Exhibit A

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Research Paper

The Introduction of Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine Among Young Infants in an Urban African Community: A Natural Experiment

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ABSTRACT

Background: We examined the introduction of diphtheria-tetanus-pertussis (DTP) and oral polio vaccine (OPV) in an urban community in Guinea-Bissau in the early 1980s.
Methods: The child population had been followed with 3-monthly nutritional weighing sessions since 1978. From June 1981 DTP and OPV were offered from 3 months of age at these sessions. Due to the 3-monthly intervals between sessions, the children were allocated by birthday in a 'natural experiment' to receive vaccinations early or late between 3 and 5 months of age. We included children who were <6 months of age when vaccinations started and children born until the end of December 1983. We compared mortality between 3 and 5 months of age of DTP-vaccinated and not-yet-DTP-vaccinated children in Cox proportional hazard models.
Results: Among 3–5-month-old children, having received DTP (±OPV) was associated with a mortality hazard ratio (HR) of 5.00 (95% CI 1.53–16.3) compared with not-yet-DTP-vaccinated children. Differences in background factors did not explain the effect. The negative effect was particularly strong for children who had received DTP-only and no OPV (HR = 10.0 (2.61–38.6)). All-cause infant mortality after 3 months of age increased after the introduction of these vaccines (HR = 2.12 (1.07–4.19)).
Conclusion: DTP was associated with increased mortality; OPV may modify the effect of DTP.

1. Introduction

Individually randomized studies to measure impact on child survival of different vaccines were not conducted when the Expanded Program on Immunization (EPI) was introduced in low-income countries in the 1970s. The disease-protective effects were well documented, so the main issue was at which age to introduce the vaccine most effectively (The Expanded Programme on Immunization, 1982). Except for measles vaccine (MV), surprisingly few studies examined the introduction of vaccines and their impact on child survival (Aaby et al., 1983, 2003a; Holt et al., 1990; The Kasongo Project Team, 1981). One trial of measles-vaccinated and measles-unvaccinated communities in Congo showed a larger than expected reduction in child mortality (Aaby et al., 1981); this observation was subsequently corroborated by community "trials" and before-after studies in several countries (Aaby et al. 1984, 1993, 2003a; Holt et al., 1990; Kapoor and Reddaiah, 1991). Hence, a vaccine may have non-specific effects (NSEs) on susceptibility to other infections (Aaby et al., 1995). WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recently reviewed the potential NSEs of BCG, diphtheria-tetanus-pertussis (DTP) and MV and recommended further research (Higgins et al., 2014; Strategic Advisory Group of experts on Immunization, 2014).

Though protective against the target diseases, DTP may increase susceptibility to unrelated infections (Aaby et al., 2003b, 2004a, 2012) (Appendix A). The SAGE review noticed that the majority of studies found a detrimental effect of DTP (Higgins et al., 2014). However, SAGE considered the evidence inconsistent because two studies reported beneficial effects (Higgins et al., 2014) and that most studies underestimated the benefit of DTP because studies were conducted in situations with herd immunity. Furthermore, all studies gave DTP and OPV together, making it impossible to separate effects of DTP and OPV (SAGE non-specific effects of vaccines Working Group, 2014).

On the other hand, the "unvaccinated" children in these studies have usually been frail children too sick or malnourish to get vaccinated, and the studies may therefore have underestimated the negative effect of DTP. We therefore examined what happened when DTP and OPV were first introduced, but not always given together, in 1981–1983 in

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the capital of Guinea-Bissau. In this situation the children were allocated by birthday to receive vaccines early or late and the "unvaccinated" were therefore not frail children.

2. Methods

2.1. Background

Bandim Health Project (BHP) has followed an urban community with a demographic surveillance system since December 1978, and took part in the introduction of vaccines well before a full-fledged national program was implemented with UNICEF support in 1986 (Aaby et al., 1984, 2004a).

2.2. Demographic Surveillance

In 1978–1979, under-five mortality was nearly 500/1000. Since malnutrition was assumed to be the main cause, a study was initiated to determine why children were malnourished (Aaby et al., 1983). However, severe malnutrition was not evident, and to understand the high mortality we started a health and demographic surveillance system (HDSS). The area was mapped and a census conducted. Four health workers were employed to identify pregnant women, encourage women to attend ante-natal clinics, and to follow children with anthropometric measurements to assess growth patterns and detect malnourished children. Each health worker followed a population of 1500–2000 individuals. The health workers were supervised by an expatriate nurse.

For each sub-district in Bandim, the responsible health worker kept a list of children under three years of age. BHP had no computerized surveillance system until 1990 but kept an A5 card ("BHP card") for each child, where weights and vaccination dates were noted. The child's growth card was kept by the mother.

The Bandim population was very mobile. It was important to maintain contact with the natal village for ceremonial purposes and to secure rice. Furthermore, mothers were not supposed to have sexual relations during breastfeeding (Jakobsen et al., 2004). Breastfeeding was prolonged in Guinea-Bissau. Thus, many women stayed in the rural areas with their natal family while breastfeeding. These cultural traditions introduced variability in the participation in weighing and vaccination sessions.

2.3. Anthropometry

We arranged quarterly weighing sessions in each sub-district. The responsible health worker advised mothers the day before a community weighing. The following morning, the weight was measured and noted on the child's growth card and the BHP card. When the World Food Program provided supplementary feeding this was given to families with malnourished children.

2.4. Vaccinations

There was no community vaccination program in 1981 except that we had organized a few measles vaccination campaigns (Aaby et al., 1984). Mothers could take their children to the Mother and Child Health Program in town. However, this clinic was mainly attended by the urban elite. Few children were vaccinated before BHP organized vaccination sessions (Table 1).

In June 1981, BHP started to provide vaccinations at the quarterly weighing sessions. A health center nurse accompanied the weighing team and vaccinated eligible children. DTP and OPV were provided from 3 months and MV from 9 months of age. OPV-at-birth was not given then. The three DTP and OPV doses could be given with an interval of one month but since we only arranged weighing every three months, most children had longer intervals between doses. DTP was administered intramuscularly and OPV as an oral drop. When both vaccines were administered at the same session OPV was usually given first and then DTP; the children would usually start crying after DTP due to the pain of the injection and it would therefore have complicated the administration of OPV to give DTP first. There were several periods where either OPV or DTP was missing (Fig. 1). BCG was rarely provided at the weighing sessions since most nurses were not trained to administer intra-dermal vaccination. A total of 269 children may have been BCG vaccinated as they had a vaccination date on their card (N = 192) or were noted to have received BCG but no date given (N = 77).

The expatriate nurse sometimes organized additional vaccination sessions in which the children were not weighed. During these sessions,

Table 1
Median age of vaccination and coverage for BCG, DTP and OPV of study cohort.

	1980	1981	1982	1983	1981–1983
Median age in days (N vaccines)					
BCG	9 (4)	48.5 (50)	34 (46)	25 (68)	33 (164)
DTP1	97 (12)	127 (147)	121 (164)	117 (278)	121 (589)
OPV1	98 (12)	118 (185)	121.5 (170)	117 (225)	118 (580)
MV	181 (5)	141 (53)	157 (2)	110 (1)	141.5 (56)
Coverage at 6 months of age					
BCG	1.7% (5/289)	3.5% (12/342)	23.7% (72/304)	17.4% (57/327)	14.5% (141/973)
DTP1	4.2% (12/289)	31.3% (107/342)	61.2% (186/304)	73.1% (239/327)	54.7% (532/973)
DTP3	2.4% (7/289)	0.9% (3/342)	4.3% (13/304)	4.0% (13/327)	3.0% (29/973)
OPV1	4.2% (12/289)	43.0% (147/342)	62.5% (190/304)	69.7% (228/327)	58.1% (565/973)
OPV3	2.4% (7/289)	2.0% (7/342)	4.3% (13/304)	4.0% (13/327)	3.4% (33/973)
MV	2.8% (8/289)	15.2% (52/342)	0.7% (2/304)	0% (0/327)	5.5% (54/973)
Coverage at one year of age					
BCG	2.6% (3/116)	2.4% (7/294)	15.4% (51/332)	17.4% (46/264)	11.7% (104/890)
DTP1	2.6% (3/116)	32.7% (96/294)	71.1% (236/332)	83.0% (219/264)	61.9% (551/890)
DTP3	2.6% (3/116)	4.4% (13/294)	18.4% (61/332)	43.2% (114/264)	21.1% (188/890)
OPV1	2.6% (3/116)	37.4% (110/294)	77.4% (257/332)	84.8% (224/264)	66.4% (591/890)
OPV3	2.6% (3/116)	12.2% (36/294)	32.5% (108/332)	44.3% (117/264)	29.3% (261/890)
MV	15.5% (18/116)	68.0% (200/294)	34.0% (113/332)	51.1% (135/264)	50.3% (448/890)

Notes: The inclusion criteria for the cohort in Table 1 are the same as for our study cohort: weight examination after 15 days of age and contribute time between 91 and 183 days of age. Median age: 'year' means the year the vaccination was given, and median age is the median age at time of vaccination with a given vaccine among children vaccinated before turning 6 months. E.g. the 4 BCG vaccines in the 1980 column were given in 1980 to children with a median age of 9 days.
Coverage: 'year' means the year when the child turned exactly 1 year (or 6 months) old and coverage was assessed. Only children surviving to 1 year (or 6 months) of age were assessed for coverage. Children turning 1 year in 1984 were thus not presented in the table.

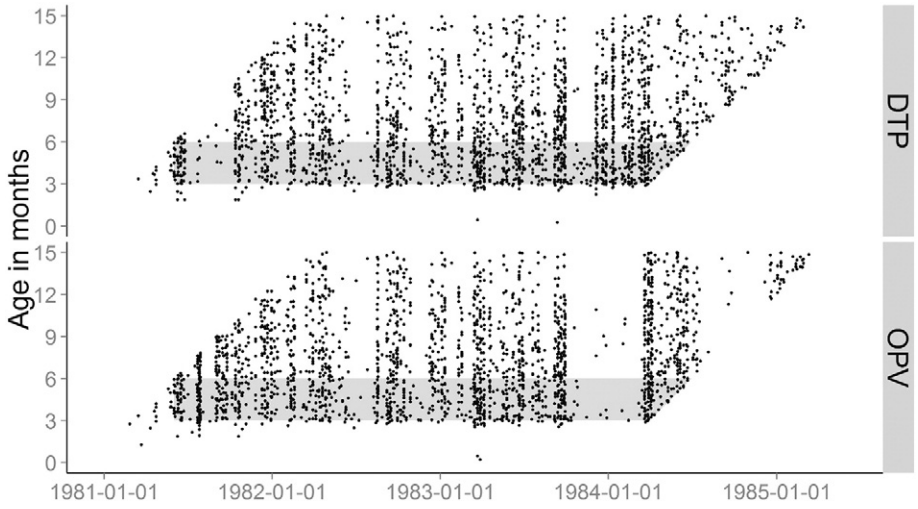

Fig. 1. Each vaccination of the specified type is plotted according age of the recipient and date of vaccination.

vaccinations were noted on the BHP cards. Both nurses and mothers thought that sick children should not be vaccinated; the BHP card often indicated that the child was 'sick', 'malnourished' or 'orphan' as an explanation of why an age-eligible child had not been vaccinated.

