilus influenzae type B conjugate vaccine on prevention of pneumonia  
461 and meningitis in Bangladeshi children: a case-control study. *The Pediatric infectious disease*  
462 *journal* 2007;**26**(7):565-571.
- 463 18. Muganga N, Uwimana J, Fidele N, Gahimbare L, Gessner B, Mueller J, Mhlanga B, Katsande R,  
464 Herbinger K-H, Rugambwa C. Haemophilus influenzae type b conjugate vaccine impact against  
465 purulent meningitis in Rwanda. *Vaccine* 2007;**25**(39-40):7001-7005.
- 466 19. Lee E, Lewis R, Makumbi I, Kekitiinwa A, Ediamu T, Bazibu M, Braka F, Flannery B, Zuber P, Feikin  
467 D. Haemophilus influenzae type b conjugate vaccine is highly effective in the Ugandan routine  
468 immunization program: a case-control study. *TM & IH. Tropical medicine and international*  
469 *health* 2008;**13**(4):495-502.
- 470 20. Lewis R, Kisakye A, Gessner B, Duku C, Odipio J, Iriso R, Nansera D, Braka F, Makumbi I,  
471 Kekitiinwa A. Action for child survival: elimination of Haemophilus influenzae type b meningitis  
472 in Uganda. *Bulletin of the World Health Organization* 2008;**86**(4):292-301.
- 473 21. Lee E, Corcino M, Moore A, Garib Z, Peña S, Sánchez J, Fernández J, Feris Iglesias JAs,  
474 Flannery B. Impact of Haemophilus influenzae type b conjugate vaccine on bacterial meningitis  
475 in the Dominican Republic. *Revista panamericana de salud pública* 2008;**24**(3):161-168.
- 476 22. Fleming J, Dieye Y, Ba O, Mutombo wa Mutombo B, Diallo N, Faye P, Ba M, Cisse M, Diallo A,  
477 Slack MPE, Weiss N. Effectiveness of haemophilus influenzae type B conjugate vaccine for  
478 prevention of meningitis in Senegal. *The Pediatric infectious disease journal* 2011;**30**(5):430-432.
- 479 23. Pilishvili T, Chernyshova L, Bondarenko A, Lapiy F, Sychova I, Cohen A, Flannery B, Hajjeh R.  
480 Evaluation of the effectiveness of Haemophilus influenzae type b conjugate vaccine introduction  
481 against radiologically-confirmed hospitalized pneumonia in young children in Ukraine. *The*  
482 *journal of pediatrics* 2013;**163**(1 Suppl):S12-S18.
- 483 24. Khowaja A, Mohiuddin S, Cohen A, Mirza W, Nadeem N, Zuberi T, Salam B, Mubarak F, Rizvi B,  
484 Husen Y, Pardhan K, Khan KMA, Raza S, Zuberi H, Mustafa S, Sheikh S, Nizamani A, Lohana H,  
485 Mulholland K, Zell E, Hajjeh R, Bosan A, Zaidi AKM. Effectiveness of Haemophilus influenzae type  
486 b conjugate vaccine on radiologically-confirmed pneumonia in young children in Pakistan. *The*  
487 *journal of pediatrics* 2013;**163**(1 Suppl):S79-S85.e1.
- 488 25. Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, Nyquist AC, Gershman KA,  
489 Vazquez M, Bennett NM, Reingold A, Thomas A, Glode MP, Zell ER, Jorgensen JH, Beall B,  
490 Schuchat A. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive  
491 pneumococcal disease: a matched case-control study. *Lancet* 2006;**368**(9546):1495-502.
- 492 26. Barricarte A, Castilla J, Gil-Setas A, Torroba L, Navarro-Alonso JA, Irisarri F, Arriazu M.  
493 Effectiveness of the 7-valent pneumococcal conjugate vaccine: a population-based case-control  
494 study. *Clin Infect Dis* 2007;**44**(11):1436-41.
- 495 27. Deceuninck G, De Wals P, Boulianne N, De Serres G. Effectiveness of pneumococcal conjugate  
496 vaccine using a 2+1 infant schedule in Quebec, Canada. *Pediatr Infect Dis J* 2010;**29**(6):546-9.

