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Reduced Mortality After Oral Polio Vaccination and Increased Mortality After Diphtheria-tetanus-pertussis Vaccination in Children in a Low-income Setting

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ABSTRACT

Purpose: The diphtheria-tetanus-pertussis vaccine (DTP) and oral polio vaccine (OPV) were introduced in children 3 of 5 months of age in 1981–1983 in Bandim, in the capital of Guinea-Bissau. Because DTP has been linked to deleterious nonspecific effects (NSEs) and OPV to beneficial NSEs, we followed up this cohort to 3 years of age and examined the effects of DTP with OPV on all-cause mortality and the interactions of DTP and OPV with the measles vaccine (MV).

Methods: DTP and OPV were offered at 3 monthly community weighing sessions. Vaccination groups were defined by the last vaccine received. We compared overall mortality for different groups in Cox proportional hazards regression models, reporting hazards ratios (HRs) with 95% CIs.

Findings: The study cohort included 1491 children born in Bandim from December 1980 to December 1983. From 3 to 35 months of age, with censoring for MV, children vaccinated with DTP and/or OPV had higher mortality than both unvaccinated children (HR = 1.66; 95% CI, 1.03–2.69) and OPV-only vaccinated children (HR = 2.81; 95% CI, 1.02–7.69); DTP-only vaccinated children had higher mortality than OPV-only vaccinated children (HR = 3.38; 95% CI, 1.15–9.93). In the age group of 3–8 months, before MV is administered, DTP-only vaccination was associated with a higher mortality than DTP with OPV (HR = 3.38; 95% CI, 1.59–7.20). Between 9 and 35 months of age, when MV is given, DTP-vaccinated and MV-unvaccinated children had higher mortality (HR = 2.76; 95% CI, 1.36–5.59) than children who had received MV after DTP, and among children who received DTP with MV or after MV, DTP-only vaccination was associated with a higher mortality than DTP with OPV (HR = 6.25; 95% CI, 2.55–15.37).

Implications: Because the 2 vaccines had differential effects and the healthiest children were vaccinated first, selection biases are unlikely to explain the estimated impact on child survival. OPV had beneficial NSEs, and administration of OPV with DTP may have reduced the negative effects of DTP. (Clin Ther. 2021;43:172–184) © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: child mortality, diphtheria-tetanus-pertussis vaccine, DTP, measles vaccine, non-specific effects of vaccines, oral polio vaccine.

INTRODUCTION

The effect of vaccines on overall survival had not been assessed in randomized clinical trials (RCTs) when the Expanded Program on Immunization was initiated in...
1974. The disease-protective effects were known; effects on survival were assumed to be proportional to the burden of infection. Hence, the main interest was at which age to vaccinate. However, subsequent studies of the introduction of measles vaccine (MV) suggested that the MV had beneficial nonspecific effects (NSEs) on child survival (ie, effects on survival not explained by prevention of the vaccine-targeted disease). The World Health Organization (WHO) recently sponsored a review of the potential NSEs of the BCG vaccine, diphtheria-tetanus-pertussis vaccine (DTP), and MV for child mortality in low-income countries. BCG and MV had beneficial NSEs. The point estimate for DTP was in the opposite direction. Although protective against the 3 target diseases, DTP apparently increased susceptibility to unrelated infections. Other nonlive vaccines may also be associated with increased mortality. OPV was not examined. There are surprisingly few studies of OPV and DTP and child survival in the medical literature. We have data from 40 years ago when OPV and DTP were introduced in Guinea-Bissau in the 1980s. Few sites have similar data, so we have gone back to examine the natural experiment of introducing DTP and OPV. In an urban area, weighing sessions were organized every 3 months to identify malnourished children. When vaccines became available in June 1981, OPV and DTP were offered from 3 months of age in connection with the weighing sessions. Inadvertently, this created a natural experiment among 3- to 5-month-old children; some received vaccines when just 3 months old, whereas others were nearly 6 months old before they were vaccinated. Thus, allocation was determined by birthdays and the dates of weighing sessions and not by selection biases. In this natural experiment, DTP-vaccinated children had higher mortality than children not yet vaccinated with DTP from 3 to 5 months of age. We examine the effects of OPV and DTP up to 3 years of age in the same cohort. After 6 months of age, the unvaccinated group was increasingly composed of children who had not been vaccinated because they were frail or malnourished or had traveled to rural areas. Because most children were subsequently vaccinated with MV, we also examined possible interactions between DTP and OPV with MV. Because there are plans to stop OPV globally in 2024, we have particularly tried to assess the NSEs of OPV on child survival.

METHODS

Demographic Surveillance

Bandim Health Project (BHP) was started in 1978 in an urban district. In 1978–1979, mortality among children younger than 5 years was nearly 500 per 1000. Malnutrition was assumed to be the main cause; BHP was initiated to determine why children were malnourished. However, severe malnutrition was not evident, and to understand the high mortality, we started population follow-up. Four health workers identified pregnant women, encouraged women to attend antenatal clinics, and followed up children younger than 3 years with anthropometric measurements. Each health care worker supervised 2 subdistricts; they kept lists of pregnant women and children younger than 3 years. BHP had no computerized registration system until 1990 but kept an A5 BHP card with weights and vaccination dates for each child. Growth cards were kept by the mother. The study of nutritional status was planned by the Swedish Agency for Research Collaboration and the Ministry of Health in Guinea-Bissau.

Anthropometry

The health care workers arranged 3 monthly weighing sessions in each subdistrict. Mothers were notified before a community weighing. The following morning, the child’s weight was measured and noted on the BHP card.

Vaccinations

BHP organized MV campaigns in December 1979 and December 1980. In June 1981, BHP started to provide vaccines at the weighing sessions. A nurse from the health center followed the weighing team and vaccinated eligible children. DTP and OPV were provided to children from 3 months of age and MV to children from 9 months of age. OPV was not given at birth. Doses of DTP and OPV could be given with 1-month intervals, but because we only arranged quarterly weighing sessions, most children had longer intervals. In several periods, either OPV or DTP was missing. BCG was rarely provided because nurses were not trained to administer intradermal vaccinations.

An expatriate nurse of the supervising field staff sometimes organized catch-up vaccination sessions without weighing, but vaccinations were noted on BHP cards. Both nurses and mothers thought that
sick children should not be vaccinated; BHP cards often indicated that the child was sick, malnourished, or orphan to explain why an eligible child had not been vaccinated at a weighing session.

