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1 Selection bias introduced by informative censoring
2 in studies examining effects of vaccination in infancy
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- 18 - Analysis, survival
19 - Bias, selection
20 - Vaccination
21 - DTP vaccine
22

23 [Abstract](#)

24 Background

25 Many studies have examined ‘non-specific’ vaccine effects on infant mortality: attention has been
26 particularly drawn to diphtheria-tetanus-pertussis (DTP) vaccine, which has been proposed to be
27 associated with an increased mortality risk. Both right and left censoring are common in such
28 studies.

29 Method

30 We conducted simulation studies examining right censoring (at measles vaccination) and left
31 censoring (by excluding early follow-up) in a variety of scenarios in which confounding was and was
32 not present. We estimated both unadjusted and adjusted hazard ratios (HRs), averaged across
33 simulations.

34 Results

35 We identified scenarios in which right-censoring at measles vaccination was informative and so
36 introduced bias in the direction of a detrimental effect of DTP vaccine. In some, but not all,
37 situations, adjusting for confounding by health status removed the bias caused by censoring.
38 However, such adjustment will not always remove bias due to informative censoring: inverse
39 probability weighting was required in one scenario. Bias due to left censoring arose when both
40 health status and DTP vaccination were associated with mortality during the censored early follow
41 up, and was in the direction of attenuating a beneficial effect of DTP on mortality. Such bias was
42 more severe when the effect of DTP changed over time.

43 Conclusions

44 Estimates of non-specific effects of vaccines may be biased by informative right or left censoring.
45 Authors of studies estimating such effects should consider the potential for such bias, and use
46 appropriate statistical approaches to control for it. Such approaches require measurement of
47 prognostic factors that predict censoring.

48 **Keywords:** survival analysis, time-to-event data, censoring, selection bias, vaccine non-specific
49 effects, DTP vaccine

50 Key messages

1. Censoring may introduce biases in the estimation of the non-specific effect of DTP vaccine
2. Censoring at measles vaccination may lead to biased estimates of DTP effect in both directions
3. Excluding early follow-up can be problematic if the vaccine effect varies over time
4. Use of DAGs is advised to decide which potential confounders need to be considered

51

52 Background

53 Some authors have suggested that receipt of Bacillus Calmette-Guérin (BCG) vaccine and measles
54 vaccine (MV) are associated with reduced risks of mortality for reasons other than tuberculosis and
55 measles, respectively. Conversely, receipt of diphtheria-tetanus-pertussis (DTP) vaccine is postulated
56 to be associated with an increased risk of mortality beyond its effects on the diseases it targets.(1-7)
57 Such effects of vaccines on mortality beyond those on the specific diseases against which the vaccines
58 are targeted are often referred to as 'non-specific' or 'heterologous' vaccine effects. Since these
59 vaccines are administered to a large proportion of the world's children, the potential impact of non-
60 specific effects on infant mortality is substantial. Hence, much attention has been drawn to these
61 effects, in particular the possibility of a deleterious effect of DTP.

62 In a systematic review that motivated the work presented here, we aimed to integrate information
63 from primary studies (both randomized trials and observational studies) that analysed non-specific
64 effects of BCG, DTP and measles vaccines on all-cause mortality in children up to five years.(8) The
65 findings appeared to concur with the claims summarized in the previous paragraph: most studies
66 indicated that receipt of BCG and MV were associated with lower mortality and receipt of DTP was
67 associated with higher mortality. However, most of the retrieved studies were observational studies
68 and results were variable across studies, particularly for DTP. Poorly-controlled or uncontrolled
69 confounding and various types of information bias have been suggested as alternative explanations
70 for some of the findings.(9) In addition, most of these studies reported on time-to-event data, raising
71 the possibility of biases being introduced by the phenomenon known as *censoring*.