- 497 28. Dominguez A, Ciruela P, Garcia-Garcia JJ, Moraga F, de Sevilla MF, Selva L, Coll F, Munoz-  
498 Almagro C, Planes AM, Codina G, Jordan I, Esteva C, Hernandez S, Soldevila N, Cardenosa N,  
499 Batalla J, Salleras L. Effectiveness of 7-valent pneumococcal conjugate vaccine in the prevention  
500 of invasive pneumococcal disease in children aged 7-59 months. A matched case-control study.  
501 *Vaccine* 2011;**29**(48):9020-5.
- 502 29. Picon T, Alonso L, Garcia-Gabarro G, Speranza N, Casas M, Arrieta F, Camou T, Rosa R, De  
503 Oliveira L, Verani J. Effectiveness of the 7-valent pneumococcal conjugate vaccine against  
504 vaccine-type invasive disease among children in Uruguay: an evaluation using existing data.  
505 *Vaccine* 2013;**31** Suppl 3:C109-C113.
- 506 30. Domingues CMAS, Verani J, Montenegro Renoier E, de Cunto Brandileone MC, Flannery B, de  
507 Oliveira L, Santos Jo, de-Moraes J. Effectiveness of ten-valent pneumococcal conjugate vaccine  
508 against invasive pneumococcal disease in Brazil: a matched case-control study. *The Lancet*  
509 *Respiratory Medicine* 2014;**2**(6):464-471.
- 510 31. Cohen C, von Mollendorf C, de Gouveia L, Naidoo N, Meiring S, Quan V, Nokeri V, Fortuin-de  
511 Smit M, Malope-Kgokong B, Moore D, Reubenson G, Moshe M, Madhi SA, Eley B, Hallbauer U,  
512 Kularatne R, Conklin L, O'Brien KL, Zell ER, Klugman K, Whitney CG, von Gottberg A, South  
513 African Invasive Pneumococcal Disease Case-Control Study G. Effectiveness of 7-valent  
514 pneumococcal conjugate vaccine against invasive pneumococcal disease in HIV-infected and -  
515 uninfected children in south africa: a matched case-control study. *Clin Infect Dis* 2014;**59**(6):808-  
516 18.
- 517 32. Madhi SA, Groome MJ, Zar HJ, Kapongo CN, Mulligan C, Nzenze S, Moore DP, Zell ER, Whitney  
518 CG, Verani JR. Effectiveness of pneumococcal conjugate vaccine against presumed bacterial  
519 pneumonia hospitalisation in HIV-uninfected South African children: a case-control study.  
520 *Thorax* 2015;**70**(12):1149-55.
- 521 33. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza  
522 in healthy children. *Cochrane Database of Systematic Reviews* 2012;**8**:CD004879-CD004879.
- 523 34. Patel M, Glass R, Desai R, Tate J, Parashar U. Fulfilling the promise of rotavirus vaccines: how far  
524 have we come since licensure? *The Lancet infectious diseases* 2012;**12**(7):561-570.
- 525 35. Boom J, Tate J, Sahni L, Rench M, Hull J, Gentsch J, Patel M, Baker C, Parashar U. Effectiveness of  
526 pentavalent rotavirus vaccine in a large urban population in the United States. *Pediatrics*  
527 2010;**125**(2):e199-e207.
- 528 36. Castilla JÂs, Beristain X, MartÃfnez-Artola Vc, NavascuÃfs A, GarcÃfa-Cenoz M, Alvarez N, Polo I,  
529 MazÃfÃ³n A, Gil Setas A, Barricarte A. Effectiveness of rotavirus vaccines in preventing cases and  
530 hospitalizations due to rotavirus gastroenteritis in Navarre, Spain. *Vaccine* 2012;**30**(3):539-543.
- 531 37. Correia J, Patel M, Nakagomi O, Montenegro FMU, Germano E, Correia N, Cuevas L, Parashar U,  
532 Cunliffe N, Nakagomi T. Effectiveness of monovalent rotavirus vaccine (Rotarix) against severe  
533 diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. *The Journal of infectious*  
534 *diseases* 2010;**201**(3):363-369.
- 535 38. Cortese M, Immergluck L, Held M, Jain S, Chan T, Grizas A, Khizer S, Barrett C, Quaye O,  
536 Mijatovic Rustempasic S, Gautam R, Bowen M, Moore J, Tate J, Parashar U, VÃfzquez M.  
537 Effectiveness of monovalent and pentavalent rotavirus vaccine. *Pediatrics* 2013;**132**(1):e25-e33.
- 538 39. de Palma O, Cruz L, Ramos H, de Baires A, Villatoro N, Pastor D, de Oliveira L, Kerin T, Bowen M,  
539 Gentsch J, Esposito D, Parashar U, Tate J, Patel M. Effectiveness of rotavirus vaccination against  
540 childhood diarrhoea in El Salvador: case-control study. *BMJ. British medical journal*  
541 2010;**340**:c2825-c2825.
- 542 40. Justino MC, Linhares AC, Lanzieri TM, Miranda Y, Mascarenhas JD, Abreu E, Guerra SF, Oliveira  
543 AS, da Silva VB, Sanchez N, Meyer N, Shafi F, Ortega-Barría E, Soriano-Gabarro M, Colindres RE.