2.5. Data Control

When a computerized system became available in 1990–1991, weights and vaccinations from the BHP cards were entered. For the present analysis, all information on dates of visit, weights and vaccination dates was checked against the original cards. A few cards were not available or could no longer be found (Fig. 2).

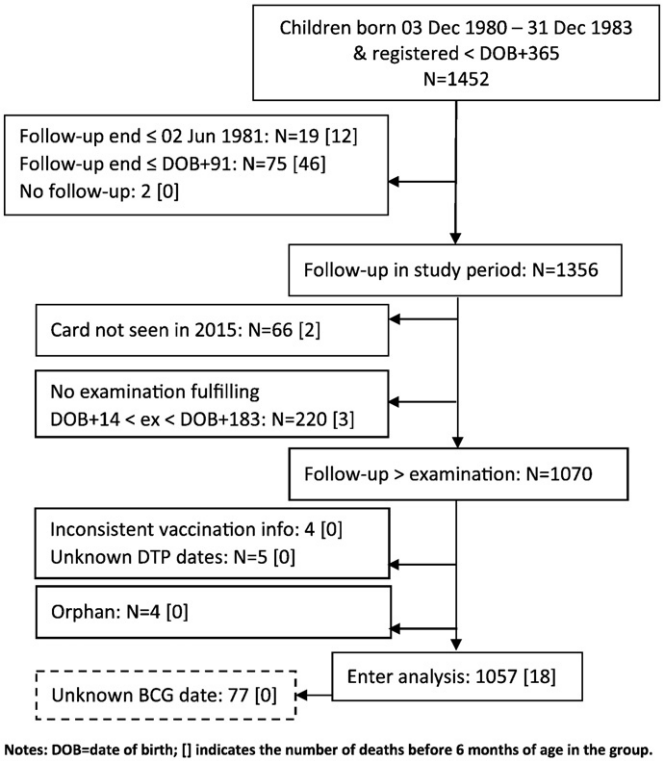

Fig. 2. Flowchart of study population and children included in the analyses. Notes: DOB = date of birth; [] indicates the number of deaths before 6 months of age in the group.

2.6. The Study Cohort

We included children born from December 3, 1980 as they would become eligible for vaccination before 6 months of age (Fig. 2). Few children were vaccinated with BCG (Table 1). Children who travelled and never attended any session were not included in the 'unvaccinated' group. Children weighed within a fortnight of their birth to obtain a birth weight were only included if they took part in a subsequent community weighing session. Furthermore, we excluded orphans since they were not breastfed and were likely to have different care. The cohort is depicted in Supplementary Fig. 1.

2.7. Natural Experiment for 3–5-month-old Children

Though not individually randomized, the present study is a natural experiment with limited bias in group allocation: With 3-monthly intervals between weighing sessions, children were allocated by their birthday to receive their first vaccinations early or late between 3 and 5 months of age (Fig. 3). We therefore compared 3–5-month-old children who had received DTP (±OPV) vaccinations early with children who had not yet received these vaccinations. Since there were no healthy "unvaccinated" children after 6 months of age unless they had travelled, we censored follow-up of all children at 6 months of age (Fig. 3).

Sick children were not vaccinated, in the main analysis we therefore censored 'unvaccinated' children who attended a weighing session but did not receive a vaccination (Fig. 3). Since the censoring of sick children could have introduced a bias, we also conducted an intention-to-treat analysis in which the censored children were transferred to the DTP group. Hence, in this analysis we compared the mortality of the intended-DTP-vaccinated group and the not yet DTP-vaccinated group.

Children were included from 91 days of age if they had been examined in a weighing session before 91 days; if they were only seen in a weighing session after 3 months of age they were only included from the day seen. DTP was not administered elsewhere and the follow-up time of children was therefore counted as DTP-unvaccinated time in the survival analysis until BHP provided the vaccine. Time as DTP-unvaccinated also came from children who did not turn up at the weighing sessions between 3 and 5 months of age but had been seen before 3 months of age and therefore were part of the community cohort (Fig. 3). Hence, the DTP-vaccinated and DTP-unvaccinated children were all children from the same cohort of children born in Bandim and their allocation depended on the timing of their birth date, the timing of the weighing sessions and their travelling pattern. We

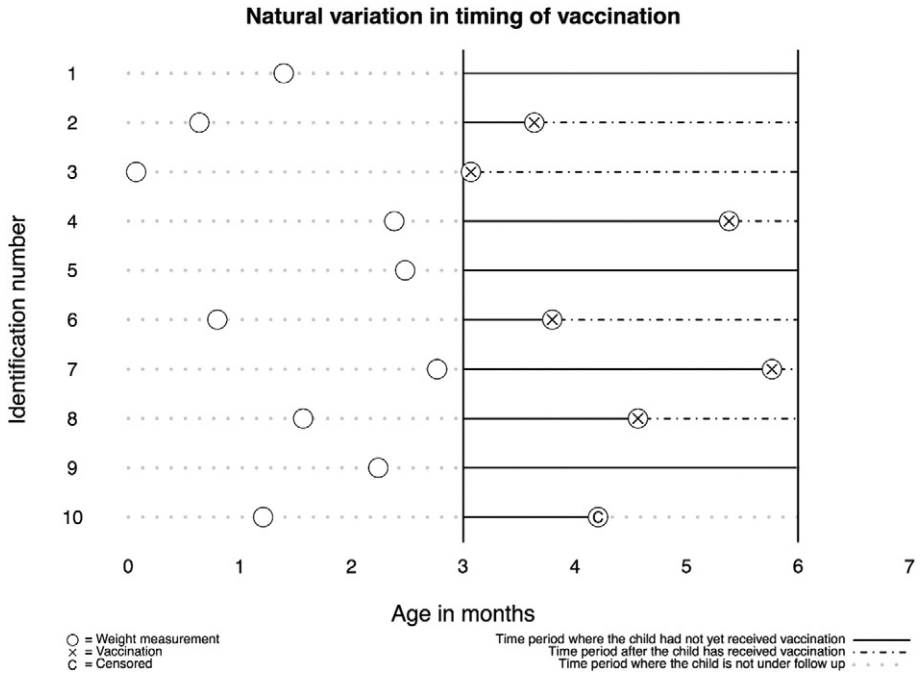

Fig. 3. Natural experiment study design. Note: Children were weighed every third month. After 3 months of age they received DTP and OPV on weighing days if they were healthy. Children who attended but were not vaccinated at a weighing session after 3 months of age were censored in the survival analysis comparing DTP-vaccinated and unvaccinated children.

compared the background factors for the children who were DTP vaccinated, attended a weighing session between 3 and 5 months but were not vaccinated and those who did not attend a weighing session (Table 2).

We also examined the mortality of children who due to logistic reasons had received DTP-only. Absences and travelling patterns are unlikely to differ between children who at their first vaccination had received DTP1 + OPV versus DTP1-only; these two groups were equally likely to receive subsequent vaccinations both with respect to timing of subsequent vaccinations and coverage (data available on request).

2.8. Statistical Methods

First possible enrolment date was June 2, 1981, when DTP and OPV vaccinations were introduced. Different vaccination groups were compared using a Cox proportional hazard model with age as underlying time.

Children were classified according to their most recent vaccination (Supplementary Table 1). We ignored BCG vaccinations in the main analysis because we gave few BCG vaccinations (Table 1) and some children had received BCG at the maternity ward without proper documentation as some children had a BCG scar but no vaccination card. To avoid survival bias, we used a landmark approach (Jensen et al., 2007); hence, a child's vaccination status was only updated from the day the information was collected. Due to the additional vaccination sessions organized by the expatriate nurse some "unvaccinated" children received a vaccine before the weighing session where they changed status to "vaccinated"; it is noted in the footnote to Table 3 how many had received such vaccinations. As a sensitivity analysis we also did an analysis including the additional vaccination sessions as landmarks. For the remainder of this paper, we will refer to these landmarks as vaccination-days-without-weighing.

The WHO z-score for weight-for-age was used to assess nutritional status. Control for sub-district, ethnic group and twinning did not change the results (data not shown). There was no obvious clustering

Table 2
Background factors children in the main analysis of vaccination and mortality between 3 and 5 months of age.

		DTP-vaccinated at 3–5 months	Attended weighing session at 3–5 months, not vaccinated	Did not attend weighing session at 3–5 months
Number		662	186	209
Male sex		52.1%	53.2%	54.1%
Twin		2.7%	2.2%	2.9%
Birth weight (SD)		3.23 (0.025)	3.28 (0.061)	3.22 (0.051)
Ethnic group				
• Pepel		46.8%	54.8%	45.0%
• Balanta		11.8%	13.4%	16.3%
• Other ethnic groups		41.4%	31.7%	38.8%
Mean weight-for-age z-score (SD) at examination before 3 months of age		−0.30 (0.037)	−0.34 (0.084)	−0.43 (0.066)
Follow-up time (person-years) between 3 and 5 months;	All time	135.5 [92]	36.8 [86]	47.4 [92]
[Median number of days of follow]	As DTP vaccinated	73.3	1.8	2.0
	As unvaccinated	62.2	35.1	45.4
Mean number (SD) of weighing sessions per year between 6 and 11 months of age		2.7 (0.03)	2.2 (0.07)	1.6 (0.08)

Table 3
Mortality rate and hazard rate (HR) for children from 3 months of age until first examination without vaccination or 6 months of age. Natural experiment.