72 Time-to-event data, also known as survival data, provide information about both the occurrence of an
73 event and the time of its occurrence. The target in survival analysis is to follow up each subject from
74 the starting point until the event of interest is observed. Follow-up is said to be censored when the
75 information about the event time is incomplete.(10-12) The most commonly occurring type of
76 censoring is right censoring, where follow-up ends before the event is observed. In contrast,

77 observations are said to be left censored if follow-up starts after the time of onset of risk, such as the
78 time at which an intervention was received (sometimes referred to as 'time zero'). If participants'
79 censoring times are associated with their time to event, then censoring is said to be informative and
80 will lead to bias.(13) If participants' censoring times are statistically independent of their time to event,
81 then censoring is said to be non-informative, and does not lead to bias.

82 The vaccination sequence currently advocated by the WHO, displayed in Figure 1, recommends that
83 BCG be administered soon after birth, three DTP doses at ages 6, 10 and 14 weeks, and measles
84 vaccine between ages 9 and 12 months.(14) To isolate the effect of DTP from that of BCG and measles
85 vaccines, some analyses included in our review involved left-censoring (children were included in the
86 analysis only from a time point after most DTP vaccinations had taken place)(15, 16) and some
87 involved right censoring (follow-up was censored on receipt of measles vaccine).(17-21)

88 FIGURE 1 HERE

89 In this paper we examine the potential impact of these two types of censoring on the results of studies
90 examining non-specific effects of vaccines. We focus on estimating non-specific effects of DTP vaccine,
91 which were the most inconsistent and controversial estimates across studies in our systematic review.
92 For simplicity, we focus on administration of the first DTP dose. We start by explaining how right
93 censoring and left censoring may lead to bias by considering directed acyclic graphs (DAGs), which aim
94 to represent causal relationships between variables and provide a framework for thinking about bias.
95 We then present simulation studies that quantify the potential for bias, using plausible values for
96 effects of vaccination on mortality and of health status as a potential confounder of this relationship.

97 Right censoring

98 Right censoring arises when the event of interest is not observed within the period of follow-up
99 covered by the study. It may occur, for example, because the period of follow-up is short relative to
100 the probability of the event occurring, due to competing outcomes (e.g. death in studies looking at

101 non-fatal outcomes) or due to loss to follow-up. Several studies examining non-specific effects of
102 DTP vaccine censored children on receipt of measles vaccine.(18-22) Such censoring aims to avoid
103 any effect of MV on infant mortality biasing the estimated effect of DTP. However, vaccinated
104 children may be more likely to receive further vaccinations, for reasons including socio-economic
105 status, distance to vaccination centre, residence in areas targeted by vaccination campaigns, and
106 health status.(20, 23) Thus, DTP-vaccinated children may be more likely to receive measles vaccine
107 as well.

108 The DAGs displayed in Figure 2 display possible relationships between DTP, MV, death (D) and a
109 single potential confounder to represent health status (H). These are simplifications of the true
110 situation, for the purposes of explaining the concepts. In reality there will be many variables, both
111 measured and unmeasured, that influence vaccine uptake and mortality. Arrows between variables
112 indicate the direction of cause and effect. All DAGs include an arrow from DTP to MV to reflect the
113 assumption that receipt of DTP influences the probability of receiving MV, and a second arrow from
114 H to D to reflect the assumption that health status influences death. Except for Figure 2E, in which
115 DTP influences D via its effect on H, the absence of any paths from DTP or MV to D in these DAGs
116 reflects the situation in which there are no causal effects of DTP or MV on death. Censoring at
117 (conditioning on) MV is represented by the box around MV. The theory of causal inference
118 determines that censoring on a variable that is a common effect of (caused by) two other variables
119 induces an association between those variables in the uncensored participants.(13) Thus, censoring
120 on MV changes the association between DTP and H in Figure 2C, 2D and 2E.

