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Selection bias introduced by informative censoring in studies examining effects of vaccination in infancy

José A López-López, Ph.D.[1,2]

Jonathan AC Sterne, Ph.D.[1]

Julian PT Higgins, Ph.D.[1]

[1]Department of Population Health Sciences, Bristol Medical School, University of Bristol, UK

[2]Department of Basic Psychology & Methodology, Faculty of Psychology, University of Murcia, Spain

Correspondence to: Dr. José Antonio López-López, josealopezlopez@um.es. , Tel. +34 86888 4574, Department of Basic Psychology & Methodology, Faculty of Psychology, University of Murcia, Espinardo Campus, Postcode 30100, Murcia (Spain)

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- Bias, selection
- Vaccination
- DTP vaccine

Abstract

Background

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

Method

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

Results

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

Conclusions

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

Keywords: survival analysis, time-to-event data, censoring, selection bias, vaccine non-specific 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

Background

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

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

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

4

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

Simulation studies

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

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

Right censoring simulation

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

Results of simulation studies

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

TABLE 2 HERE

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

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

13

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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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

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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)

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454 Figures

455

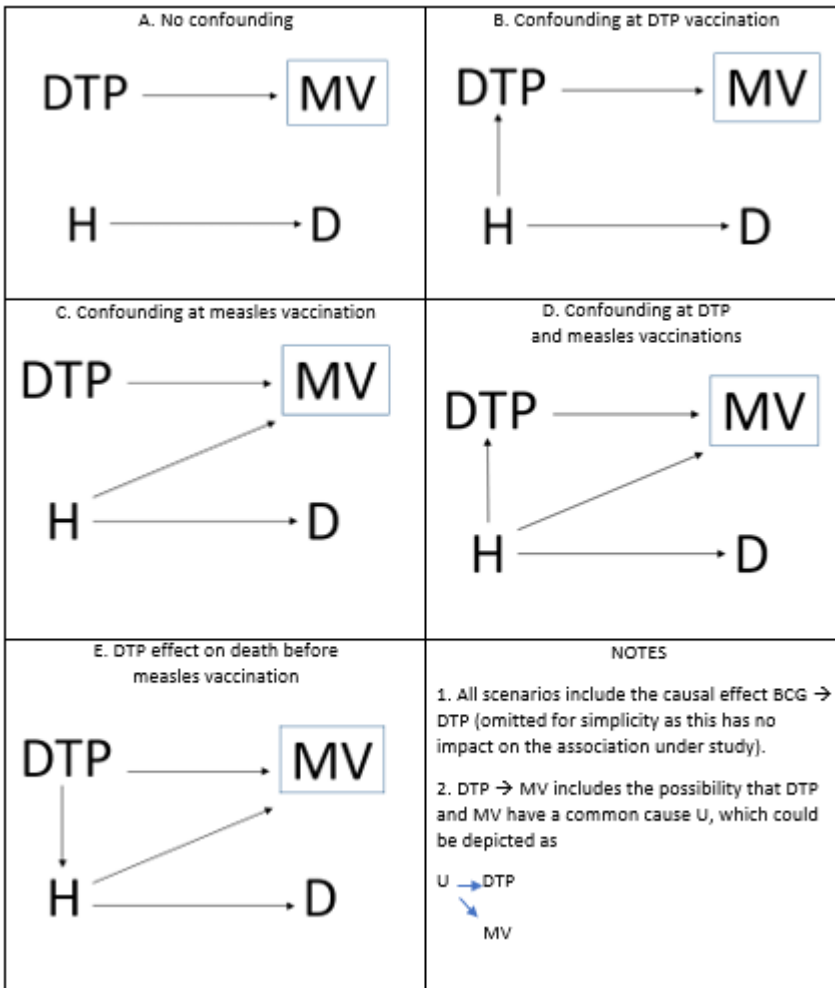456 Figure 1. Vaccination sequence recommended by WHO at present

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

458 MV: measles vaccine

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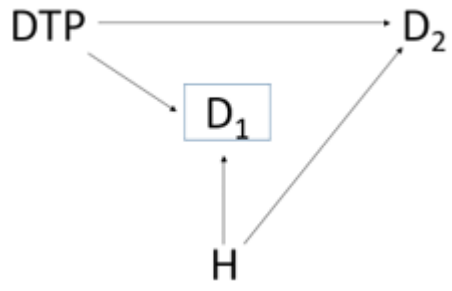Figure 2. Non-informative and informative right censoring using DAGs

Footnote: DTP: diphtheria-tetanus-pertussis (1st dose); MV: measles vaccine; H: health status; D: death; Boxes indicate selection (censoring) of follow-up time according to the boxed variable

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470   Figure 3. DAG for left censoring

471   Footnote: DTP: diphtheria-tetanus-pertussis (1st dose); H: health status; D_1: death at time point 1; D_2:

472   death at time point 2

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