Age group 3–5 months	Mortality rate (deaths/person-years)			HR (95% CI) for DTP vs unvaccinated
All				
Unvaccinated (N = 651)	4.5 (5/111.4)	DTP (±OPV) (N = 462)	17.4 (11/63.1)	5.00 (1.53–16.3)
		DTP only (N = 101)	35.2 (5/14.2)	10.0 (2.61–38.6)
		DTP + OPV (N = 361)	12.3 (6/48.9)	3.52 (0.96–12.9)
Girls				
Unvaccinated (N = 313)	1.9 (1/51.9)	DTP (±OPV) (N = 222)	13.3 (4/30.1)	9.98 (0.81–123.0)
		DTP only (N = 44)	16.2 (1/6.2)	12.0 (0.56–257.2)
		DTP + OPV (N = 178)	12.5 (3/23.9)	9.50 (0.73–124.0)
Boys				
Unvaccinated (N = 338)	6.7 (4/59.5)	DTP (±OPV) (N = 240)	21.2 (7/33.0)	3.93 (1.01–15.3)
		DTP only (N = 57)	49.8 (4/8.0)	8.93 (2.01–39.7)
		DTP + OPV (N = 183)	12.0 (3/24.9)	2.21 (0.44–11.0)

Notes: There were no deaths due accidents in this age group. BCG is disregarded in the analysis. Hence, the unvaccinated children have not received DTP, OPV or MV but may have received BCG. Of the 651 unvaccinated children, 219 received DTP and/or OPV before their first weighing examination. These children counted as 'unvaccinated' until their first weighing examination. Of the 462 children who received DTP (±OPV), 177 received an additional DTP or OPV before 6 months of age. The OPV-only is not presented in the table because there were no deaths and very little follow-up time in this age group.

of deaths and control for season and calendar time did not change estimates (data not shown).

There were 18 deaths between 3 and 5 months of age: 3 had cough and respiratory infections as the main symptom, 3 had fever (presumed malaria), 2 were due to diarrhea, 5 had diarrhea and vomiting, 1 was a sudden death, and 4 had no information on cause.

2.9. Ethics

The study of nutritional status was planned by SAREC (Swedish Agency for Research Collaboration with Developing Countries) and the Ministry of Health in Guinea-Bissau.

3. Results

Of 1356 children registered in Bandim and followed to 3 months of age (Fig. 2), 286 were never weighed, had no card or their card was lost. An additional 13 children had inconsistent information, vaccinations marked with a cross but without dates or were orphans. Hence, 1057 children were included in the study cohort. The median ages for DTP1 and OPV1 were 121 and 118 days, respectively (Table 1). The vaccination coverage at 6 months of age was 55% for DTP1; 3% got DTP3 (Table 1). Coverage for MV was only 6%. Of the DTP1, OPV1 and MV vaccinations noted on the BHP card 90–95% had been administered by the BHP.

For children examined after 91 days, a one-unit increase in w/a z-score was associated with an odds ratio of 1.07 (0.93–1.24) for receiving a vaccination at that weighing session.

3.1. Natural Experiment with 3–5-month-old Children

There were no marked differences in background factors for the three groups of children who were DTP vaccinated at 3–5 months of age, those who attended a weighing session but were not vaccinated, and those who did not attend a weighing session at 3–5 months of age (Table 2). Birth weight was similar in the three groups. Weight-for-age z-score before 3 months of age did not differ for the three groups (Table 2). Those who did not attend a weighing session at 3–5 months of age were significantly less likely to attend later weighing sessions during infancy, the mean number of visits being lower for those not attending than for those being DTP-vaccinated ($p < 0.001$) (Table 2); hence, they are likely to have travelled more than those who were DTP-vaccinated.

In the main experiment depicted in Fig. 3, DTP vaccination (±OPV) compared with 'DTP-unvaccinated' was associated with a HR of 5.00 (1.53–16.3) (Table 3); the HR was 9.98 (0.81–123) for girls and 3.93 (1.01–15.3) for boys. If we also included vaccinations given on vaccinations-days-without-weighing in the landmark analysis, DTP (±OPV) compared with unvaccinated was associated with a HR of 3.90 (1.20–12.3). When DTP had been given alone without OPV the HR was 10.0 (2.61–38.6) (Table 3). The difference between DTP-only children and DTP-plus-OPV does not reflect differences in follow-up and other vaccinations since the time to DTP2 and prevalence of DTP2 was the same for DTP-only and DTP-plus-OPV vaccinated children (data not shown). If we excluded the 269 children who may have been BCG vaccinated results were similar (Supplementary Table 2).

If the analysis was conducted as an intention-to-treat analysis in which the children weighed but not vaccinated were not censored but transferred to the DTP group, the intended-DTP-vaccinated group had a HR of 3.92 (1.20–12.8) compared with the not-yet vaccinated group (Supplementary Table 3).

3.2. Secondary Analyses

Since the introduction of DTP and OPV apparently was associated with increased mortality, we examined what happened to infant mortality from 3 to 12 months of age after the introduction of these vaccines. The mortality rate for all 3–11 months old children increased 2-fold (HR = 2.12 (1.07–4.19)) from 1980, before vaccinations, to 1982–1983, after the introduction of DTP and OPV (Table 4).

4. Discussion

4.1. Main Observations

DTP vaccinations were associated with increased infant mortality even though there was no vaccine-induced herd immunity. When unvaccinated controls were normal children who had not yet been eligible for vaccination, mortality was 5 times higher for DTP-vaccinated children. Co-administration of OPV with DTP may have reduced the negative effects of DTP.

4.2. Strength and Weaknesses

The present analysis assessed DTP and child survival in a "natural experiment" in which the children were allocated by the timing of their birth and community weighing sessions and the group allocation was therefore not influenced by the usual selection biases to the same extent as most other studies of DTP (Aaby et al., 2016). To assure that the censoring from the main analysis of children who were not vaccinated had not produced the unexpected strong result we made an intention-to-treat analysis but this did not change the result. If anything the unvaccinated children had slightly worse nutritional status before 3 months of age than the children who were subsequently DTP vaccinated ($p = 0.09$) (Table 2); the unvaccinated children travelled more than the DTP vaccinated children. These biases would tend to favor rather than increase mortality in the DTP group and the

Table 4
Mortality rates (deaths/100 person-years) between 3 and 11 months of age by study year.

Mortality rate	1980	1981	1982	1983	HR (95% CI) for 1982–1983 versus 1980
Children aged 3–11 months	4.7 (10/211.8) (N = 547)	7.2 (18/250.8) (N = 678)	8.0 (19/237.1) (N = 632)	12.1 (30/247.5) (N = 638)	2.12 (1.07–4.19)

Notes: Event recorded as accidents were not removed from this analysis.

estimates from the natural experiment may therefore still be conservative.

The estimated effects of DTP and OPV are unlikely to have been influenced by other vaccinations since very few had received other vaccines; if the children who may have received BCG were censored in the analysis the result was essentially the same (Supplementary Table 2).

The 3-monthly community examinations assured that we had follow-up information for all children and relatively accurate information on the time of death. Some children were excluded because a BHP card could not be found and we did not know whether they had been vaccinated or were travelling. Most likely, BHP cards may never have been made because the child was not coming for examination, or the card may have disappeared at community examinations, at the later handling of BHP cards by field workers or data entry clerks, or due to mice. However, the few missing cards are unlikely to have affected the main analysis as the mortality rate in this group was similar to the general mortality rate (Fig. 2).

To assure comparability of vaccinated and unvaccinated groups, also with respect to travelling, we included only children who had been weighed in Bandim in connection with the 3-monthly community examinations. This meant that children who mostly stayed outside the area were not included in the analysis; these children had no access to community vaccinations and they lived elsewhere where the mortality risk might have been quite different, e.g. due to a higher risk of malaria infection.

The present study was not a planned trial. The study would have been a cleaner natural experiment if vaccinations had only been administered at the weighing sessions. However, the expatriate nurse did organize additional vaccinations and some 'unvaccinated' children had therefore already received a vaccination before coming for a weighing session. These 'misclassifications' do not explain the increased mortality in the DTP group. The estimate for DTP-vaccinated (±OPV) compared with DTP-unvaccinated children was 4-fold higher mortality when we included these additional landmarks in the analysis.

4.3. Comparison with Previous Studies of DTP and OPV

There is only one other study of the introduction of DTP. In rural Guinea-Bissau, DTP (±OPV) was associated with 2-fold higher mortality (Aaby et al., 2004a). All studies that documented vaccination status and followed children prospectively indicate that DTP has negative effects; a meta-analysis of the eight studies found 2-fold higher mortality for DTP-vaccinated compared with DTP-unvaccinated, mostly BCG-vaccinated controls (Aaby et al., 2016) (Appendix A).

The negative effect of DTP was much worse in this natural experiment than has been reported in previous studies of DTP. This is presumably due to the "unvaccinated" control children in previous studies having been a frail subgroup too frail to get vaccinated. Previous studies have not been able to compare DTP-vaccinated children with "normal" controls. Hence, most previous studies have probably underestimated the negative effect of DTP.

The potentially differential effects of DTP and OPV have only been examined in few studies. However, we have recently been able to document marked beneficial NSEs of OPV. In an RCT, OPV at birth (OPV0) reduced infant mortality by 32% (0–57%) before the children received campaign-OPV (Lund et al., 2015). In Bissau campaign-OPV reduced the mortality rate by 19% (5–32%) (submitted). When DTP was missing for several months in Bissau, we showed that the all-cause case-fatality at the pediatric ward was 3-fold lower if the children had OPV-only as their most recent vaccination rather than the recommended combination of DTP and OPV (Aaby et al., 2004b). Thus, OPV may have modified the negative effect of DTP.

This pattern was also seen when DTP was first introduced in the rural areas of Guinea-Bissau in 1984 (Aaby et al., 2004a). OPV was not used the first year and the HR for DTP versus unvaccinated was 5.00 (0.63–39.7). In the period from 1985 to 1987, when DTP and OPV were nearly always administered together, the MRR was 1.90 (0.91–3.97). In the present study, the hazard ratio was 10.0 (2.61–38.6) for DTP-only but 3.52 (0.96–12.9) for children who received DTP and OPV simultaneously (Table 3). Based on these two studies of the introduction of DTP, the HR compared with DTP-unvaccinated children was significantly different for children who had received DTP-only (HR = 8.14 (2.63–15.2)) and for children who received both DTP and OPV (HR = 2.21 (1.16–4.19)) (test of interaction, p = 0.049). Hence, simultaneous administration of DTP and OPV may have alleviated the negative non-specific effect of DTP.

5. Conclusions

DTP was associated with 5-fold higher mortality than being unvaccinated. No prospective study has shown beneficial survival effects of DTP. Unfortunately, DTP is the most widely used vaccine, and the proportion who receives DTP3 is used globally as an indicator of the performance of national vaccination programs.