121 FIGURE 2 HERE

122 In Figures 2A and 2B, censoring at MV is not expected to bias the estimated effect of DTP. In Figure 2A
123 there is no confounding (H does not influence the probability of receiving DTP or MV), so that
124 censoring at MV does not induce any association between DTP and H, or between DTP and D.
125 However, healthy infants may be more likely to be vaccinated than frail infants (23, 24) and this is

126 depicted in Figure 2B, where H confounds the association between DTP and D. Because MV is only
127 related to H and D through DTP, censoring at MV does not change the association between DTP and
128 death. Therefore, censoring is non-informative in both these scenarios.

129 Figure 2C and Figure 2D display situations in which H confounds the association between MV and D.
130 In each figure, MV is a common effect ('collider') of H and DTP, with the consequence that censoring
131 at MV will change the association between DTP and H (and hence between DTP and D) in uncensored
132 individuals. Therefore, censoring is informative in these scenarios. In Figure 2C censoring at MV
133 induces an association between DTP and D that is not present in the whole sample.

134 In Figures 2B to 2D, differences in the risk of death for vaccinated and unvaccinated children arise only
135 because health status H influences the probability of vaccination. Therefore, adjusting for H is
136 expected to remove the bias due to the confounding. In Figure 2E, by contrast, DTP affects the risk of
137 death via its effect on H, before measles vaccination (H is on the causal path from DTP to D). Therefore,
138 adjusting for H will bias the estimated effect of DTP on D towards the null.(13)

139

140 Left censoring

141 *Left censoring* ('left truncation') occurs when a period of follow-up after the start of intervention or
142 exposure starts is omitted from the analysis, typically because of delayed entry of the participants into
143 the study.(25) In most applications, an individual with left-truncated follow-up will only be included in
144 the analysis if he or she did not experience the outcome of interest during the missing follow-up
145 period. For some observational studies of the effect of DTP on infant mortality in our systematic
146 review, children were included in the analysis only from a time point after most DTP vaccinations had
147 taken place, thus excluding early follow-up after receipt of the vaccine for some children.(15, 16)

148 In a randomized trial, follow-up of participants starts at the time of allocation to the different
149 interventions, even if this includes a period before the intervention is actually implemented. Left

150 censoring (excluding early follow-up) in a randomized trial would generally be regarded as
151 inappropriate because it discards follow up time and outcome events subsequent to randomization.
152 By contrast, the absence of a clear time at which interventions were allocated means that left
153 censoring often occurs in observational (non-randomized) studies of interventions. Left censoring will
154 introduce bias in the estimated effect of an intervention if early events that are excluded by the left
155 censoring are influenced by both the intervention and by other prognostic factors.(26) For example,
156 Figure 3 depicts a situation in which children's health status H influences their risk of death D but is
157 not associated with DTP vaccination, which also influences D. The left censoring implies that early
158 deaths occurring before time point 1 (D_1) are excluded from the analysis. Because such deaths are
159 common effects of both DTP and H (e.g. D is a collider), the censoring induces an association between
160 DTP and H during the later period, and hence the effect of DTP on later death occurring between time
161 points 1 and 2 (D_2) is confounded by H.

162 FIGURE 3 HERE

163 Left censoring is also problematic when the effect of intervention changes over time, for example
164 when the proportional hazards assumption (that the intervention rate ratio is constant during follow-
165 up) is violated. This includes situations where the effect of the vaccine is lower during the first period
166 (e.g. full protective immunity is achieved one month after vaccination) and the opposite (e.g. vaccine
167 efficacy declines with time since vaccination). In such scenarios, exclusion of early events will mean
168 that the estimated intervention hazard ratio (HR) differs from the hazard ratio averaged over the
169 whole time since the start of intervention, as would be estimated in a randomized trial. For example,
170 a proportional hazards assumption would imply that the DTP HR is the same from DTP vaccination to
171 time point 1 as from time point 1 to time point 2. Exclusion of events up to time point 1 means that
172 the estimated DTP HR only reflects the effect of DTP during the interval between time points 1 and 2.