Data Control
A computerized system became available in 1990–1991; weights and vaccination dates from the BHP cards were entered. For the present analysis, dates of visits, weights, and vaccination dates were checked against the original cards (Figure 1). As described previously a few cards could not be found.16

Study Cohort
We included children born December 3, 1980, to December 31, 1983. The vaccination program started June 2, 1981.16 Children who never attended any weighing session were not included as unvaccinated. We excluded orphans because they were not breastfed and likely to have different care. Children were included from 91 days of age if examined before 3 months of age. If first seen after 3 months, they were included from the date seen (Figure 2). DTP and OPV were not administered at other health centers; follow-up time therefore counted as

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**Figure 1.** Flowchart of study population and children included in the analyses. Numbers in parentheses indicate number of death. In the previous analysis,16 1452 children were registered before date of birth plus 183 days.
unvaccinated until BHP administered DTP or OPV (Figure 2). Time as unvaccinated also came from children not seen at 3–5 months but seen before 3 months of age (Figure 2). Hence, DTP- and OPV-vaccinated and unvaccinated children were from the same cohort born in Bandim; their randomization to the DTP/OPV vaccination group or DTP/OPV not yet vaccinated group depended on birthdate, timing of weighing sessions, and traveling. The death of a traveling child could usually be discovered from other members of the family who remained in the study area.

The 3- to 5-month age group corresponds to the natural experiment with unbiased allocation to vaccination.16 After 6 months, most unvaccinated children were frail children who had been weighed but not vaccinated or who had traveled.

Because of the lack of vaccines, some children received DTP-only or OPV-only vaccination.16 Traveling patterns did not differ between children who had received DTP1 and OPV1 or DTP1 only, and these groups were equally likely to receive subsequent vaccinations (data not shown).

This cohort born between December 1980 and December 1983 is entirely different from the cohort of children aged 6–35 months born between June 1978 and December 1980, which we have described elsewhere.13

### Statistical Analysis

DTP and OPV vaccinations started on June 2, 1981. Groups defined by the most recent vaccination(s) were compared using Cox proportional hazards regression models with age as the underlying time; proportional hazard assumptions were tested using the Schoenfeld residuals test and visual inspection of the cumulative hazard ratios (HRs). A few children had received BCG vaccine without documentation at the maternity ward because they had a BCG scar but no vaccination card, and BCG vaccinations were therefore ignored in the analyses. In a sensitivity analysis, we censored the children who had documented BCG vaccination. Although this reduced the power of the study, it did not change the estimates (data not shown).

To avoid survival bias, we used a landmark approach20; hence, vaccination status was only updated from the day the information was collected.

We conducted 3 main analyses. First, we compared DTP and/or OPV-vaccinated with unvaccinated children in the 3- to 35-month period; children were censored when known to have received MV. Second, we conducted an analysis between 3 and 8 months of age before children receive MV. Third, we examined whether DTP and OPV interacted with MV; this

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**Figure 2.** Natural variation in the timing of vaccination.
analysis included only the 9- to 35-month age group. Because vaccine effects often differ by sex, we present main analyses by sex.

Control for confounders was conducted in the 3- to 35-month age group. Subdistrict, ethnic group, and twinning did not change results. Control for year of birth slightly increased the HR of DTP-vaccinated compared with unvaccinated children. There was no clustering of deaths, and control for season did not change the estimates (data not shown). The WHO z score for weight for age (WAZ) was used to assess nutritional status. However, we did not adjust for WAZ because most unvaccinated children had traveled and had therefore not been weighed at a similar age as the vaccinated children. In the comparison of vaccinated groups, the last observation of WAZ was carried forward if an observation was missing.

RESULTS
DTP and OPV
A total of 1184 children were included in the analysis of the 6- to 35-month age group (Figure 1). The vaccination coverage is indicated in Supplemental Table I; 95% received DTP1 and OPV1 before 3 years of age, but coverage for the third dose was approximately 80%. The groups did not differ with respect to background factors, such as birthweight and weight before 6 months of age (Table I). At 6–8 months, WAZ was better for children who had received DTP and OPV, DTP only, or OPV only than for children who remained unvaccinated after participating in a weighing session. After 9 months of age, there was no clear difference in nutritional status measured by WAZ. Background factors after 12 months of age are listed in Supplemental Table II; unvaccinated children participated in fewer weighing sessions, reflecting that they traveled more.

In the first analysis, with censoring for MV, the DTP- and/or OPV-vaccinated children had a HR of 1.22 (95% CI, 0.73–2.04) between 6 and 35 months of age compared with unvaccinated children. Between 3 and 35 months, the HR was 1.66 (95% CI, 1.03–2.69) (Table II): 2.13 (95% CI, 1.00–4.54) for girls and 1.43 (95% CI, 0.78–2.59) for boys (Supplemental Table II). The results for different age groups have been visually presented in Figure 3 (Supplemental Figure 1). DTP- and/or OPV-vaccinated children had also higher mortality than OPV-only vaccinated children (HR = 2.81; 95% CI, 1.02–7.69), and DTP-only vaccination was associated with a higher mortality than OPV-only vaccination (HR = 3.38; 95% CI, 1.15–9.93) (Table II). Adjusting for WAZ, these HRs were 2.89 (95% CI, 1.06–7.94) and 3.33 (95% CI, 1.13–9.79), respectively.

Both analyses with OPV only as the comparator (Table II) failed the Schoenfeld test of the proportional hazards assumption. Visual inspection of the cumulative HRs and the partitions presented in Table II indicates that this could be explained by the estimated HR for DTP and OPV versus OPV being larger at ages 3–8 years than at ages 9–35 months although >1 in both intervals (HR not defined at 3–8 months because of no OPV deaths; HR = 2.08; 95% CI, 0.74–5.85 at 9–35 months). Hence, the cumulative HRs of the groups having received DTP and OPV and OPV only did not cross and stayed apart (Figure 4).

In the second analysis of children aged 3–8 months, before MV, children vaccinated with DTP only (13 deaths) had significantly higher mortality than children vaccinated with OPV only (0 deaths) (log-rank test: \( P = 0.006 \) ) (Table III). Furthermore, children vaccinated with DTP only had an HR of 3.92 (95% CI, 1.59–7.20) compared with children who received MV after DTP and OPV vaccinated with DTP and OPV.