- 544 Effectiveness of the monovalent G1P[8] human rotavirus vaccine against hospitalization for  
545 severe G2P[4] rotavirus gastroenteritis in Belem, Brazil. *Pediatr Infect Dis J* 2011;**30**(5):396-401.
- 546 41. Muhsen K, Shulman L, Kasem E, Rubinstein U, Shachter J, Kremer A, Goren S, Zilberstein I,  
547 Chodick G, Ephros M, Cohen D. Effectiveness of rotavirus vaccines for prevention of rotavirus  
548 gastroenteritis-associated hospitalizations in Israel: a case-control study. *Human vaccines*  
549 2010;**6**(6):450-454.
- 550 42. Patel M, Pedreira C, De Oliveira L, Tate J, Orozco M, Mercado J, Gonzalez A, Malespin O, Amador  
551 J, Umaña J, Balmaseda A, Perez M, Gentsch J, Kerin T, Hull J, Mijatovic S, Andrus J, Parashar U.  
552 Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among  
553 children in Nicaragua. *JAMA: the Journal of the American Medical Association*  
554 2009;**301**(21):2243-2251.
- 555 43. Patel M, Pedreira C, De Oliveira L, Umaña J, Tate J, Lopman B, Sanchez E, Reyes M, Mercado J,  
556 Gonzalez A, Perez M, Balmaceda A, Andrus J, Parashar U. Duration of protection of pentavalent  
557 rotavirus vaccination in Nicaragua. *Pediatrics* 2012;**130**(2):e365-e372.
- 558 44. Snelling TL, Andrews RM, Kirkwood CD, Culvenor S, Carapetis JR. Case-control evaluation of the  
559 effectiveness of the G1P[8] human rotavirus vaccine during an outbreak of rotavirus G2P[4]  
560 infection in central Australia. *Clin Infect Dis* 2011;**52**(2):191-9.
- 561 45. Snelling TL, Schultz R, Graham J, Roseby R, Barnes GL, Andrews RM, Carapetis JR. Rotavirus and  
562 the indigenous children of the Australian outback: monovalent vaccine effective in a high-  
563 burden setting. *Clin Infect Dis* 2009;**49**(3):428-31.
- 564 46. Staat MA, Payne DC, Donauer S, Weinberg GA, Edwards KM, Szilagyi PG, Griffin MR, Hall CB,  
565 Curns AT, Gentsch JR, Salisbury S, Fairbrother G, Parashar UD, New Vaccine Surveillance N.  
566 Effectiveness of pentavalent rotavirus vaccine against severe disease. *Pediatrics*  
567 2011;**128**(2):e267-75.
- 568 47. Ichihara MY, Rodrigues LC, Teles Santos CA, Teixeira Mda G, De Jesus SR, Alvim De Matos SM,  
569 Gagliardi Leite JP, Barreto ML. Effectiveness of rotavirus vaccine against hospitalized rotavirus  
570 diarrhea: A case-control study. *Vaccine* 2014;**32**(23):2740-7.
- 571 48. Lucas MES, Deen J, von Seidlein L, Wang X-Y, Ampuero J, Puri M, Ali M, Ansaruzzaman M, Amos  
572 J, Macuamule A, Cavailler P, Guerin P, Mahoudeau C, Kahazi Sangwa P, Chaignat C-L, Barreto A,  
573 Songane F, Clemens J. Effectiveness of mass oral cholera vaccination in Beira, Mozambique. *The*  
574 *New England journal of medicine* 2005;**352**(8):757-767.
- 575 49. Anh D, Lopez A, Thiem V, Grahek S, Duong T, Park J, Kwon H, Favorov M, Hien N, Clemens J. Use  
576 of oral cholera vaccines in an outbreak in Vietnam: a case control study. *PLoS Neglected Tropical*  
577 *Diseases* 2011;**5**(1):e1006-e1006.
- 578 50. Luquero F, Grout L, Ciglenecki I, Sakoba K, Traore B, Heile M, Diallo A, Itama C, Page A-L, Quilici  
579 M-L, Mengel M, Eiros J, Serafini M, Legros D, Grais R. Use of *Vibrio cholerae* vaccine in an  
580 outbreak in Guinea. *The New England journal of medicine* 2014;**370**(22):2111-2120.
- 581 51. Kopec JA, Esdaile JM. Bias in case-control studies. A review. *Journal of epidemiology and*  
582 *community health* 1990;**44**(3):179-186.
- 583 52. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology* 3rd edition. Philadelphia, PA Wolters  
584 Kluwer Health/Lippincott Williams & Wilkins, 2008.
- 585 53. Keogh RH, Cox DR. *Case-Control Studies*. Cambridge Cambridge University Press, 2014.
- 586 54. Madhi S, Klugman K. World Health Organisation definition of "radiologically-confirmed  
587 pneumonia" may under-estimate the true public health value of conjugate pneumococcal  
588 vaccines. *Vaccine* 2007;**25**(13):2413-2419.
- 589 55. Deutscher M, Van Beneden C, Burton D, Shultz A, Morgan O, Chamany S, Jordan H, Zhang X,  
590 Flannery B, Feikin D, Olack B, Lindblade K, Breiman R, Olsen S. Putting surveillance data into