173

174 Simulation studies

175 We conducted Monte Carlo simulation studies to examine the potential influence of right and left
176 censoring when estimating the effect of DTP on death, using HRs as effect measures. In both studies,
177 we simulated cohorts of 1,000 children and generated lifetimes within a range of plausible values in
178 deprived countries, according to infant mortality rates collected by UNICEF over the last six
179 decades.(27). We scheduled administration of BCG, DTP (one dose) and measles vaccines at 0, 1.5 and
180 12 months, respectively. We set the probabilities of receiving each vaccine according to information
181 reported from studies conducted in various countries.(1, 3, 6, 28, 29) To ensure simulation errors
182 below 0.01 in all scenarios, 20,000 replicas were simulated for each condition,(30) and the effect
183 estimates for each condition were defined as the arithmetic mean of the HRs obtained across replicas.
184 All simulations were undertaken using R (v3.3.3)(31), with Cox regression models for HRs performed
185 using the survival package.(32)

186 We defined children's health status by setting 30% of children as 'frail' and the other 70% as 'healthy'.
187 Healthy children had lifetimes generated from a Weibull distribution with values of 1 and 15 for the
188 shape and scale parameters, respectively. These correspond to a median lifetime of 13.9 years, with
189 first and third quartiles of 4.3 and 20.8 years and a proportion of deaths before 5 years slightly above
190 0.28. Frail children had rates of death four times greater than healthy children, throughout follow-up.
191 This was achieved by using Weibull distribution scale parameter 3.75.(10) We used the same strategy
192 in the scenarios where a vaccine effect was introduced.

193 Right censoring simulation

194 We conducted simulations corresponding to the scenarios depicted in Figures 2A to 2E, by setting
195 conditions with no confounding as well as with confounding at DTP vaccination, at MV, or both. In
196 different scenarios, the probability of vaccination with DTP was influenced or not by health status H,
197 while probabilities of MV were influenced by H or by prior receipt of DTP. We present the vaccination
198 probabilities in Table 1.

199 TABLE 1 HERE

200 In scenarios 2A to 2D DTP vaccination did not influence D (causal HR=1), while in scenario E DTP
201 reduced death rates (causal HR=0.5). The effect of DTP on death between 1.5 and 60 months was
202 estimated both with and without censoring at measles vaccination, and both with and without
203 adjustment for H. Follow-up was censored at age 60 months. For scenario E, we performed an
204 additional analysis in which we corrected bias due to left censoring by estimating the probability of
205 remaining uncensored based on H and DTP, and weighting the analysis based on the inverse of these
206 probabilities.

207 Left censoring simulation

208 For this simulation study, both frail and healthy children had a probability of DTP vaccination of 0.5,
209 ignoring other vaccination events. We defined effects of DTP vaccine on death from 0-6 months (early
210 effect) and from 7-12 months (late effect). We considered large (HR=0.5) and small (HR=0.8) effects:
211 and the combination of two values and two follow-up periods resulted in four different scenarios: (A)
212 HR=0.5 throughout follow-up; (B) larger early effect (HR=0.5) and smaller late effect (HR=0.8); (C)
213 smaller early effect (HR=0.8) and larger late effect (HR=0.5); and (D) HR=0.8 throughout follow-up.
214 The effect of DTP on death after 12 months of follow-up, was estimated using both the complete
215 follow-up period (uncensored) and excluding the first 6 months of follow-up (left censoring). It is
216 pertinent to note here that effect measures such as odds ratios and hazard ratios are 'non-collapsible':
217 even in the absence of confounding the conditional odds ratios within strata (e.g. healthy and frail
218 children) are further from the null than marginal (overall) odds ratio. This property implies that, even
219 in the absence of confounding and selection bias, when odds ratios and hazard ratios are used to
220 estimate an association across strata the average of the within-stratum (conditional) estimates will
221 not match the value of a single estimate across strata (marginal estimate).