It should be of concern that the effect of routine vaccinations on all-cause mortality was not tested in randomized trials. All currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis. Though a vaccine protects children against the target disease it may simultaneously increase susceptibility to unrelated infections.

The recently published SAGE review called for randomized trials of DTP (Higgins et al., 2014). However, at the same time the IVIR-AC committee to which SAGE delegated the follow-up studies of the NSEs of vaccines has indicated that it will not be possible to examine the effect of DTP in an unbiased way. If that decision by IVIR-AC remains unchallenged, the present study may remain the closest we will ever come to a RCT of the NSEs of DTP.

Funding

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Conflict of Interest

Nothing to declare

Contributions

CSB and PA proposed the study. PA collected the original data. AR is responsible for the demographic surveillance system. SWM and PA cleaned the data. SWM and AA conducted the statistical analyses. The first draft was written by PA; all authors contributed to the final version of the paper. PA and SWM will act as guarantors of the study.

Independence

The funding agencies had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Data Sharing

Through request to the authors

Appendix A. The DTP Controversy

The issue of DTP vaccination and child mortality in high mortality areas was raised 15 years ago when a study from rural Guinea-Bissau showed 1.84-fold higher mortality for children who had received DTP1 vaccination (Aaby et al., 2016; Kristensen et al., 2000). All subsequent prospective studies have supported a negative effect (Aaby et al., 2016). Furthermore, DTP may have a negative effect when given simultaneously with or after MV (Aaby at el., 2003b, 2012). For example, the negative effect of high-titer measles vaccination (HTMV) in girls, which led to the global withdrawal of HTMV, was due to DTP being administered after MV because HTMV had been given early at 4–5 months of age (Aaby et al., 2003b).

DTP has not been shown to have beneficial effects in RCTs or natural experiments. The current policy for DTP has only been examined by reanalyses of existing data sets collected for other purposes. All such studies have had methodological problems related to different forms of frailty and survival bias (Aaby et al., 2012). These studies have updated follow-up time for DTP-vaccinated children who survived but children who died without their vaccination status being documented were classified as “unvaccinated”. Such procedures give a misleading high mortality rate in the unvaccinated group, and the comparison of DTP-vaccinated survivors and “unvaccinated” children will therefore give a beneficial estimate for DTP (Aaby et al., 2016). If the mortality rate of unvaccinated children is unnaturally increased, the HR of unvaccinated children versus children who have received at least one vaccine may indicate how much bias there might be in the study, and we have called this HR the “bias-index”. All studies with prospective follow-up have had a bias index below 2.0 (Aaby et al., 2016); in the present study the bias index was 0.41 (0.15–1.15) in the 3–5 months age group (Supplementary Table 2). In studies with survival bias and unnaturally high mortality in the unvaccinated group, the bias index has been 3–8 times higher (Aaby et al., 2016).

SAGE recently reviewed the potential NSEs of BCG, MV and DTP (Higgins et al., 2014; Strategic Advisory Group of experts on Immunization, 2014). The reviewers indicated that the majority of studies showed a deleterious effect of DTP but they concluded that the results were inconsistent because two studies showed a beneficial effect. The beneficial effect in these studies was not surprising because the mortality rate in the unvaccinated group was unnaturally high, and the bias index was 3.40 (2.93–3.95) and 7.52 (5.15–10.97), respectively (Aaby et al., 2016).

SAGE's working group on non-specific effects of vaccines further emphasized that the overall effect remains unclear because DTP has been given in combination with other vaccines and under circumstances where the burden of the target diseases has been reduced to a very low level. However, several previous studies have shown that the negative effect of DTP-plus-OPV was not due to OPV (Aaby et al., 2004a,b, 2012). OPV has probably reduced the overall negative effect of DTP. Previous studies have indicated that DTP (±OPV) was associated with a 2-fold higher mortality than DTP-unvaccinated children (Aaby et al., 2016). Since pertussis did not account for >5–6% of infant deaths in the only existing African study of the impact of pertussis on child mortality (Mahieu et al., 1978), it is not surprising that DTP is also associated with a strong negative effect prior to vaccine-induced herd immunity (Aaby et al., 2012).

Appendix B. Supplementary Data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2017.01.041.

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Exhibit B

frontiers in Public Health

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Evidence of Increase in Mortality After the Introduction of Diphtheria–Tetanus–Pertussis Vaccine to Children Aged 6–35 Months in Guinea-Bissau: A Time for Reflection?

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Background: Whole-cell diphtheria–tetanus–pertussis (DTP) and oral polio vaccine (OPV) were introduced to children in Guinea-Bissau in 1981. We previously reported that DTP in the target age group from 3 to 5 months of age was associated with higher overall mortality. DTP and OPV were also given to older children and in this study we tested the effect on mortality in children aged 6–35 months.

Methods: In the 1980s, the suburb Bandim in the capital of Guinea-Bissau was followed with demographic surveillance and tri-monthly weighing sessions for children under 3 years of age. From June 1981, routine vaccinations were offered at the weighing sessions. We calculated mortality hazard ratio (HR) for DTP-vaccinated and DTP-unvaccinated children aged 6–35 months using Cox proportional hazard models. Including this study, the introduction of DTP vaccine and child mortality has been studied in three studies; we made a meta-estimate of these studies.

Results: At the first weighing session after the introduction of vaccines, 6–35-month-old children who received DTP vaccination had better weight-for-age *z*-scores (WAZ) than children who did not receive DTP; one unit increase in WAZ was associated with an odds ratio of 1.32 (95% CI = 1.13–1.55) for receiving DTP vaccination. Though lower mortality compared with not being DTP-vaccinated was, therefore, expected, DTP vaccination was associated with a non-significant trend in the opposite direction, the HR being 2.22 (0.82–6.04) adjusted for WAZ. In a sensitivity analysis, including all children weighed at least once before the vaccination program started, DTP (±OPV) as the most recent vaccination compared with live vaccines or no vaccine was associated with a HR of 1.89 (1.00–3.55). In the three studies of the introduction of DTP in rural and urban Guinea-Bissau, DTP-vaccinated children had an HR of 2.14 (1.42–3.23) compared to DTP-unvaccinated children; this effect was separately significant for girls [HR = 2.60 (1.57–4.32)], but not for boys [HR = 1.71 (0.99–2.93)] (test for interaction $p = 0.27$).

Conclusion: Although having better nutritional status and being protected against three infections, 6–35 months old DTP-vaccinated children tended to have higher mortality than DTP-unvaccinated children. All studies of the introduction of DTP have found increased overall mortality.

Keywords: bias in vaccine studies, diphtheria–tetanus–pertussis vaccine, heterologous effects, measles vaccine, non-specific effects of vaccines, oral polio vaccine

KEY OBSERVATIONS

- DTP and oral polio vaccine (OPV) were first introduced to children aged 6–35 months in June 1981 in an urban area in Guinea-Bissau. Children who were DTP-vaccinated at the first weighing session after the introduction of DTP had significantly better weight-for-age *z*-scores than those not vaccinated.
- Although better survival was expected, the DTP-vaccinated children had twofold higher mortality than DTP-unvaccinated children.
- In a meta-analysis of the three studies of the introduction of DTP in urban and rural Guinea-Bissau, DTP-vaccinated children had twofold higher mortality than DTP-unvaccinated children.

INTRODUCTION

Whole-cell diphtheria–tetanus–pertussis (DTP) vaccine is the most commonly used vaccine in low-income countries with poor health infrastructure, and the coverage for the third dose of DTP-containing vaccines (DTP3) is the main performance indicator for vaccination programs (1). However, no prospective study has shown that receiving DTP is associated with better child survival (2, 3). On the contrary, in the past 20 years several studies have suggested that DTP is associated with increased child mortality, particularly for girls (2–4).

We recently examined what happened when DTP and oral polio vaccine (OPV) were introduced to infants aged 3–5 months in Guinea-Bissau in June 1981 in connection with tri-monthly weighing sessions in an urban community in Bandim (5). In this age group, the child's date of birth determined whether a child was vaccinated early or late. Children who were just over 3 months old at the time of the tri-monthly weighing sessions were vaccinated at that age; those who were just below 3 months old would only be vaccinated for the first time at almost 6 months of age. In this "natural experiment," DTP-vaccinated children had fivefold higher mortality between 3 and 6 months of age than children not yet vaccinated with DTP (5).

When we initiated vaccination with DTP and OPV in Guinea-Bissau in June 1981, we also offered a catch-up program to children aged 6–35 months attending the weighing sessions. This situation provides an opportunity to compare the survival of older DTP-vaccinated and DTP-unvaccinated children.

In principle, children above 3 months of age attending the weighing sessions were offered vaccination if vaccines and equipment (syringes, sterilization stove) were available. However, nurses and mothers were reluctant to vaccinate sick or weak children. Other reasons for not being vaccinated were that the children were temporarily traveling, or that they stayed for prolonged periods in the rural areas where access to health care was limited and child mortality was higher. Thus, apart from the specific disease-protective effect of DTP, inherent biases would lead one to expect that DTP-vaccinated children had better survival than DTP-unvaccinated children.

MATERIALS AND METHODS

Background

Bandim Health Project (BHP) has followed an urban community in the capital of Guinea-Bissau with a demographic surveillance system since December 1978. The national immunization program in Guinea-Bissau started in 1986 with funding from UNICEF. From January 1980, BHP conducted tri-monthly weighing sessions of all children in the community to identify malnourished children. From June 1981, vaccinations were offered in connection with these weighing sessions.

Demographic Surveillance

When the project started in 1978, child mortality was very high. Malnutrition was assumed to be the main cause and a study was, therefore, initiated to determine why children were malnourished (6–8). The area was mapped and a census was conducted (5). Four female health workers identified pregnant women, encouraged women to attend the antenatal clinic in the study area, and followed children with anthropometric measurements to assess growth patterns and detect malnourished children. Each health worker followed a population of 1,500–2,000 individuals, the total number of individuals in Bandim being around 6,300 at the beginning of the study. The health worker kept a list of children under 3 years of age in each of the eight sub-districts in Bandim. An expatriate nurse supervised the health workers. BHP had no computerized surveillance system when the study started, but BHP kept an A5 card ("BHP card") for each child, where weights and vaccination dates were noted. With a birth rate around 5%, the annual birth cohort was around 300–350 newborns.