MV Period
In the third analysis, we followed up all children after 9 months of age when most children receive MV (Table IV and Supplemental Figure 2). Compared with children who received MV after DTP, DTP-vaccinated and MV-unvaccinated children had a HR of 2.76 (95% CI, 1.36–5.59). This negative effect may have been more pronounced for girls (HR = 5.13; 95% CI, 1.52–17.28) than boys (HR = 1.76; 95% CI, 0.74–4.20) (test for interaction: \( P = 0.16 \) ) (Supplemental Table IV). Children with out-of-sequence vaccinations (ie, DTP with MV or DTP after MV) tended to have higher mortality than the MV after DTP children (Table IV and Supplemental Table V). When we compared no OPV with OPV among children who had DTP with or after MV, the HR was 6.25 (95% CI, 2.55–15.37); this effect may have been worse for girls, who had a HR of 13.31 (95% CI, 4.21–42.03) (test of interaction: \( P = 0.11 \) ) (Supplemental Table VI).
<table>
<thead>
<tr>
<th>Factor</th>
<th>Unvaccinated (n = 731)</th>
<th>DTP Only (No MV) (n = 225)</th>
<th>DTP and OPV (No MV) (n = 633)</th>
<th>OPV Only (No MV) (n = 155)</th>
<th>MV (n = 400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth WAZ, mean (SD) z</td>
<td>-0.18 (0.98) [313]</td>
<td>-0.17 (1.02) [105]</td>
<td>-0.26 (0.92) [281]</td>
<td>-0.12 (1.25) [68]</td>
<td>-0.18 (0.93) [156]</td>
</tr>
<tr>
<td>WAZ at &lt;6 months of age, mean (SD) [n]</td>
<td>-0.37 (1.21) [685]</td>
<td>-0.52 (1.36) [119]</td>
<td>-0.38 (1.16) [394]</td>
<td>-0.50 (1.35) [66]</td>
<td>-0.86 (1.21) [8]</td>
</tr>
<tr>
<td>WAZ at 6–8 months of age, mean (SD) [n]</td>
<td>-1.07 (1.49) [77]</td>
<td>-0.79 (1.27) [104]</td>
<td>-0.65 (1.25) [344]</td>
<td>-0.79 (1.22) [81]</td>
<td>-0.78 (1.11) [75]</td>
</tr>
<tr>
<td>WAZ at 9–11 months of age, mean (SD) [n]</td>
<td>-0.98 (1.39) [42]</td>
<td>-1.22 (1.15) [49]</td>
<td>-1.11 (1.25) [117]</td>
<td>-1.24 (1.36) [29]</td>
<td>-0.87 (1.17) [359]</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>52.3</td>
<td>53.8</td>
<td>49.3</td>
<td>52.9</td>
<td>54.7</td>
</tr>
<tr>
<td>Twin, %</td>
<td>2.5</td>
<td>4.6</td>
<td>1.9</td>
<td>4.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Ethnic group, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pepel</td>
<td>48.7</td>
<td>45.1</td>
<td>50.0</td>
<td>48.5</td>
<td>50.7</td>
</tr>
<tr>
<td>Balanta</td>
<td>13.2</td>
<td>11.8</td>
<td>13.2</td>
<td>15.4</td>
<td>10.7</td>
</tr>
<tr>
<td>Other</td>
<td>38.1</td>
<td>43.1</td>
<td>36.8</td>
<td>36.0</td>
<td>38.7</td>
</tr>
<tr>
<td>Examination rate, (events/person-years)</td>
<td>3.78 (728/192.8)</td>
<td>3.44 (74/21.5)</td>
<td>3.14 (273/87.0)</td>
<td>3.06 (41/13.4)</td>
<td>6.47 (48/7.4)</td>
</tr>
</tbody>
</table>

DTP = diphtheria-tetanus-pertussis vaccine; MV = measles vaccine; OPV = oral polio vaccine; WAZ = weight for age z score.

* Sample sizes are the number of children in the group, using only 1 observation per child but allowing a child to be included in all groups at once.

† MV includes all children who have received MV and is therefore not necessarily the most recent vaccination.

MV includes all children who have received MV and is therefore not necessarily the most recent vaccination.

‡WAZ is defined as the WAZ measured at birth or before 14 days of age.

§The proportions of sex, twins, and ethnic group calculated before 9 months of age (where MV is scheduled).

|| Examination rate calculated as the number of all observations starting with the child being present divided by person-years.
DISCUSSION

Main Observations

Children who received only the OPV had lower mortality than children who had received DTP only or DTP and OPV. Although unvaccinated children were increasingly frail after 6 months of age, DTP vaccination was associated with slightly higher mortality than being unvaccinated. DTP vaccinated and MV-unvaccinated children had a nearly 3-fold higher mortality than children having MV after DTP as their most recent vaccination. Nonlive DTP was associated with negative NSEs, whereas live OPV and MV were associated with beneficial effects. OPV reduced the negative effects of DTP because children who received DTP and OPV had lower mortality than children who received DTP only at 3–8 months of age before MV and when vaccines were given out of sequence with MV after 9 months of age.

Strengths and Weaknesses

We used 40-year-old data to assess the effects of OPV and DTP, when given separately and combined. Few sites have data from when these vaccines were first introduced in low-income countries with high mortality. When introducing these vaccines, there were many natural experiments in which only 1 vaccine was given. Because the removal of OPV is planned, it is particularly important to understand the nonspecific and specific effects of OPV.

Table II. Mortality rates and HRs by most recent vaccination and age (MV has been censored).