222

223 Results of simulation studies

224 Table 2 shows results of the right censoring simulations. Average HRs were close to 1.0 (true causal
225 effect) in the unconfounded scenario 2A, in which censoring was not informative. When
226 confounding at DTP vaccination was introduced (scenario 2B), the average unadjusted HR, either
227 with or without right censoring, suggested a beneficial effect of DTP vaccine (HR approximately
228 0.54). For scenarios 2C and 2D, censoring at MV is informative. For scenario 2C, the analysis without
229 censoring at MV yielded an average unadjusted HR close to one, whereas the analysis censoring at
230 MV estimated DTP to be harmful (HR=1.324). For scenario 2D, in which H confounds the effects of
231 both DTP and MV, the unadjusted HRs suggested that DTP reduced mortality, but the informative
232 censoring attenuated this beneficial effect towards the null.

233 TABLE 2 HERE

234 For scenarios 2B to 2D, average HRs for DTP were close to 1.0 (the true causal effect) after adjusting
235 for health status H. This is because adjusting for H controls the confounding, and also blocks the
236 backdoor path from H to DTP that is introduced by right censoring on MV. By contrast, adjusting for
237 H did not correct the bias caused by informative censoring in scenario 2E. In this scenario there is no
238 confounding, so that the unadjusted analysis without right censoring is unbiased (HR=0.5). Right
239 censoring at MV yields a biased unadjusted HR of 0.66. Adjusting for H, which is on the causal
240 pathway from DTP to D, introduced bias in the uncensored analysis (HR=0.536) and did not
241 completely remove the bias in the censored analysis (HR=0.553). In this scenario an analysis that is
242 weighted by the inverse probabilities of remaining uncensored is required for unbiased estimation of
243 the effect of DTP vaccine in the presence of right censoring (13): the average HR from analyses
244 employing this approach was 0.496.

245 TABLE 3 HERE

246 Results from the left censoring simulation are presented in Table 3. In scenarios A and D, the effect
247 of DTP on D is constant over time. The adjusted analyses in these scenarios (both with and without
248 left censoring) yielded estimates that are close to the true HR. The average unadjusted HRs in the
249 uncensored analysis (0.521 and 0.818 for true HRs 0.5 and 0.8, respectively) are closer to the null
250 than the true early and late HRs. These differences are *not* due to bias – they arise because the
251 simulation analyses were stratified within time period and because the ‘non-collapsibility’ of HRs
252 implies that, in the absence of confounding, ‘marginal’ HR averaged across strata are closer to the
253 null than ‘conditional’ HR within strata.(11, 13) In the presence of left censoring, the unadjusted HR
254 were further biased towards the null (average HRs 0.539 and 0.829 for true HRs 0.5 and 0.8,
255 respectively), because the left censoring induces an association between H and DTP).

256 In scenarios B and C, where the true HR varies over time, the results in the absence of censoring
257 were an average of the true early and late HR, with the unadjusted estimates closer to the null
258 because of the non-collapsibility of the HR. In the presence of left-censoring, the adjusted HR was
259 closer to the true late HR, while the unadjusted HR was biased towards the null (compared with the
260 true late HR) because the left censoring induces an association between H and DTP.

261 Discussion

262 In the absence of evidence from randomized trials, cohort studies comparing vaccinated with
263 unvaccinated children provide an opportunity to study ‘non-specific’ effects of vaccines. Confounding,
264 together with different forms of selection and information biases, have been suggested as possible
265 explanations for inconsistent findings from studies of such effects.(9, 33) Statistical analyses
266 examining non-specific vaccine effects may be subject to both right and left censoring that arises
267 because investigators wish to focus on a single vaccine within the WHO-recommended vaccination
268 sequence. We used simulated data to explore the impact of censoring at measles vaccination (right
269 censoring) and exclusion of early follow-up (left censoring) on estimates of the effect of DTP vaccine,
270 which has been found to increase infant mortality in some studies.(8) Analyses of these simulated data