The Bandim population was very mobile for many reasons. First, it was important to maintain contact with the natal village for ceremonial purposes and to secure access to rice, often by helping the family during the rice production cycle. Second, many women tried to obtain cash income by growing fruits or vegetables in the rural areas or by producing cashew wine to be sold in Bissau. Third, mothers were not supposed to have sexual relations during breastfeeding as semen is believed to damage breastmilk causing diarrhea in the child (9). Breastfeeding

was prolonged in Guinea-Bissau, between 18 and 36 months in different ethnic groups. Thus, many women preferred to stay in the rural areas with their family while breastfeeding. These cultural patterns meant that some mothers and children were away for long periods. Typically, there would be family members in Bandim, who we could ask about the whereabouts of the child.

Tri-Monthly Weighing Sessions

We arranged tri-monthly weighing sessions in each sub-district (8). The health worker in charge advised mothers the day before a session. If a child was not present, its vital status was ascertained by asking the family. The following morning, the child's weight was measured on a hanging Salter scale and noted on the child's health card and the BHP card.

Vaccinations

There was no community vaccination program in Guinea-Bissau when BHP started vaccinations. Mother could have taken their children to the clinic of the Mother and Child Health Program in town. This clinic was mainly attended by the urban elite so very few children from Bandim had received routine vaccinations (5). In June 1981, BHP started to provide vaccinations at the tri-monthly weighing sessions. A health center nurse accompanied the nutrition team and vaccinated eligible children.

Eligible children were between 3 months and 3 years of the age. However, some children in this age group were not vaccinated. Both nurses and mothers thought that sick or otherwise weak children should not be vaccinated. The BHP card often indicated that the child was "sick," "malnourished," or "orphan" as an explanation of why an age-eligible child had not been vaccinated. Other reasons for not vaccinating an age-eligible child were temporary shortages of vaccines or syringes.

The three DTP and OPV doses could be given from 3 months of age with an interval of 1 month, but since we only performed weighing sessions every 3 months, most children had longer intervals between the three doses. Also, there were several periods where either OPV or DTP was missing [Ref. (5), **Figure 1**]. The expatriate nurse sometimes organized additional vaccination sessions in which the children were not weighed, but vaccinations were noted on the BHP cards.

Data Control

Weights and vaccinations from the BHP cards were entered into a computerized system in 1990–1991. For the present analysis, information on dates of visit, weights, and vaccination dates was checked against the original cards in 2015.

The Study Cohort and Vaccination Analyses

We included children born between June 1978 and December 1980 and hence aged 6 and 35 months in June 1981 when DTP and OPV vaccines became available (**Figure 1**). Furthermore, it was an inclusion criterion that children were registered in the area before the vaccinations started. We excluded orphans, since they were not breastfed and were likely to have different care; their mortality was very high (10). Children who never attended a weighing session after birth registration were not included in the analysis, since their mothers had likely left for the rural areas. In the analyses, we restricted the data set to children taking part in at least one weighing session after October 1980, 8–9 months before vaccinations started. This was done to assure that the children had been seen fairly recently and were, therefore, likely to be around when the vaccinations started. Since the children were called every 3 months, the time of death or migration out of the area is fairly accurate.

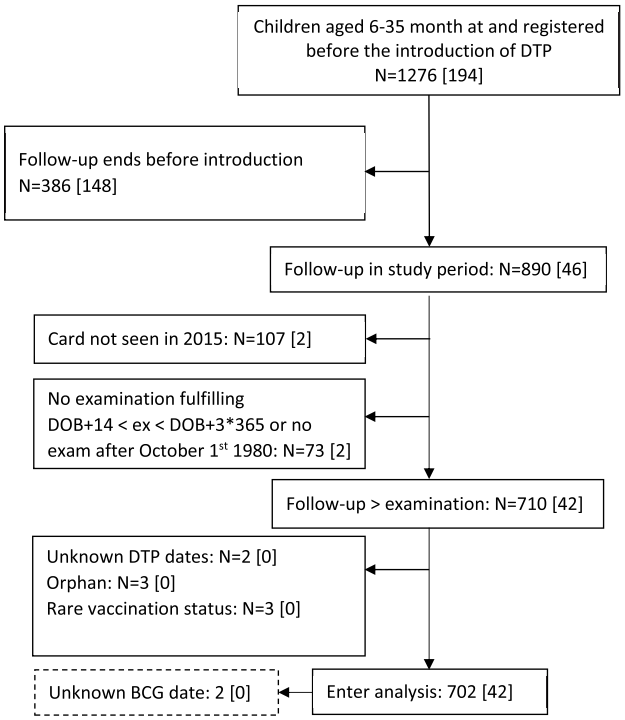

FIGURE 1 | Flowchart of study population and children included in the analyses. DOB, date of birth; [], died during follow-up. Children were only included in the main analysis if they had taken part in a weighing session after October 1, 1980.

Vaccination Analyses

We conducted three complementary analyses to assess the effect of DTP on child survival.

Analysis 1

We compared DTP-vaccinated children and those who were not DTP-vaccinated when they came for their first weighing session after the introduction of vaccinations in June 1981. Since not all children were included, the analysis had less power. We followed children from their first weighing session and until they received their next vaccination or they migrated, died, or turned 3 years of age. Thus, children had to be present at a weighing session to be included in this analysis and we could adjust for the weight-for-age *z*-score (WAZ) obtained at that session.

Analysis 2

In this analysis, children were considered DTP-vaccinated from the date they received their first DTP vaccination (with or without OPV) in June 1981, or at one of the subsequent weighing sessions (**Figure 2**). Children were considered DTP-unvaccinated from the date vaccination was first offered in their sub-district, irrespective of whether they were present at the weighing session, and until they were DTP-vaccinated at a subsequent session, migrated, died, or turned 3 years of age. (The difference between this analysis and Analysis 1 was that children were considered DTP-unvaccinated if they were age-eligible, irrespective of whether they had attended a weighing session or not, and vaccination status could change during follow-up, so a child could contribute risk time first as DTP-unvaccinated and then as DTP-vaccinated.)

Analysis 3

In the third analysis, we compared mortality of children according to their most recent vaccination status; DTP-vaccinated children were compared with children who had received no vaccination or live vaccine only (MV, OPV, or MV + OPV) as their most recent vaccination.

Statistical Analyses

The survival of different vaccination groups was compared using a Cox proportional hazard model with age as underlying time. Thus, age was inherently controlled in this analysis. The WHO WAZ was used to assess nutritional status. In analysis 1 in which we compared children who had attended weighing sessions and been vaccinated or not vaccinated we adjusted the analysis for nutritional status (WAZ score). Since we provided almost all vaccines, most vaccinations were known from the date of vaccination, but a few children were vaccinated elsewhere. To avoid survival bias, we used a landmark approach in all analyses (11); hence, a child's vaccination status was only updated from the day the information was collected.

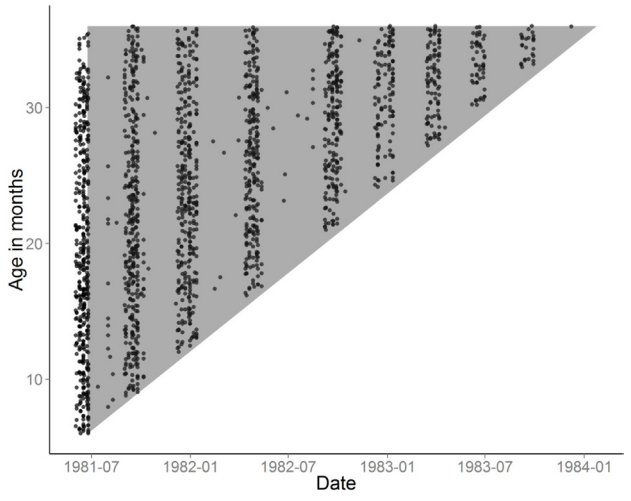

FIGURE 2 | Examinations are plotted on the axes of age and calendar time. Each dot corresponds to a weighing examination of a child. The gray triangle illustrates the age groups and periods, where follow-up time was included in the survival analysis. The approximate tri-monthly regime of examinations is visible in the distribution of dots on the horizontal axis.

Studies of the Introduction of DTP

Including this study, there are only three studies of the introduction of DTP, all from Guinea-Bissau (5, 12). We made a meta-estimate for these studies, since they represent an unusual set of circumstances in relation to the discussion of potential biases in studies of the non-specific effects of vaccines (13–17). First, in all three studies the nutritional status was worse for children not vaccinated. Second, we administered nearly all vaccines, so most dates of vaccination were known precisely. Third, there were no campaigns with other vaccines or micronutrient supplements at the time of these studies. Fourth, they represent all the data sets available on the introduction of DTP in Guinea-Bissau, so reporting bias is not an issue (15).

RESULTS

Of the 890 children aged 6–35 months registered in Bandim in June 1981, we were not able to locate the BHP card of 107 (12%) children in 2015; most will not have attended an examination, but some cards may have been lost. A further 81 had a BHP card, but had not attended a weighing session since October 1980, had no precise vaccination dates, or were excluded due to other considerations (see **Figure 1**). Hence, 702 children were included in the study cohort; the number of deaths and person-years in the different vaccine groups was, therefore, limited (Table S1 in Supplementary Material).

The temporal distribution of weighing sessions in this cohort is shown in **Figure 2**. As documented in Table S2 in Supplementary Material, 82 and 84% received DTP1 and OPV1 before they reached 3 years of age, the median ages of vaccination being 633 and 614 days, respectively. It should be noted that only 38 and 49% of the children received all three doses of DTP and OPV, respectively, before 3 years of age. Due to earlier MV campaigns (6, 7), 82% had received MV at a median age of 348 days. There were 42 deaths between 6 and 35 months of age; 14 had fever as the main symptom, 13 had diarrhea or diarrhea and vomiting, 6 died from measles, 1 had respiratory infection, 1 was malnourished, 1 had anemia, 1 did not eat, and 5 had no information, most likely because the mother/family had moved.

We compared background factors for DTP-vaccinated children and children who remained DTP-unvaccinated until at least 3 years of age (**Table 1**). The DTP-vaccinated children were far more likely to have attended weighing sessions, to have received measles vaccine (MV) in the campaigns, or to have received DTP at the Mother and Child Clinic before June 1981 (6, 7). There were no differences in distribution of the sexes, twins, or ethnic groups.

Analysis 1

At the first weighing session after the vaccinations started in June 1981, the WAZ was much higher for the children who received DTP (WAZ −0.83) than for those children who did not receive DTP (WAZ −1.17) (**Table 1**). An increase of one *z*-score was associated with an odds ratio (OR) of 1.32 (95% CI = 1.13–1.55)

for being vaccinated at the first weighing session. Compared with not being DTP-vaccinated, DTP vaccination at the first weighing session was associated with a non-significant mortality hazard ratio (aHR) of 2.22 (95% CI = 0.82–6.04) adjusted for WAZ (**Table 2**), the aHR being 7.03 (0.88–56.04) for girls, and 1.28 (0.38–4.25) for boys (test for interaction $p = 0.17$).