<table>
<thead>
<tr>
<th>All*</th>
<th>Unvaccinated</th>
<th>DTP and OPV</th>
<th>DTP Only</th>
<th>OPV Only</th>
<th>DTP and/or OPV</th>
<th>DTP and/or OPV vs Unvaccinated</th>
<th>DTP Only vs Unvaccinated</th>
<th>DTP and/or OPV vs OPV Only</th>
<th>DTP Only vs OPV Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group, mo</td>
<td>3–5</td>
<td>4.8 (6/125.3)</td>
<td>13.6 (7/51.3)</td>
<td>37.5 (6/16.0)</td>
<td>0 (0/8.2)</td>
<td>19.3 (13/67.3)</td>
<td>4.98 (1.73–14.30)</td>
<td>9.54 (2.86–31.87)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>6–11</td>
<td>9.1 (12/131.2)</td>
<td>11.9 (25/211.0)</td>
<td>14.2 (8/56.3)</td>
<td>2.4 (1/41.2)</td>
<td>12.3 (33/267.3)</td>
<td>1.27 (0.66–2.46)</td>
<td>1.46 (0.60–3.57)</td>
<td>5.22</td>
</tr>
<tr>
<td></td>
<td>12–23</td>
<td>6.5 (7/107.2)</td>
<td>7.1 (13/183.6)</td>
<td>4.8 (3/62.0)</td>
<td>2.2 (1/45.3)</td>
<td>6.5 (16/246.5)</td>
<td>0.99 (0.41–2.40)</td>
<td>0.74 (0.19–2.86)</td>
<td>2.91</td>
</tr>
<tr>
<td></td>
<td>24–35</td>
<td>2.6 (1/39.1)</td>
<td>5.8 (5/86.9)</td>
<td>6.9 (2/29.0)</td>
<td>9.0 (2/22.1)</td>
<td>6.0 (7/115.9)</td>
<td>2.38 (0.29–19.34)</td>
<td>2.75 (0.25–30.37)</td>
<td>0.64 (0.13–3.11)</td>
</tr>
<tr>
<td></td>
<td>3–35</td>
<td>6.5 (26/403.0)</td>
<td>9.4 (50/532.8)</td>
<td>11.6 (19/163.3)</td>
<td>3.4 (4/116.8)</td>
<td>9.9 (69/696.1)</td>
<td>1.66 (1.03–2.69)</td>
<td>2.00 (1.08–3.70)</td>
<td>2.81 (1.02–7.69)</td>
</tr>
</tbody>
</table>

DTP = diphtheria-tetanus-pertussis vaccine; HR = hazard ratio; MV = measles vaccine; OPV = oral polio vaccine.

* Children with no registered sex included.

† Mortality rate is presented as (event/person-years) × 100.

[Log-rank test for equality.]

[HR fails the Schoenfeld residual test of the proportional hazards assumption (P < 0.05).]
children not being vaccinated with MV). However, following this logic, unvaccinated children should be even weaker than DTP-vaccinated children and should have had higher HR compared with children vaccinated with MV after DTP. That was not the case (Table IV); unvaccinated children had only slightly higher mortality than children vaccinated with MV after DTP, and DTP-vaccinated children had higher mortality than unvaccinated children.

Most studies of vaccines and their impact on survival report only 1 mortality estimate. However, the dynamics of vaccination programs imply that the unvaccinated group will become increasingly frail with age because mothers and health care workers are reluctant to vaccinate ill children. As a result, the HR changes over time. So, if the initial estimate was negative, one might actually get a positive estimate by waiting until only very frail children are left in the unvaccinated group. As a result, the HR changes over time. So, if the initial estimate was negative,16 one might actually get a positive estimate by waiting until only very frail children are left in the unvaccinated group, as done in a study from Cebu, the Philippines.22 We followed up DTP-vaccinated and unvaccinated children to see whether frailty bias would eventually produce a beneficial HR for DTP, but that did not happen. From 3 to 5 months of age, when the comparison was a natural experiment, DTP-vaccinated children had an HR 5 times that of unvaccinated children.16 Subsequently, the HR decreased, but it continued to be at ≥1 among older children despite frailty bias.

Comparison With Previous Studies of DTP and OPV

In the WHO-sponsored meta-analysis of the NSEs of DTP, BCG, and MV, for child mortality before 5 years of age, DTP was associated with a 38% (95% CI, −8%−108%)8 increase in mortality that was not statistically significant. However, the WHO-sponsored review included studies with survival bias. Excluding studies with survival bias, DTP-vaccinated children had a 2-fold higher mortality (HR = 2.00; 95% CI, 1.50−2.67).21 This unfortunate result is further strengthened by 2 recent studies of the introduction of DTP to children aged 3−5 months and 6−35 months; both found DTP to be associated with 2-fold higher mortality.13,16 Negative NSEs of DTP were stronger for girls than for boys.13,16

The DTP estimates are consistent, but they may underestimate the harm from DTP: unvaccinated children are inherently disadvantaged; they have poorer WAZ scores, and their BHP card usually indicates that the child is sick or malnourished.

This study found evidence that OPV has beneficial NSEs: OPV only was associated with a lower mortality than DTP only, and OPV and DTP were associated with a lower mortality than DTP only when given with or after MV. Only 2 previous studies have tested the NSEs of OPV: in an RCT in Guinea-Bissau, OPV at birth reduced infant mortality.

Figure 3. Summary of comparisons of different vaccines at different ages. DTP = diphtheria-tetanus-pertussis vaccine; HR = hazard ratio; MV = measles vaccine; OPV = oral polio vaccine.
by 32% (range, 0%–57%) before the children received campaign OPV, and, in natural experiments, campaigns with OPV were associated with 19% (range, 5%–32%) lower mortality. Hence, all the available studies point to OPV having beneficial NSEs.

In other words, DTP and OPV have contrasting effects. When DTP was first introduced in 1984 in rural Guinea-Bissau, OPV was not used, and the HR for DTP-vaccinated versus DTP-unvaccinated children was 5.00 (95% CI, 0.63–39.7). From 1985 to 1987, DTP and OPV were coadministered, and the HR was 1.90 (95% CI, 0.91–3.97). In the 3- to 8-month age group in the present study, DTP only was associated with higher mortality than DTP and OPV (HR = 3.38; 95% CI, 1.59–7.20). Likewise, when DTP was administered with MV or after MV, DTP only versus DTP and OPV was associated with higher mortality (HR = 6.25; 95% CI, 2.55–15.37).

**Interpretation**

Epidemiologic studies have found increased all-cause mortality associated with nonlive DTP vaccination compared with reduced all-cause mortality associated with live OPV and MV that is not explained by reduced mortality from polio or measles. The beneficial NSEs of live vaccines, including BCG and vaccinia, may relate to epigenetic reprogramming of the innate immune system, enhancing protection against unrelated infections. On the other hand, nonlive vaccines may have the opposite effect, including tolerance and increased susceptibility to unrelated infections. In an experimental study among young Dutch girls, diphtheria and tetanus toxoids and acellular pertussis (DTaP)—inactivated polio vaccine (IPV) was associated with down-regulation of cytokine responses, which were abrogated if the child received BCG together with DTaP-IPV or BCG after DTaP-IPV.

After the WHO-sponsored review, WHO requested RCTs to settle the dispute about the importance of NSEs. The Strategic Advisory Group of Experts on Immunization delegated the setting of priorities and planning of RCTs to the Immunization and Vaccines Related Implementation Research Advisory Committee; 6 years later nothing has happened in relation to assessing the potential negative NSEs of DTP in an RCT.