271 show that both left and right censoring may bias estimates of non-specific vaccine effects. In some
272 circumstances, such bias may be adjusted for by controlling for prognostic factors (such as children's
273 underlying health status) that predict censoring. However, conventional adjustment using regression
274 models does not necessarily correct bias due to left or right censoring, even if the whole set of
275 confounding factors can be identified and measured (which is unlikely in practice). This is because
276 predictors of censoring may also be on the causal pathway from vaccination to the outcome (as is the
277 case in our scenario E), in which case adjustment through regression modelling is not appropriate to
278 deal with the bias caused by censoring (alternative methods such as inverse probability weighting are
279 required). Although many of our simulations assumed no effect of DTP vaccine on mortality, our
280 findings apply in the presence of an effect (in either direction). This is because the distortion created
281 by selection bias may induce an apparent vaccine effect when none is present, or may alter the
282 estimated magnitude (and even the direction) of a vaccine effect when it is present.

283 Unadjusted estimates of the effect of DTP that censor children on receipt of measles vaccine may be
284 biased towards a beneficial DTP vaccine if healthier children are more likely to receive DTP vaccine.
285 However, if healthier children are more likely to receive measles vaccine, then the right censoring will
286 bias estimated effects towards a harmful effect of DTP vaccine. We showed that such bias can be
287 removed by fully adjusting for the confounding but, importantly, this depends on perfectly measuring
288 prognostic variables such as health status (defined as a binary variable in our simulations) that predict
289 receipt of measles vaccine. Further, such adjustment does not remove bias if such variables are on the
290 causal pathway from DTP vaccination to measles vaccination. We found that in such a situation,
291 weighting by the inverse of the probability of remaining uncensored would remove the bias.(13)

292 The potential for bias due to left censoring (exclusion of early follow up) has received little
293 consideration in studies of non-specific vaccine effects. Our simulation study examining left censoring
294 showed that, even in the absence of confounding of the effect of DTP on mortality, left censoring will
295 lead to bias if a prognostic factor such as health status predicts both early and later deaths. Such bias

296 could be controlled by adjusting for such prognostic factors, provided that they had been perfectly
297 measured. Left censoring also implies that estimated vaccine effects are based only on later follow up,
298 so that they cannot be compared with the effects that would be observed in a randomized trial (in
299 which participants are analysed from the time of assignment to intervention groups. In practice, left
300 censoring is best avoided by starting follow-up for each individual at the time at which they are
301 vaccinated, or eligible for vaccination but not vaccinated. Interpretation of our simulation study of left
302 censoring was complicated by the 'non-collapsibility' of the HR, which is reflected in the difference
303 between unadjusted and adjusted estimates, even in the absence of confounding. Non-collapsibility
304 has been documented for odds ratios (13) as well as effect measures that are used for time-to-event
305 data.(11)

306 Our findings have important implications for studies assessing non-specific effects of vaccines. In our
307 recent systematic review, all studies examining the effect of DTP on all-cause mortality in childhood
308 were observational.(34) It is plausible that frail children are less likely to receive vaccination than
309 healthy children.(23, 24) Furthermore, recent research suggests that a substantial part of the
310 population in West African countries – where most studies showing a deleterious effect for DTP have
311 been conducted – are suspicious about the effects of vaccines (35, 36): this might differentially affect
312 vaccination coverage among healthy and frail infants. Thus, censoring at measles vaccination, which
313 is presented in some studies as the primary analysis (or even the only analysis reported), may lead to
314 bias through the mechanisms examined in our studies of right censoring. Future such studies should
315 consider whether prognostic factors (such as health status in our simulations) may predict both
316 measles vaccination and mortality. If this is the case, such factors should be measured and their effects
317 adjusted for using appropriate statistical methods. Similarly, the potential for bias due to left censoring
318 (exclusion of early follow up) should be considered. Directed acyclic graphs (DAGs) can be useful to
319 clarify assumptions about censoring mechanisms, and choice of appropriate statistical analyses.