Analysis 2

Including all children in the cohort, following them to 3 years of age and allowing children to change status during follow-up when new information was collected at a weighing session, having received DTP was associated with a non-significant HR of 1.48 (0.72–3.06) (**Table 3**). The HR was 2.91 (0.84–10.00) for girls and 0.88 (0.34–2.62) for boys.

Analysis 3

Children who received DTP (with or without OPV) as the most recent vaccination had an HR of 1.77 (0.93–3.38) compared with children who had received a live vaccine or no vaccine at all and had a HR of 1.90 (0.92–3.94) if compared only with children who had received live vaccine only (**Table 4**). In a sensitivity analysis, including also the 47 children whose most recent weighing session had been before October 1980, the HRs for DTP was 1.89 (1.00–3.55) (**Table 4**), the HR being 2.76 (1.07–7.07) for girls, and 1.34 (0.56–3.22) for boys.

Though the group was small, it is worth noting that children who received OPV-only had low mortality (Table S1 in Supplementary Material), the HR for DTP(±OPV)-vaccinated compared with OPV-only vaccinated children was 3.76 (0.89–15.83).

Studies of the Introduction of DTP

In the three studies of introduction of DTP in rural and urban Guinea-Bissau, DTP vaccination was associated with a HR of 2.14 (1.42–3.23) compared with DTP-unvaccinated children (**Figure 3**). The negative effect was separately significant for girls [HR = 2.60 (1.57–4.32)], but not for boys [HR = 1.71 (0.99–2.93)] (Table S3 in Supplementary Material) (test for interaction $p = 0.27$).

TABLE 1 | Background factors for 6–35 months old children who were vaccinated or not vaccinated at their first weighing session in June 1981.

Analysis 1	**Diphtheria–tetanus–pertussis (DTP)-vaccinated at or before first session**	**DTP-unvaccinated in first session**
Mean weight-for-age *z*-score (SD) at first examination	−0.83 (0.06) [394][¤]	−1.17 (0.08) [197][¤]
Analysis 2	**DTP-vaccinated during follow-up**	**Not DTP-vaccinated during follow-up**
N	553	149
Male sex	51% (282)	53% (78)
Twin	3% (15)	2% (3)
Ethnic group		
Pepel	51% (282)	48% (71)
Balanta	15% (84)	17% (25)
Other ethnic groups	34% (187)	36% (53)
Measles vaccinated before June 1981	71% (391)	58% (86)
DTP before June 1981	6% (32)	
Classified as malnourished	6% (33)	5% (8)
Mean number (SD) of weighing sessions per year after start of vaccinations	2.57 (0.06)[#]	0.91 (0.09)[#]

[#]*Comparison p < 0.0001.*
[¤]*Comparison p = 0.001.*

DISCUSSION

Although lower mortality was expected for DTP-vaccinated children compared with the frail unvaccinated children, DTP vaccination was associated with higher mortality, particularly in girls.

Strength and Weaknesses

The home-visits preceding each of the tri-monthly weighing sessions ensured that we had follow-up information for all children and relatively accurate information on the time of movement or death. In the initial analyses, we included only children who had attended the 3-monthly weighing sessions at least once within the last 8–9 months (5). This meant that children mostly living outside the area were not included; these children had no access to community vaccinations and they lived elsewhere where the mortality risk may well have been much higher. We had to exclude some children because their card could not be found (**Figure 1**). The excluded groups (**Figure 1**) did not have high mortality so the increased mortality of DTP-vaccinated children is not due to exclusion of unvaccinated children with a particularly high mortality. When we increased the power of the study by including children only seen before October 1980 (**Figure 1**),

TABLE 2 | Analysis 1: mortality rates (MR) per 100 person-years and hazard ratios (HR) of 6–35 months old children who were either diphtheria–tetanus–pertussis (DTP)-vaccinated or not DTP-vaccinated at their first examination.

	Mortality rate (deaths/person-years)		**HR (95% CI)**	**HR (95% CI), adjusted for weight-for-agez-scores (WAZ)**
Vaccination status	**DTP (±OPV)**	**No DTP**		
All children	9.68 (18/185.9) [394]	4.80 (5/104.1) [197]	2.01 (0.74–5.41)	2.22 (0.82–6.04)
Girls	11.15 (9/80.7) [191]	1.86 (1/53.7) [100]	6.67 (0.84–52.84)	7.03 (0.88–56.04)
Boys	8.58 (9/104.9) [202]	8.07 (4/49.6) [96]	1.04 (0.32–3.40)	1.28 (0.38–4.25)

Bandim, 1981–1983.
Children who have received DTP before June 2, 1981 were censored from the analysis.

the HR estimate for DTP-vaccinated versus DTP-unvaccinated as most recent vaccine changed from 1.77 (0.93–3.38) to 1.89 (1.00–3.55).

TABLE 3 | Analysis 2: mortality rates (MR) per 100 person-years and hazard ratios (HR) of 6–35 months old DTP-vaccinated and diphtheria–tetanus–pertussis (DTP)-unvaccinated children.

	Mortality rate (deaths/person-years)		HR (95% CI)
	DTP(±OPV)	No DTP	
All	5.4 (32/590.6) [553]	4.1 (10/242.5) [327]	1.48 (0.72–3.06)
Girls	6.9 (19/273.5) [270]	2.6 (3/116.4) [155]	2.91 (0.84–10.00)
Boys	4.1 (13/316.5) [282]	5.6 (7/125.1) [170]	0.88 (0.34–2.62)

Bandim, 1981–1983.
178 children were first DTP-unvaccinated and then received DTP during follow-up. Three children had no information on sex. If we adjusted for the most recent WAZ measurement, the HR of 1.48 (0.72–3.06) became 1.52 (0.74–3.15).

The inherent biases in this study are clearly in favor of the DTP-vaccinated children (2): first, the DTP vaccine protects against three severe diseases. Second, the DTP-unvaccinated children were usually children deemed too sick or too weak to be vaccinated, as evidenced by the nurse's notes on the BHP card and by the fact that these children had worse nutritional status. Third, DTP-unvaccinated children attended the weighing sessions less frequently (**Table 1**) and were, therefore, more likely to be staying for longer periods in the rural areas where the mortality risk was higher (12). Noteworthy, we were able to obtain mortality information from these children because their father and other relatives stayed in the study area.

WHO experts have argued that the negative effect of DTP is exaggerated, because studies have only been conducted in situations with herd immunity against pertussis and where the benefit of preventing pertussis would not be seen (13). However, pertussis was endemic in the 1980s before the roll

TABLE 4 | Analysis 3: mortality rates (MR) per 100 person-years and hazard ratios (HR) of 6–35 months old children in relation to most recent vaccination.

Vaccination status	Mortality rate (deaths/person-years)		HR (95% CI) Had weighing session after October 1, 1980[a]	HR (95% CI) All children[b]
	Diphtheria–tetanus–pertussis (DTP) (±OPV)	No DTP		
All	6.2 (28/451.0) [535]	3.7 (14/382.0) [539]	1.77 (0.93–3.38)	1.89 (1.00–3.55)
Vaccination status	DTP(±OPV)	Only live vaccine (MV, OPV, or MV + OPV)		
All	6.2 (28/451.0) [535]	3.3 (10/303.84) [473]	1.90 (0.92–3.94)	1.99 (0.96–4.12)

Bandim, 1981–1983.
[a]*See **Figure 1**; Adjustment for the most recent weight-for-age z-scores measurement did not change the estimate.*
[b]*Include 47 children whose most recent weighing session prior to June 1981 had been before October 1980.*

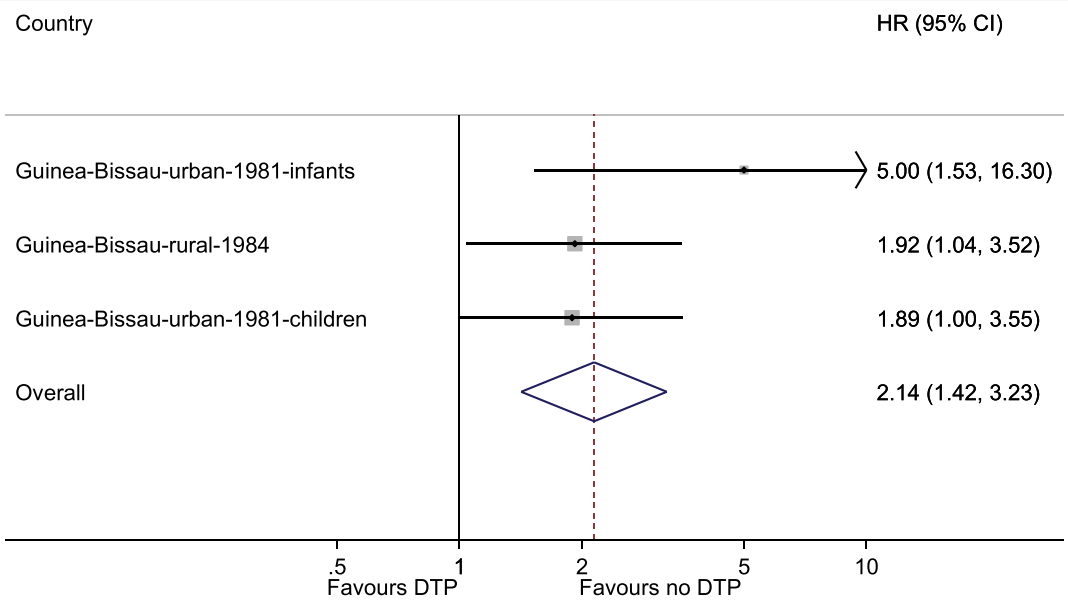

FIGURE 3 | Meta-analysis of the three studies of the introduction of diphtheria–tetanus–pertussis. The fixed effects model gave an estimate of 2.14 (1.42–3.23) and the random effects model gave 2.17 (1.39–3.38).

out of the vaccination program in Guinea-Bissau, but all three studies of the introduction of DTP into urban and rural areas of Guinea-Bissau showed excess mortality associated with DTP vaccination (5, 12).