Hence, we need to triangulate all available data to evaluate the impact of DTP. First, DTP would be expected to be associated with reduced mortality because inherent biases favor the DTP-vaccinated group. Second, all studies of DTP introduction have found a negative effect. Third, routine DTP is consistently associated with increased female mortality. Fourth, DTP after MV is associated with increased female mortality. Fifth, live high-titer
MV (HTMV) was given at 4–5 months of age, and girls had a 2-fold increase in mortality if they received nonlive vaccines (DTP or IPV) after HTMV. Hence, HTMV became associated with 2-fold higher female mortality. Sixth, other nonlive vaccines (pentavalent, hepatitis B virus, IPV, RTS,S, and H1N1) are also associated with increased female mortality even though girls did not have higher mortality in the prevaccination era. Seventh, a live vaccine given shortly after DTP may reduce the negative NSEs. With this level of consistency among independent observations, it is likely that DTP has negative effects. To paraphrase Cornfield, “If only one hypothesis can explain all the evidence, then the question is settled, even if the evidence is observational.”

Implications

More studies should investigate ways to reduce negative effects of DTP and pentavalent. One solution might be to replace the whole-cell pertussis vaccine in DTP with the live pertussis vaccine that has beneficial NSEs in animal studies. We have previously reported that live vaccines may reduce the negative effect if given shortly after a nonlive vaccine; however, when OPV campaigns were conducted before children received early MV, early MV did not reduce the mortality associated with DTP. Another strategy might be to give OPV with DTP or MV after DTP. In addition, administration of BCG with DTP may reduce the adverse effects of DTP, which suggests that it is important to conduct RCTs of giving (or not) a second dose of BCG with the third and last priming dose of DTP at 14 weeks of age. Such studies are possible and could contribute to bringing the negative effects of DTP under better control.

Because polio is about to be eradicated, the use of OPV is planned to stop in 2024. Our findings suggest that withdrawing OPVs might increase child mortality. OPV only was associated with lower mortality than DTP only, and OPV with DTP reduced the negative effects of DTP only. This possibility is supported by RCTs and observational studies of routine OPV vaccinations and OPV campaigns. Hence, we need to mitigate the potential negative effects of removing a vaccine with highly beneficial NSEs. For example, we need to test whether more frequent use of MV and BCG can replace the beneficial effects of OPV when it is withdrawn.

---

**Table IV. Mortality rates and hazard ratios (HR) by disjoint vaccination groups exploring timing of vaccination and most recent vaccination, children aged 9–36 months of age.**

<table>
<thead>
<tr>
<th>Group (Most Recent Vaccines)</th>
<th>Mortality Rate* (Deaths/Person-Years)</th>
<th>HR (95% CI) With MV After DTP as Reference</th>
<th>HR (95% CI) With Unvaccinated as Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV after DTP (with or without OPV)</td>
<td>2.2 (10/448.0)</td>
<td>Reference</td>
<td>0.53 (0.22–1.25)</td>
</tr>
<tr>
<td>DTP with MV (with or without OPV)</td>
<td>4.7 (14/295.6)</td>
<td>1.96 (0.87–4.41)</td>
<td>1.03 (0.47–2.26)</td>
</tr>
<tr>
<td>DTP after MV (with or without OPV)</td>
<td>2.9 (16/554.1)</td>
<td>1.44 (0.65–3.18)</td>
<td>0.76 (0.34–1.67)</td>
</tr>
<tr>
<td>DTP with or without OPV (no MV)</td>
<td>8.5 (46/543.3)</td>
<td>2.76 (1.36–5.59)</td>
<td>1.45 (0.77–2.74)</td>
</tr>
<tr>
<td>Most recent vaccine containing only live vaccines, MV, and/or OPV (no DTP)</td>
<td>4.1 (3/73.5)</td>
<td>1.40 (0.38–5.12)</td>
<td>0.74 (0.21–2.61)</td>
</tr>
<tr>
<td>Unvaccinated (no DTP, MV, or OPV)</td>
<td>6.0 (12/199.3)</td>
<td>1.90 (0.80–4.49)</td>
<td>Reference</td>
</tr>
<tr>
<td>DTP with or after MV (with or without OPV)</td>
<td>3.5 (30/849.7)</td>
<td>1.64 (0.80–3.36)</td>
<td>0.88 (0.43–1.77)</td>
</tr>
</tbody>
</table>

* Mortality rate presented as (event/person-years) × 100.
† All groups represented in model with the 2 groups (DTP with MV [with or without OPV] and DTP after MV [with or without OPV]) combined.

DTP = diphtheria-tetanus-pertussis vaccine; HR = hazard ratio; MV = measles vaccine; OPV = oral polio vaccine.
CONCLUSIONS
It is a sad conclusion that DTP is associated with increased female mortality. No data, without survival bias, contradict this statement. Although the WHO-sponsored review concluded 6 years ago that DTP was associated with 38% (95% CI, −8%–108%) higher mortality and had completely different effects than BCG and MV,

there has been no attempt to define how this issue should be resolved.

DTP is the most commonly used vaccine, and the possibility that it might increase mortality demands that we urgently obtain more information about the effect of DTP on all-cause mortality.

Given the beneficial NSEs of OPV, OPV should be tested to see if it reduces the risk of severe COVID-19 infection. If such RCTs find that OPV reduces the risk of COVID-19, it may lead to a reconsideration of the current plans to stop using OPV.

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REFERENCES

DISCLOSURES
The authors have indicated that they have no conflicts of interest regarding the content of this article.

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C. Bjerregård Øland and P. Aaby proposed the study. P. Aaby collected the original data. A. Rodrigues is responsible for the demographic surveillance system. SWM and P. Aaby cleaned the data. C. Bjerregård Øland and S. Wengel Mogensen conducted the statistical analyses. The first draft was written by P. Aaby and C. Bjerregård Øland; all authors contributed to the final version of the paper. C. Bjerregård Øland and P. Aaby will act as guarantors of the study.


15. Aaby P, Fisker AB, Björkman, Benn CS. Rolling out the RTS,S malaria vaccine: to test or not to test the effect on mortality? BMJ. 2020;368:l6920.


EDITOR’S NOTE
At the outset of the COVID-19 pandemic and while we await formal approval and widespread distribution of a specific vaccine, there has been a revival in the concept of the “collateral benefit” that other live vaccines could offer against SARS-CoV2.1–3 This could be particularly useful in resource-limited settings where, due to disparities between rich and poor countries, the wait for COVID-19 vaccines may be several years.4

In this issue of Clinical Therapeutics, we feature a paper by Dr. Peter Aaby and co-authors that describes work to support this hypothesis. They studied children who received oral polio vaccine in the country of Guinea-Bissau and demonstrated a decreased overall mortality beyond the direct attributable effect of the vaccine. This research is difficult to perform and often met with concerns about confounding factors that could account for the effect.2 However, we commend the authors for their efforts and are pleased to feature this content for our readers.