320 Our results do not necessarily explain the findings of an adverse effect of DTP vaccine on mortality
321 reported by a number of studies that were included in our systematic review.(8) The biases observed
322 in our simulation studies are probably too small to account fully for the inconsistent effect estimates
323 reported in this field. Future empirical studies are warranted to clarify aspects such as the magnitude
324 and direction of the non-specific effects of DTP and the impact of the vaccination sequence. Given the
325 practical challenges of identifying and perfectly measuring all relevant confounders in this context,
326 randomized controlled trials examining the non-specific effects of DTP vaccine (where ethically
327 acceptable) have the potential to provide valuable insights. Nonetheless, randomized trials may suffer
328 from selection bias due to right censoring, if the risk of the outcome differs between participants who
329 were and were not lost to follow up.

330 To conclude, the scenarios and results that we presented in this paper illustrate the potential for a
331 type of bias that has been insufficiently considered to date. Authors of studies estimating non-specific
332 vaccine effects should consider the potential for selection biases introduced by right and left censoring
333 and, if possible, use appropriate statistical approaches to control for them. Such approaches require
334 measurement of prognostic factors that predict censoring.

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340

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434

435

436 Tables

437 Table 1. Probabilities of vaccination set for the right censoring simulation

Scenario	Health	P(DTP BCG)	P(DTP no BCG)	P(MV DTP)	P(MV no DTP)
A. No confounding	Frail	0.85	0.7	0.7	0.4
	Healthy	0.85	0.7	0.7	0.4
B. Confounding DTP	Frail	0.65	0.5	0.7	0.4
	Healthy	0.95	0.8	0.7	0.4
C. Confounding MV	Frail	0.85	0.7	0.3	0.1
	Healthy	0.85	0.7	0.9	0.5
D. Confounding DTP & MV	Frail	0.65	0.5	0.3	0.1
	Healthy	0.95	0.8	0.9	0.5
DTP effect on death	Frail	0.85	0.7	0.3	0.1
	Healthy	0.85	0.7	0.9	0.5

438

439 Risk of death within the first 5 years of life was 0.28 for healthy children and 0.74 for frail children,
 440 respectively. Probability of BCG vaccination was 0.85 for both frail and healthy children across all
 441 scenarios

442

443

444 Table 2. Average hazard ratios (HR) for the effect of DTP on mortality, in the right censoring
 445 simulation studies.

Scenario	True HR	Unadjusted HR		Adjusted HR	
		No censoring	Right censoring*	No censoring	Right censoring*
A - Unconfounded	1.0	1.003	1.004	1.002	1.004
B – Confounding at DTP	1.0	0.539	0.540	1.002	1.003
C – Confounding at MV	1.0	1.004	1.324	1.003	1.002
D – Confounding at DTP and MV	1.0	0.539	0.728	1.001	1.001
E – Prior effect of DTP	0.5	0.506	0.660	0.536	0.553

446 DTP: diphtheria-tetanus-pertussis vaccine; MV: measles vaccine;

447 *Right censoring is at the time of MV.

448

449 Table 3. Average hazard ratios (HR) for the effect of DTP on mortality, in the left censoring
 450 simulation studies.