Comparison With Previous Studies of DTP and OPV

This study was small (Table S1 in Supplementary Material) and many results were not statistically significant; some variability was, therefore, also to be expected. Still the results were very similar to the previous studies of the introduction of DTP and OPV. All three studies have accurate assessment of vaccination status and prospective follow-up; all three studies have found that DTP is associated with an increase in all-cause mortality (3). A previous meta-analysis suggested twofold higher mortality for DTP-vaccinated children (3). However, this is probably an underestimation of the "true" effect since the unvaccinated group is usually affected by various negative health selection biases, including frailty bias. In the best studies, with no selection bias or good control for frailty bias, DTP has been associated with four to five times higher mortality (2, 5).

As in this study, we have previously found excess female mortality after DTP vaccination (4). In our previous meta-analysis, we compared DTP-vaccinated females with DTP-unvaccinated, but BCG-vaccinated females, and DTP was associated with an HR of 2.54 (1.68–3.86). In the three studies of the introduction of DTP very few of the DTP-unvaccinated had received BCG. Hence, DTP seems to have a marked negative effect for females irrespective of whether one compares DTP-vaccinated girls with totally unvaccinated or with BCG-vaccinated girls.

There have been few studies of OPV administered alone (5). It is, therefore, worth noting that the small number of children who received OPV only had lower mortality than DTP-vaccinated children in this study (Table S1 in Supplementary Material), although the difference was not statistically significant. We have recently been able to document marked beneficial effects of OPV on all-cause mortality in both randomized trials and in natural experiments with OPV campaigns (18, 19).

Interpretation

Various WHO committees have previously reviewed the non-specific effects of vaccines and have dismissed the possibility that DTP could have negative effects, and have suggested that the negative effect of DTP is likely to be explained by uncontrolled confounding or bias (13–17). Recently, the Strategic Advisory Group of Experts on Immunization sponsored a review of the potential non-specific effects of BCG, DTP, and MV (15, 16). Though it was noted that the majority of studies (7/10) showed a deleterious effect of DTP, the evidence was considered inconsistent because two studies showed a beneficial effect. Furthermore, the review invoked "a high risk of bias" for all the observational studies (17).

However, it is important to consider the direction of bias. All documented biases favor the vaccinated group because vaccination is usually delayed in unhealthy children, and DTP-unvaccinated children should, therefore, have a higher mortality than vaccinated children (2, 3). The WHO review mentioned four potential biases, which would favor the unvaccinated group (15). First, sick children might come more often to a health center for consultation and, therefore, be more likely to receive DTP, since WHO has recommended vaccination of sick children; this bias was clearly not relevant in Guinea-Bissau, where neither nurses nor mothers thought that a sick child should be vaccinated. Second, starting follow-up from a survey sometime after the actual DTP vaccinations had been administered, as would often happen in a setting, where vaccination information is collected with intervals, could potentially mean that frail children in the unvaccinated group had already died, and that the DTP-vaccinated children, therefore, had an "unnaturally" high mortality (15). The one study testing this found no evidence for such a bias (20) and more importantly, several studies, including all three studies of the introduction of DTP in Guinea-Bissau, started observation at the date of vaccination for almost all children and found strong negative effects. Hence, this bias was not relevant in the present study. Third, censoring follow-up at subsequent MV would remove some of the best children from the DTP-vaccinated group and, therefore, gives higher mortality in the DTP group (15). Again, the studies that have tested this potential bias have not found evidence for such a bias (21) but, more importantly, several studies—like the present one—did not censor for MV and found equally strong negative effects for DTP (2). Hence, this bias was not relevant in this study. Fourth, it has been discussed whether a bias in reporting could have played a role (15). The observation of increased mortality after DTP was reported more than 15 years ago (22), and has not been contradicted by a properly conducted prospective study. In contrast, several other groups have reported that DTP was associated with increased overall mortality (23–25) or higher female than male mortality (23, 26–28). Hence, reporting bias is a very unlikely explanation. We have now reported all the possible data sets from when DTP was introduced in both urban and rural areas of Guinea-Bissau (5, 12); all showed a negative effect of DTP vaccination. Hence, reporting bias is not relevant in relation to the studies of the introduction of DTP from Guinea-Bissau. Therefore, the three studies of the introduction of DTP from Guinea-Bissau (5, 12) are not affected by the theoretical biases used to recommend caution in the interpretation of observational studies suggesting deleterious effects from DTP (15–17).

The specific immunological mechanisms explaining why DTP and OPV have NSEs have not yet been identified. However, there is an increasing evidence that live vaccines (BCG, Vaccinia) induce innate immune training producing stronger pro-inflammatory responses which may lead to protection against unrelated infections (29, 30). In contrast, studies of non-live vaccine have suggested that they may induce tolerance which could enhance the susceptibility to unrelated infections (31). The pattern of worse effects for females than for males have turned out to be systematic for several non-live vaccines, including DTP (4, 26), inactivated polio vaccine (32), hepatitis B vaccine (33), pentavalent vaccine (34), and RTS,S malaria vaccine (35). This pattern has not been studied from an immunological perspective and an explanation has still to be found.

Implications and Conclusion

Our data clearly showed that DTP vaccinations were delayed in unhealthy children. Hence, healthier children received DTP first, and DTP-unvaccinated children should, therefore, have had a higher mortality rate. Despite this, DTP was associated with increased child mortality, particularly for girls. All three studies of the introduction of DTP vaccine found negative effects which are different from what should have been expected due to the disease-preventive effects of the vaccine and the inherent biases favoring vaccinated children (5, 12). The results are also in stark contrast to the studies of the introduction of measles vaccine, which uniformly show very strong mortality reductions (6, 7, 15). Hence, the studies of the introduction of DTP constitute a clear danger signal that DTP may substantially increase all-cause mortality.

Adding to the danger signal, DTP is associated with increased female mortality relative to male mortality in all available studies. Girls did not have higher mortality than boys in the pre-vaccination era in West Africa (2). Hence, there is a need for further research to assess the overall mortality effect of DTP and how the negative effects of DTP can be removed or modified. For example, co-administration of BCG and DTP may reduce the negative effect of DTP (21). Randomized trials have also shown that MV or BCG administered shortly after DTP may reduce the negative effect of DTP and lower mortality (2). Such alternative immunization strategies should be further tested in randomized trials.

Given the threat from diphtheria, tetanus, and pertussis and the less-effective acellular pertussis vaccine used in many countries, it is understandable that there has been reluctance in accepting that DTP could have negative effects for overall health in low-income countries. However, the studies from low-income countries have been consistent in showing deleterious effect of DTP (3); furthermore, the first studies are now showing that non-live and live vaccines have differential NSEs on hospital admissions for infectious diseases in high-income countries (36, 37). Hence, it would seem to be high time to settle whether DTP has negative effects on overall child health and if it has negative effects to explore whether alternative vaccination schedules could remove the problem.

In the current global immunization system, the coverage for the third dose of DTP (DTP3) is used as the main performance indicator for national immunization programs. This will clearly lead to an emphasis on increasing the coverage for DTP3 (1) more than the coverage for other vaccines. Given that all studies, including the present one, suggest that DTP is associated with increased female mortality, this is really an illogical position. We need to use program performance indicators which are positively associated with better child survival.

INDEPENDENCE

The funding agencies had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

TRANSPARENCY

The first author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING

Through request to the authors.

ETHICS STATEMENT

The study of nutritional status was planned between the SAREC (Swedish Agency for Research Collaboration with Developing Countries) and the Ministry of Health in Guinea-Bissau. There were no ethical committees for approval of health research at the time of the study. The study was explained to the population in community meetings organized by the local committee and the researchers prior to initiation of data collection. Consent was not sought from individual mothers, since the project implemented intended national policies for nutritional surveillance and immunization.

AUTHOR CONTRIBUTIONS

CB and PA proposed the study. PA collected the original data. AR is responsible for the demographic surveillance system. SM and PA cleaned the data. SM conducted the statistical analyses. The first draft was written by PA; all authors contributed to the final version of the paper. PA will act as guarantor of the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fpubh.2018.00079/full#supplementary-material.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Exhibit C

ICAN
Informed Consent Action Network

VIA FEDEX

December 5, 2017

UNICEF House
Dr. Anthony Lake
Executive Director
3 United Nations Plaza
New York, NY 10017
Telephone: +1(212) 32 67 490
Facsimile: +1(212) 32 67 477

Re: Deaths caused by DTP

Dear Dr. Lake,

UNICEF has been instrumental in vaccination campaigns in many countries, including their prior and ongoing DTP vaccination campaign. We write to bring to your attention an alarming study, published this year, which found that children vaccinated with DTP were 10 times more likely to die in the first six months of life than those children that were unvaccinated.[1] A copy of this study is enclosed.

Dr. Peter Aaby, the lead author of this study, is renowned for studying and promoting vaccines in Africa with over 300 published studies.[2] Dr. Aaby, after concluding that children vaccinated with DTP were 10 times more likely to die in the first 6 months of life than the unvaccinated, states:

> "All currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis."[3]

[1] A copy of this study can also be found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/
[2] https://www.ncbi.nlm.nih.gov/pubmed/?term=PETER+AABY%5BAuthor+-+Full%5D
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/

This study also found that children vaccinated with DTP were dying from causes never associated with this vaccine, such as respiratory infections, diarrhea, and malaria.[4] This indicated that while DTP reduced the incidence of diphtheria, tetanus, and pertussis, it increased susceptibility to other infections.[5]

Unlike most vaccine safety studies in which subjects are not well matched, Dr. Aaby's study is reliable because the subjects were accurately matched. People with pre-existing health problems are reluctant to receive a vaccine, and are therefore unwittingly used as controls. When this happens, the control group is sicker than the vaccine-exposed group at the outset of the study. Studies with this problem give wrong results, and make the vaccine look much safer than it really is. (This issue is explained in detail in a publication by vaccine safety scientists at the U.S. Centers for Disease Control.[6]) Dr. Aaby's study is the only study looking at death from DTP specifically designed to avoid this error.

When an extremely well-designed study from accomplished vaccine proponents at the Research Centre for Vitamins and Vaccines and Institute of Clinical Research at the University of Southern Denmark/Odense University Hospital finds that children receiving a certain product are dying at 10 times the rate of children not receiving that product, prudence dictates pausing the distribution of that product. Please confirm that UNICEF has ceased distributing DTP and kindly advise what research UNICEF is undertaking regarding deaths from DTP vaccine, including identifying the families killed by this vaccine in order to provide them with reparations.