Ravi Jhaveri
Co-Editor-in-Chief

REFERENCES

Address correspondence to: Peter Aaby, DMSc, Statens Serum Institut, Bandim Health Project, Statens Serum Institut, Artillerivej 5, Copenhagen S 2300, Denmark. E-mail: p.aaby@bandim.org
Supplementary Figure 1. Visual presentation of the mortality rates and the HR estimates for comparing different vaccines in different age groups. Mortality rates of the two groups compared are overlaid over each other (blue represent the comparator groups (i.e. DTP ± OPV or DTP-only) and black represent the baseline groups (i.e. unvaccinated or OPV-only)); mortality rate presented as (event/pyrs)*100; the hazard ratio estimates of the Cox proportional hazards model are then presented graphically in a log transformed axis; Log-rank test for equality in case one arm had no fatalities.
Supplementary Figure 2. Visual presentation of the mortality rates and HR estimates for comparing different vaccines after introduction of measles vaccine. Mortality rate presented as (event/pyrs)*100; Hazard ratio estimates of the Cox proportional hazards model are presented graphically in a log transformed axis.
## Supplementary Table 1. Accumulated vaccination coverages up to 3 years of age.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 32</td>
<td>N = 433</td>
<td>N = 354</td>
<td>N = 398</td>
<td>N = 1217</td>
</tr>
<tr>
<td><strong>Median age [IQR]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPV1</td>
<td>182 (166–222)</td>
<td>152.5 (113–263)</td>
<td>155 (110–248.5)</td>
<td>175 (115–284)</td>
<td>161 (113–264)</td>
</tr>
<tr>
<td>MV1</td>
<td>389 (344–713)</td>
<td>387 (305–570)</td>
<td>323 (285–433)</td>
<td>349 (301–445)</td>
<td>355 (298–487.5)</td>
</tr>
<tr>
<td>BCG</td>
<td>296.5 (292–301)</td>
<td>66 (29–113)</td>
<td>34 (10–64)</td>
<td>33 (13–108.5)</td>
<td>39 (15–94)</td>
</tr>
</tbody>
</table>

Vaccine coverage at 6 months of age. (censoring children ending observation time before 6 months of age)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>DTP1</th>
<th>DTP3</th>
<th>OPV1</th>
<th>OPV3</th>
<th>MV1</th>
<th>BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage</td>
<td>48.39%</td>
<td>3.23%</td>
<td>48.39%</td>
<td>3.23%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

Vaccine coverage at 1 year of age. (censoring children ending observation time before 1 year of age)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>DTP1</th>
<th>DTP3</th>
<th>OPV1</th>
<th>OPV3</th>
<th>MV1</th>
<th>BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage</td>
<td>86.21%</td>
<td>10.34%</td>
<td>89.66%</td>
<td>51.72%</td>
<td>24.14%</td>
<td>6.90%</td>
</tr>
</tbody>
</table>

Vaccine coverage at 3 years of age. (censoring children ending observation time before 3 years of age)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>DTP1</th>
<th>DTP3</th>
<th>OPV1</th>
<th>OPV3</th>
<th>MV1</th>
<th>BCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage</td>
<td>95.83%</td>
<td>62.50%</td>
<td>95.83%</td>
<td>87.50%</td>
<td>79.17%</td>
<td>4.17%</td>
</tr>
</tbody>
</table>

Note: N denotes the total number of children in the group.
## Supplementary Table 2. Background factors for different most recent vaccination groups observed between 12 and 35 months of age.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>86</td>
<td>94</td>
<td>186</td>
<td>48</td>
<td>314</td>
<td>229</td>
<td>439</td>
<td>41</td>
</tr>
</tbody>
</table>

**Birth WAZ (SD) [N]**
- Unvaccinated: -0.02 (0.95) [25]
- DTP-only [no MV]: -0.50 (1.21) [40]
- DTP + OPV [no MV]: -0.22 (1.06) [74]
- OPV-only [no MV]: -0.41 (1.35) [22]
- MV-after-DTP: -0.23 (0.96) [146]
- MV- with-DTP: -0.28 (1.03) [93]
- DTP-after-MV: -0.18 (0.89) [172]
- MV ± OPV No DTP: -1.03 (1.22) [14]

**Mean WAZ (SD) [N] at 12–23 months of age**
- Unvaccinated: -1.44 (1.50) [45]
- DTP-only [no MV]: -1.20 (1.31) [62]
- DTP + OPV [no MV]: -1.17 (1.15) [132]
- OPV-only [no MV]: -1.33 (1.30) [36]
- MV-after-DTP: -0.83 (1.06) [270]
- MV- with-DTP: -1.16 (1.17) [179]
- DTP-after-MV: -1.04 (1.10) [337]
- MV ± OPV No DTP: -0.94 (1.48) [30]

**Mean WAZ (SD) [N] at 24–35 months of age**
- Unvaccinated: -0.66 (0.59) [4]
- DTP-only [no MV]: -0.94 (1.67) [17]
- DTP + OPV [no MV]: -1.29 (1.22) [38]
- OPV-only [no MV]: -1.07 (0.81) [11]
- MV-after-DTP: -1.03 (0.99) [212]
- MV- with-DTP: -1.17 (1.01) [124]
- DTP-after-MV: -1.10 (0.96) [330]
- MV ± OPV No DTP: -1.12 (0.59) [7]

**Male sex**
- Unvaccinated: 59.3%
- DTP-only [no MV]: 52.1%
- DTP + OPV [no MV]: 49.5%
- OPV-only [no MV]: 41.7%
- MV-after-DTP: 50.3%
- MV- with-DTP: 49.8%
- DTP-after-MV: 51.3%
- MV ± OPV No DTP: 43.9%

**Twin**
- Unvaccinated: 4.7%
- DTP-only [no MV]: 4.3%
- DTP + OPV [no MV]: 3.2%
- OPV-only [no MV]: 4.2%
- MV-after-DTP: 2.9%
- MV- with-DTP: 3.1%
- DTP-after-MV: 2.1%
- MV ± OPV No DTP: 4.9%