Scenario	True early HR	True late HR	Unadjusted HR		Adjusted HR	
			No censoring	Left censoring*	No censoring	Left censoring*
A	0.5	0.5	0.521	0.539	0.505	0.506
B	0.5	0.8	0.662	0.845	0.644	0.809
C	0.8	0.5	0.678	0.527	0.668	0.505
D	0.8	0.8	0.818	0.829	0.808	0.809

451 *Left censoring is at 6 months (the end of the early period after DTP vaccination)

452

453

454 Figures



455

456 Figure 1. Vaccination sequence recommended by WHO at present

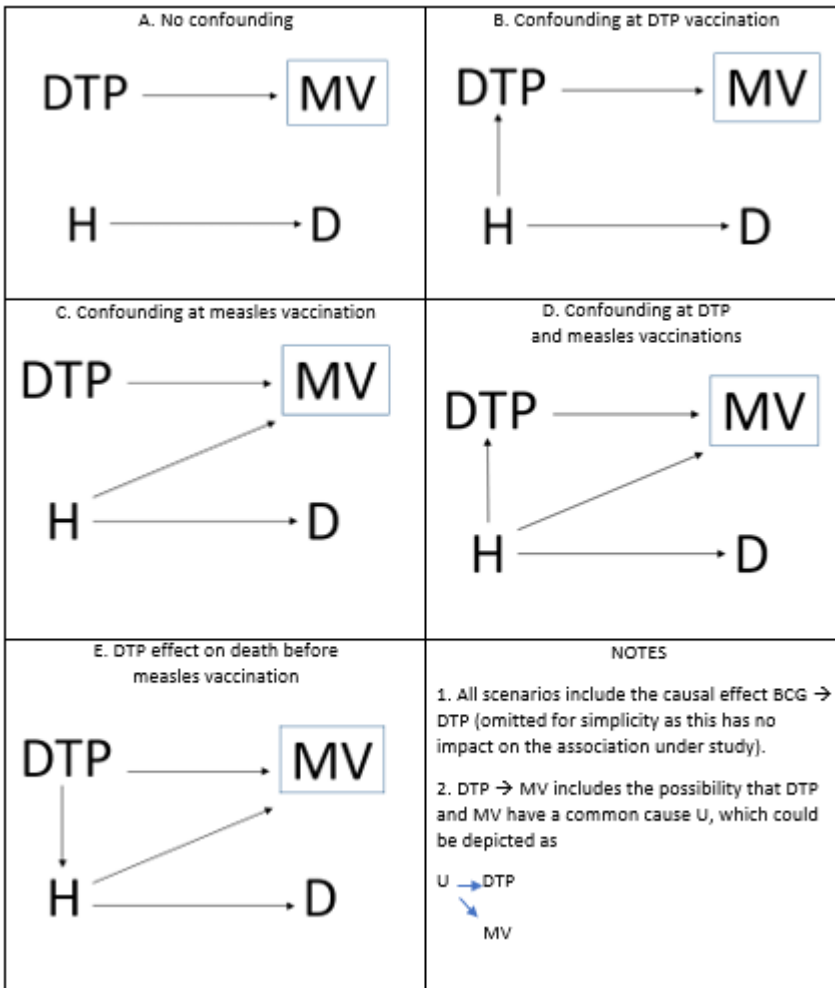
457 Footnote: BCG: Bacillus Calmette-Guérin; DTP: diphtheria-tetanus-pertussis (1st, 2nd and 3rd dose);

458 MV: measles vaccine

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463 Figure 2. Non-informative and informative right censoring using DAGs

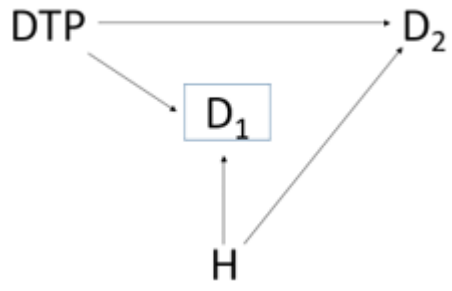
464 Footnote: DTP: diphtheria-tetanus-pertussis (1st dose); MV: measles vaccine; H: health status; D:

465 death; Boxes indicate selection (censoring) of follow-up time according to the boxed variable

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469

470 Figure 3. DAG for left censoring

471 Footnote: DTP: diphtheria-tetanus-pertussis (1st dose); H: health status; D₁: death at time point 1; D₂:

472 death at time point 2

473