- 591 context: the role of health care utilization surveys in understanding population burden of  
592 pneumonia in developing countries. *Journal of Epidemiology and Global Health* 2012;**2**(2):73-81.
- 593 56. Krumkamp R, Sarpong N, Kreuels B, Ehlkes L, Loag W, Schwarz N, Zeeb H, Adu Sarkodie Y, May  
594 JÅr. Health care utilization and symptom severity in Ghanaian children--a cross-sectional study.  
595 *PLoS ONE* 2013;**8**(11):e80598-e80598.
- 596 57. Omore R, O'Reilly C, Williamson J, Moke F, Were V, Farag T, van Eijk A, Kotloff K, Levine M, Obor  
597 D, Odhiambo F, Vulule J, Laserson K, Mintz E, Breiman R. Health care-seeking behavior during  
598 childhood diarrheal illness: results of health care utilization and attitudes surveys of caretakers  
599 in western Kenya, 2007-2010. *The American journal of tropical medicine and hygiene* 2013;**89**(1  
600 Suppl):29-40.
- 601 58. Immunization coverage cluster survey -- Reference manual. Department of Immunization,  
602 Vaccines and Biologicals, World Health Organization, 2005.
- 603 59. Kelly K, Maxwell SE, Rausch RJ. Obtaining power or obtaining precision: delineating methods of  
604 sample-size planning. *Eval Health Prof*;3(26):258-287.
- 605 60. Mast TC, Khawaja S, Espinoza F, Paniagua M, Del Carmen LP, Cardellino A, Sanchez E. Case-  
606 control study of the effectiveness of vaccination with pentavalent rotavirus vaccine in  
607 Nicaragua. *Pediatr Infect Dis J* 2011;**30**(11):e209-15.
- 608 61. O'Loughlin R, Edmond K, Mangtani P, Cohen A, Shetty S, Hajjeh R, Mulholland K. Methodology  
609 and measurement of the effectiveness of Haemophilus influenzae type b vaccine: systematic  
610 review. *Vaccine* 2010;**28**(38):6128-6136.
- 611 62. Grimes D, Schulz K. Compared to what? Finding controls for case-control studies. *Lancet*  
612 (*London, England*) 2005;**365**(9468):1429-1433.
- 613 63. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology 3rd edition. Philadelphia, PA Wolters  
614 Kluwer Health/Lippincott Williams & Wilkins, 2008;111-127.
- 615 64. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control  
616 studies. I. Principles. *American journal of epidemiology* 1992;**135**(9):1019-1028.
- 617 65. Wacholder S, Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control  
618 studies. II. Types of controls. *American journal of epidemiology* 1992;**135**(9):1029-1041.
- 619 66. Domingues CMAS, Verani J, Montenegro Renoier E, de Cunto Brandileone MC, Flannery B, de  
620 Oliveira L, Santos J, de-Moraes J. Effectiveness of ten-valent pneumococcal conjugate vaccine  
621 against invasive pneumococcal disease in Brazil: a matched case-control study. *The Lancet*  
622 *Respiratory Medicine* 2014;**2**(6):464-471.
- 623 67. Baqui A, El Arifeen S, Saha S, Persson L, Zaman K, Gessner B, Moulton L, Black R, Santosham M.  
624 Effectiveness of Haemophilus influenzae type B conjugate vaccine on prevention of pneumonia  
625 and meningitis in Bangladeshi children: a case-control study. *The Pediatric infectious disease*  
626 *journal* 2007;**26**(7):565-571.
- 627 68. de la Hoz F, Higuera A, Di Fabio J, Luna M, Naranjo A, de la Luz Valencia Ma, Pastor D, Hall A.  
628 Effectiveness of Haemophilus influenzae type b vaccination against bacterial pneumonia in  
629 Colombia. *Vaccine* 2004;**23**(1):36-42.
- 630 69. Dantas OM, Ximenes RA, de Albuquerque Mde F, Montarroyos UR, de Souza WV, Varejao P,  
631 Rodrigues LC. Selection bias: neighbourhood controls and controls selected from those  
632 presenting to a Health Unit in a case control study of efficacy of BCG revaccination. *BMC Med*  
633 *Res Methodol* 2007;**7**:11.
- 634 70. De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy  
635 and precision of vaccine efficacy estimates compared to the gold standard of randomised  
636 placebo-controlled clinical trials. *Euro surveillance* 2013;**18**(37).
- 637 71. Jackson M, Nelson J. The test-negative design for estimating influenza vaccine effectiveness.  
638 *Vaccine* 2013;**31**(17):2165-2168.