**Ethnic group**
- **Pepel**
  - Unvaccinated: 50.0%
  - DTP-only [no MV]: 51.1%
  - DTP + OPV [no MV]: 52.2%
  - OPV-only [no MV]: 60.4%
  - MV-after-DTP: 50.6%
  - MV- with-DTP: 53.3%
  - DTP-after-MV: 54.4%
  - MV ± OPV No DTP: 61.0%

- **Balanta**
  - Unvaccinated: 15.1%
  - DTP-only [no MV]: 13.8%
  - DTP + OPV [no MV]: 15.1%
  - OPV-only [no MV]: 12.5%
  - MV-after-DTP: 15.9%
  - MV- with-DTP: 11.8%
  - DTP-after-MV: 13.2%
  - MV ± OPV No DTP: 4.9%

- **Other**
  - Unvaccinated: 34.9%
  - DTP-only [no MV]: 35.1%
  - DTP + OPV [no MV]: 32.8%
  - OPV-only [no MV]: 27.1%
  - MV-after-DTP: 33.4%
  - MV- with-DTP: 34.9%
  - DTP-after-MV: 32.3%
  - MV ± OPV No DTP: 34.1%

**Examination rate [event/PYRS]**
- Unvaccinated: 0.34 [46/136.2]
- DTP-only [no MV]: 0.93 [57/61.4]
- DTP + OPV [no MV]: 0.60 [120/199.1]
- OPV-only [no MV]: 0.57 [26/45.7]
- MV-after-DTP: 1.77 [201/113.5]
- MV- with-DTP: 1.59 [172/107.9]
- DTP-after-MV: 2.26 [237/104.7]
- MV ± OPV No DTP: 1.21 [29/24.0]

Note: N denotes the number of children having been in the group; only one landmark outside these definitions due to most recent vaccine being OPV with no DTP but having received MV (did not die); only using one observation per child but allowing a child to be included in all groups once.

- Birth WAZ defined as the WAZ measured at or before 14 days of age.
- Examination rate calculated as the number of all observations starting the observation with the child being present divided by PYRS in the specified age period.
**Supplementary Table 3. Mortality rates and hazard ratios (HR) by most recent vaccination, sex and age; MV has been censored.**

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Girls</th>
<th>Mortality rate [Deaths/Pyrs]</th>
<th>HR (CI)</th>
<th>Boys</th>
<th>Mortality rate [Deaths/Pyrs]</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>DTP + OPV</td>
<td>DTP-Only</td>
<td>OPV-only</td>
<td>DTP ± OPV</td>
<td>DTP ± OPV vs. Unvaccinated</td>
</tr>
<tr>
<td>3–5 months</td>
<td>1.7 [1/58.4]</td>
<td>11.6 [3/25.8]</td>
<td>27.2 [2/7.4]</td>
<td>0 [0/4.1]</td>
<td>15.1 [5/33.1]</td>
<td>11.07 (1.23–99.31)</td>
</tr>
<tr>
<td>6–11 months</td>
<td>10.2 [6/58.7]</td>
<td>13.1 [14/107.2]</td>
<td>11.8 [3/25.5]</td>
<td>0 [0/19.6]</td>
<td>12.8 [17/132.7]</td>
<td>1.17 (0.46–2.98)</td>
</tr>
<tr>
<td>12–23 months</td>
<td>4.3 [2/46.3]</td>
<td>7.6 [7/92.0]</td>
<td>4.2 [1/24.0]</td>
<td>6.1 [7/115.6]</td>
<td>1.37 (0.29–6.61)</td>
<td>P = 0.30a</td>
</tr>
<tr>
<td>24–35 months</td>
<td>0 [0/15.5]</td>
<td>7.6 [3/39.7]</td>
<td>7.5 [1/13.3]</td>
<td>7.5 [4/53.0]</td>
<td>P = 0.28a</td>
<td>P = 0.24a</td>
</tr>
<tr>
<td>3–35 months</td>
<td>5.0 [9/179.0]</td>
<td>10.2 [27/264.7]</td>
<td>8.6 [6/69.8]</td>
<td>3.3 [2/60.9]</td>
<td>9.9 [33/334.4]</td>
<td>2.13 (1.00–4.54)</td>
</tr>
<tr>
<td>3–5 months</td>
<td>7.5 [5/66.9]</td>
<td>15.7 [4/25.5]</td>
<td>46.3 [4/8.6]</td>
<td>0 [0/4.1]</td>
<td>23.4 [8/34.2]</td>
<td>3.79 (1.16–12.39)</td>
</tr>
<tr>
<td>6–11 months</td>
<td>8.3 [6/72.5]</td>
<td>10.6 [11/103.8]</td>
<td>16.2 [5/30.8]</td>
<td>4.6 [1/21.6]</td>
<td>11.2 [16/134.6]</td>
<td>1.36 (0.53–3.48)</td>
</tr>
<tr>
<td>12–23 months</td>
<td>8.2 [5/60.9]</td>
<td>6.5 [6/91.6]</td>
<td>7.8 [3/38.4]</td>
<td>0 [0/21.3]</td>
<td>6.9 [9/130.0]</td>
<td>0.84 (0.28–2.51)</td>
</tr>
<tr>
<td>24–35 months</td>
<td>4.2 [1/23.7]</td>
<td>4.2 [2/47.2]</td>
<td>6.4 [1/15.7]</td>
<td>11.3 [1/8.9]</td>
<td>4.8 [3/62.9]</td>
<td>1.15 (0.12–11.03)</td>
</tr>
<tr>
<td>3–35 months</td>
<td>7.6 [17/224.0]</td>
<td>8.6 [23/268.1]</td>
<td>13.9 [13/93.6]</td>
<td>3.6 [2/55.9]</td>
<td>10.0 [36/361.7]</td>
<td>1.43 (0.78–2.59)</td>
</tr>
</tbody>
</table>