639 72. Foppa I, Haber M, Ferdinands J, Shay D. The case test-negative design for studies of the  
640 effectiveness of influenza vaccine. *Vaccine* 2013;**31**(30):3104-3109.

641 73. Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an  
642 alternative method to estimate the efficacy of pneumococcal vaccine. *The New England journal*  
643 *of medicine* 1980;**303**(10):549-552.

644 74. Andrews N, Waight P, Borrow R, Ladhani S, George R, Slack MPE, Miller E. Using the indirect  
645 cohort design to estimate the effectiveness of the seven valent pneumococcal conjugate vaccine  
646 in England and Wales. *PLoS ONE* 2011;**6**(12):e28435-e28435.

647 75. Ruckinger S, van der Linden M, Reinert R, von Kries R. Efficacy of 7-valent pneumococcal  
648 conjugate vaccination in Germany: An analysis using the indirect cohort method. *Vaccine*  
649 2010;**28**(31):5012-5016.

650 76. De Serres G, Pilishvili T, Link Gelles R, Reingold A, Gershman K, Petit S, Farley M, Harrison L,  
651 Lynfield R, Bennett N, Baumbach J, Thomas A, Schaffner W, Beall B, Whitney C, Moore M. Use of  
652 surveillance data to estimate the effectiveness of the 7-valent conjugate pneumococcal vaccine  
653 in children less than 5 years of age over a 9 year period. *Vaccine* 2012;**30**(27):4067-4072.

654 77. Verani JR, Domingues CM, Moraes JC, Brazilian Pneumococcal Conjugate Vaccine Effectiveness  
655 Study G. Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness  
656 against vaccine-type and vaccine-related invasive pneumococcal disease. *Vaccine*  
657 2015;**33**(46):6145-8.

658 78. Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, Orenstein WA.  
659 Methodologic issues regarding the use of three observational study designs to assess influenza  
660 vaccine effectiveness. *Int J Epidemiol* 2007;**36**(3):623-31.

661 79. Schwartz L, Halloran ME, Rowhani Rahbar A, Neuzil K, Victor J. Rotavirus vaccine effectiveness in  
662 low-income settings: An evaluation of the test-negative design. *Vaccine* 2017;**35**(1):184-190.

663 80. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal  
664 vaccination. *Lancet* 2011;**378**(9807):1962-73.

665 81. Suzuki M, Camacho A, Ariyoshi K. Potential effect of virus interference on influenza vaccine  
666 effectiveness estimates in test-negative designs. *Epidemiol Infect* 2014;**142**(12):2642-6.

667 82. Rose S, van der Laan M. Why match? Investigating matched case-control study designs with  
668 causal effect estimation. *The international journal of biostatistics* 2009;**5**(1):Article1-Article 1.

669 83. Hosmer JDW, Lemeshow S, Sturdivant RX. Logistic Regression for Matched Case-Control Studies.  
670 *Applied Logistic Regression* John Wiley & Sons, Inc., 2013;243-268.

671 84. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology 3rd edition. Philadelphia, PA Wolters  
672 Kluwer Health/Lippincott Williams & Wilkins, 2008;168-182.

673 85. Hajjeh RA, Privor Dumm L, Edmond K, O'Loughlin R, Shetty S, Griffiths UK, Bear AP, Cohen AL,  
674 Chandran A, Schuchat A, Mulholland EK, Santosham M. Supporting new vaccine introduction  
675 decisions: lessons learned from the Hib Initiative experience. *Vaccine* 2010;**28**(43):7123-7129.

676 86. Mahoney RT, Maynard JE. The introduction of new vaccines into developing countries. *Vaccine*  
677 1999;**17**(7-8):646-652.

678