Note: Mortality rate presented as (event/Pyrs) × 100; a: log-rank test for equality; b: children with no registered sex included; c: HR fails the Schoenfeld residual test of the proportional hazards assumption (p < 0.05).
Supplementary Table 4. Mortality rates and hazard ratios (HR) by disjoint vaccination groups exploring timing of vaccination and most recent vaccination, and sex, children aged 9–36 months of age.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Sex</th>
<th>Mortality rate [deaths/Pyrs]</th>
<th>HR (CI) [With MV-after-DTP as reference]</th>
<th>HR (CI) [With unvaccinated as reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV-after-DTP (±OPV)</td>
<td>Girl</td>
<td>1.3 [3/234.0]</td>
<td><strong>Ref.</strong></td>
<td>0.39 (0.09–1.78)</td>
</tr>
<tr>
<td></td>
<td>Boy</td>
<td>3.3 [7/214.0]</td>
<td><strong>Ref.</strong></td>
<td>0.65 (0.23–1.84)</td>
</tr>
<tr>
<td>DTP-with-MV (±OPV)</td>
<td>Girl</td>
<td>4.5 [7/156.3]</td>
<td>3.18 (0.82–12.30)</td>
<td>1.25 (0.36–4.31)</td>
</tr>
<tr>
<td></td>
<td>Boy</td>
<td>5.0 [7/139.3]</td>
<td>1.44 (0.50–4.10)</td>
<td>0.94 (0.34–2.62)</td>
</tr>
<tr>
<td>DTP-after-MV (±OPV)</td>
<td>Girl</td>
<td>2.9 [8/271.9]</td>
<td>2.53 (0.67–9.55)</td>
<td>1.00 (0.29–3.40)</td>
</tr>
<tr>
<td></td>
<td>Boy</td>
<td>2.8 [8/282.2]</td>
<td>0.97 (0.35–2.69)</td>
<td>0.64 (0.23–1.75)</td>
</tr>
<tr>
<td>DTP ± OPV (no MV)</td>
<td>Girl</td>
<td>9.1 [24/262.8]</td>
<td>5.13 (1.52–17.28)</td>
<td>2.02 (0.70–5.82)</td>
</tr>
<tr>
<td></td>
<td>Boy</td>
<td>7.8 [22/280.4]</td>
<td>1.76 (0.74–4.20)</td>
<td>1.15 (0.51–2.59)</td>
</tr>
<tr>
<td>Most recent vaccine containing only Live vaccines, MV and/or OPV (no DTP)</td>
<td>Girl</td>
<td>5.2 [2/38.4]</td>
<td>3.07 (0.51–18.50)</td>
<td>1.21 (0.22–6.60)</td>
</tr>
<tr>
<td></td>
<td>Boy</td>
<td>2.9 [1/34.3]</td>
<td>0.69 (0.08–5.65)</td>
<td>0.45 (0.06–3.62)</td>
</tr>
<tr>
<td>Unvaccinated (No DTP, MV or OPV)</td>
<td>Girl</td>
<td>4.7 [4/85.0]</td>
<td>2.54 (0.56–11.51)</td>
<td><strong>Ref.</strong></td>
</tr>
<tr>
<td></td>
<td>Boy</td>
<td>7.0 [8/114.3]</td>
<td>1.52 (0.54–4.29)</td>
<td><strong>Ref.</strong></td>
</tr>
</tbody>
</table>

Note: Mortality rate presented as (event/Pyrs)*100; There were no registered sex for one landmark/sub-child (did not die).

*HR fails the Schoenfeld test for the proportional hazards assumption.
### Supplementary Table 5. Mortality rates and hazard ratios (HR) by disjoint vaccination groups exploring timing of vaccination and most recent vaccination groups, and OPV, children aged 9–36 months of age.

<table>
<thead>
<tr>
<th>Most recent vaccination(s)</th>
<th>Mortality rate [Deaths/Pyrs]</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 MV-after-DTP-only</td>
<td>41.9 [1/2.4]</td>
<td>18.72 (2.36–148.30)</td>
</tr>
<tr>
<td>3 DTP-with-MV and OPV</td>
<td>3.6 [10/278.8]</td>
<td>1.65 (0.67–4.07)</td>
</tr>
<tr>
<td>4 DTP-with-MV, no OPV</td>
<td>23.8 [4/16.8]</td>
<td>10.18 (3.12–33.20)</td>
</tr>
<tr>
<td>5 DTP-after-MV and OPV</td>
<td>2.6 [14/541.9]</td>
<td>1.41 (0.61–3.28)</td>
</tr>
<tr>
<td>6 DTP-after-MV, no OPV</td>
<td>16.4 [2/12.2]</td>
<td>8.22 (1.77–38.11)</td>
</tr>
<tr>
<td>7 DTP-only</td>
<td>7.0 [4/57.6]</td>
<td>2.48 (0.75–8.19)</td>
</tr>
<tr>
<td>8 DTP-only, OPV previously, no MV</td>
<td>3.3 [2/59.9]</td>
<td>1.30 (0.28–6.05)</td>
</tr>
<tr>
<td>9 DTP and OPV, no MV</td>
<td>9.8 [36/367.1]</td>
<td>3.52 (1.66–7.49)</td>
</tr>
<tr>
<td>10 OPV-only, DTP previously, no MV</td>
<td>6.8 [4/58.6]</td>
<td>2.65 (0.81–8.68)</td>
</tr>
<tr>
<td>11 OPV-only</td>
<td>0 [0/29.4]</td>
<td>P = 0.28\textsuperscript{a}</td>
</tr>
<tr>
<td>12 MV and OPV, no DTP</td>
<td>8.0 [2/25.1]</td>
<td>3.06 (0.65–14.28)</td>
</tr>
<tr>
<td>13 MV, no DTP and OPV</td>
<td>5.4 [1/18.7]</td>
<td>2.44 (0.31–19.31)</td>
</tr>
<tr>
<td>14 Unvaccinated (No DTP, MV and OPV)</td>
<td>6.0 [12/199.3]</td>
<td>2.13 (0.88–5.17)</td>
</tr>
</tbody>
</table>

Note: Mortality rate presented as (event/Pyrs)*100; one landmark not included since the landmark had last vaccine VP but had MV and BCG and no DTP (did not die); using only the first dose of MV.

\textsuperscript{a}Log-rank test for equality.

### Supplementary Table 6. Mortality rates and hazard ratios (HR) for out-of-sequence Vaccinations with MV and DTP, children aged 9–36 months of age

<table>
<thead>
<tr>
<th>Groups from 9 to 36 months of age; most recent vaccination</th>
<th>Group</th>
<th>Mortality rate (deaths/100 person-years)</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP-with-or-after-MV and OPV</td>
<td>All</td>
<td>2.9 (24/820.8)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2.6 (11/417.9)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3.2 (13/402.9)</td>
<td>Ref</td>
</tr>
<tr>
<td>DTP-with-or-after-MV, no OPV</td>
<td>All</td>
<td>20.7 (6/29.0)</td>
<td>6.25 (2.55–15.37)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>38.6 (4/10.4)</td>
<td>13.31 (4.21–42.03)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>10.7 (2/18.6)</td>
<td>2.92 (0.66–12.96)</td>
</tr>
</tbody>
</table>