We also note that continued vaccination with DTP without disclosing the findings in Dr. Aaby's study would violate the Nuremberg Code which provides that:

> "The voluntary consent of the human subject is absolutely essential. This means that the person … should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision."[7]

The Nuremberg Code thus draws a sharp line when stating that no human being should receive a medical procedure and/or product without informed consent. Failing to advise

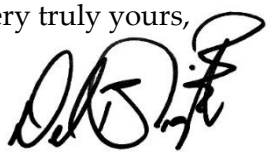
[4] Ibid.
[5] Ibid.
[6] https://www.ncbi.nlm.nih.gov/pubmed/1415136
[7] https://history.nih.gov/research/downloads/nuremberg.pdf

the findings of Dr. Aaby's study to parents prior to administering the DTP vaccine would violate this basic human right.

While medical interventions have saved countless lives, the graveyard of history is also replete with once lauded but later abandoned medical inventions and practices. When an issue with a medical procedure is identified, especially when it is killing children, immediate action is necessary. We hope that political and economic considerations will not cloud the clear moral and ethical duty to protect children from death from DTP vaccine.

If UNICEF does not intend to cease distribution of DTP vaccine or at least confirm that parents of children receiving this vaccine are advised of Dr. Aaby's findings, we intend to take appropriate legal action. We look forward to receiving a timely response to this letter so that we can follow-up with all member states cc'd on this communication with regard to what actions UNICEF intends to take in response to Dr. Aaby's extremely concerning finding that children receiving DTP vaccine had a death rate 10 times that of children that were not vaccinated.

Very truly yours,



Del Bigtree

cc: See Appendix A (*Countires Using DTP Vaccine*)

Enclosure: Mogensen S.W., Andersen A., Rodrigues A., Benn C.S., Aaby P., *The Introduction of Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine Among Young Infants in an Urban African Community: A Natural Experiment*, EBioMedicine. 2017;17:192–198.

Exhibit D

United Nations Children's Fund
Three United Nations Plaza
New York, New York 10017

Telephone 212 326 7000
Facsimile 212 888 7465
212 888 7454
www.unicef.org

Date 6 February 2018

Dear Mr Bigtree

Many thanks for your message expressing interest in learning more regarding the safety and effectiveness of the DTP vaccine. I was asked by our outgoing Executive Director, Anthony Lake to prioritize the response to your letter, as he was preparing to leave office, and he asked me to convey his apologies for not responding himself.

I would like to assure you that we take the issue of vaccine safety very seriously. Vaccine safety, along with the safety of all health interventions, are closely followed and monitored by ourselves, in close association with technical agencies like the World Health Organization (WHO). The wellbeing of children, as you are aware, is central to the mandate of UNICEF and we do not compromise in any way in fulfilling this mandate.

There are various independent and multidisciplinary expert bodies at global and national level, which regularly review the evidence on the impact of vaccines and on its safety profile and provide advice to WHO and UNICEF. Notably, the Strategic Advisory Group of Experts (SAGE) is the principal advisory group to WHO for vaccines and immunization (established in 1999). It is charged with advising on overall global policies and strategies, ranging from vaccines (impact and safety) and technology, research and development, to delivery of immunization and its linkages with other health interventions. The Global Advisory Committee on Vaccine Safety (GACVS) responds to vaccine safety issues of potential global importance (established in 1999). The GACVS provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long term national immunization programmes. The Immunization and Vaccines Related Implementation Research Advisory Committee (IVIR-AC) provides independent advice on matters related to implementation research and their relevance to immunization policies and practices, and reviews best practices relating to methods for conducting and reporting on quantitative immunization and vaccines-related research (including vaccine impact and safety evaluations).

Some authors have suggested that some of the vaccines routinely administered to infants and children also affect the risk of illness and death from conditions other than the specific infectious diseases they are designed to prevent. The hypotheses concerning these "non-specific effects" of vaccines include that, under some circumstances, some vaccines (for example, measles and Bacillus Calmette-Guérin (BCG)) lower subsequent risk, whereas others (such as DTP) increase subsequent risk of illness and death from other causes. It is further postulated that the magnitude of these effects depends on other factors, including gender and vitamin A supplementation status. The potential for non-specific vaccine effects has led some authors to question whether the vaccination schedules currently recommended by WHO should be adjusted.

WHO with the support of several independent experts has been reviewing and discussing evidence around the non-specific effects of vaccines and immunization programmes since 2001. In 2012, SAGE requested that WHO review the evidence concerning the possible non-specific effects of routine infant vaccines on mortality. A working group was established in March 2013 to review data on non-specific mortality effects and assess whether current evidence is sufficient to inform adjustments in policy recommendations, or if further scientific

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investigation is required. A systematic review was conducted to evaluate the non-specific effects on all-cause mortality, in children under 5, of Bacillus Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP), and standard titre measles containing vaccines (MCV); to examine internal validity of the studies; and to examine any modifying effects of gender, age, vaccine sequence, and co-administration of vitamin A.

In 2014 SAGE reviewed the outcomes of this review and concluded that, regarding the possible non-specific effect of DTP on all-cause mortality, the available data neither exclude nor confirm the possibility of beneficial or deleterious non-specific effects of DTP vaccines on all-cause mortality. Randomized controlled trials did not contribute any evidence on non-specific effects of DTP. Evidence was largely from observational studies considered at a high risk of bias. Further, SAGE stated that further observational studies are unlikely to contribute to policy decisions. SAGE considered that the non-specific effects on all-cause mortality warranted further research. SAGE recommended that the IVIR- AC be tasked with providing advice on which priority research questions need to be addressed to inform policy decisions, and what kinds of studies and study designs would provide answers to these questions. SAGE concluded that the evidence does not support a change in policy for DTP, and emphasized the benefit of DTP in preventing disease and the importance of the current recommendation.

In conclusion, I would like to reiterate that UNICEF (and WHO) takes the issue of vaccine safety very seriously and for several decades has reviewed the evidence to guide policy decisions. While available evidence does not support a change in DTP vaccination policy, there is substantial evidence on the benefits of DTP (and pentavalent) vaccines in preventing disease and on the substantial risk for unvaccinated population DTP vaccines as evidenced by diphtheria, pertussis and tetanus cases and deaths that we are seeing today. In a number of locations globally, we are experiencing diphtheria outbreaks with high case fatality, which is a direct result of these children not receiving the recommended doses of vaccines in their childhood. Diphtheria, Tetanus and Pertussis were among the leading causes of childhood death in the pre-vaccine era causing several hundred thousand cases each year.

I hope my message provides you with the information that you were seeking. I am copying representatives of our member states who are included in your original message.

Please do not hesitate to contact us if you have further queries or require clarifications. The appropriate point of contact in our office is Dr. Robin Nandy, Principal Advisor and Chief of Immunizations and he can be contacted at **rnandy@unicef.org**

Sincerely,

Dr. Stefan Peterson
Associate Director, Health
UNICEF Headquarters

Exhibit E

VIA FEDEX

March 15, 2018

UNICEF House
Henrietta H. Fore, Executive Director
Dr. Stefan Peterson, Associate Director, Health
3 United Nations Plaza
New York, NY 10017
Telephone: (212) 326-7490
Facsimile: (212) 326-7477

Re: *DTP Vaccine is Killing More Children Than it Saves & is Only Used in Developing Countries*

Dear Ms. Fore and Dr. Peterson,

Thank you for your response dated February 6, 2018 to our letter of December 5, 2017[1] which detailed the disturbing results of a seminal study, published February 1, 2017, which found that DTP vaccine[2] is killing more children than it is saving (the "**2017 Study**"). The 2017 Study was the only item discussed in our letter and a copy of that study was also enclosed with our letter. Yet, in response, you did not address that study. We therefore write again to emphasize the need for UNICEF to quickly join all developed nations and cease administration of DTP vaccine.

A. Dr. Aaby's 2017 Study Establishes the Danger of Administering DTP Vaccine

The primary author of the 2017 Study is internationally respected vaccine researcher Dr. Peter Aaby.[3] In his rigorous 2017 Study, Dr. Aaby and his colleagues found that the children receiving DTP vaccine were *10 times more likely to die* in the first 6 months of life than the unvaccinated children.[4] The 2017 Study was therefore forced to conclude:

[1] Copies of these letters are available at http://www.icandecide.org/
[2] "DTP vaccine" is also commonly referred to as "DTwP vaccine" or so-called "whole cell pertussis vaccine," as opposed to "DTaP vaccine" or so-called "acellular pertussis vaccine."
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/pdf/main.pdf
[4] Ibid.

> "All currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis."[5]

This 2017 Study was published in an Elsevier peer-reviewed journal which collaborates with The Lancet and was funded by the Ministry of Foreign Affairs, Denmark and the European Union.[6] As you know, Dr. Aaby is renowned for studying and promoting vaccines in Africa with over 300 published studies.[7] Dr. Aaby, among other things, in 1978, established and continues to direct the Bandim Health Project, a Health and Demographic Surveillance System site in Guinea-Bissau.[8] In 2000, he was awarded the Novo Nordisk Prize, the most important Danish award within health research.[9] In 2009, the Danish Ministry of Foreign Affairs selected Dr. Aaby as a leader in the fight against global poverty.[10]

Instead of addressing the 2017 Study, your response points to a 2014 review by SAGE regarding the possible non-specific effect of DTP vaccine on all-cause mortality. The 2014 SAGE review pre-dates the 2017 Study by three years and at that time concluded, as stated in your letter, that "the available data neither excludes nor confirm[s] the possibility of beneficial or deleterious non-specific effects of DTP vaccines on all-cause mortality." Even though your letter does not cite or provide a copy of the 2014 SAGE review, links to same are footnoted here.[11] Dr. Aaby expressly created the 2017 Study to address many of the weaknesses in prior DTP vaccine studies identified by the 2014 SAGE review. By addressing the concerns raised by SAGE, the 2017 Study's results should be considered highly reliable, providing clear evidence DTP vaccine is killing more children than it saves.

The 2014 SAGE review identified 16 studies that compared death rates between children receiving DTP vaccine and children not receiving DTP vaccine.[12] SAGE found that a "majority of studies indicated a negative effect of DTP," meaning a majority of the

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[5] Ibid.
[6] Ibid.
[7] https://www.ncbi.nlm.nih.gov/pubmed/?term=PETER+AABY%5BAuthor+-+Full%5D
[8] https://www.bandim.org/
[9] http://novonordiskfonden.dk/en/content/novo-nordisk-prize
[10] https://www.bandim.org/press
[11] http://www.who.int/immunization/sage/meetings/2014/april/1_NSE_Backgroundpaper_final.pdf; http://www.who.int/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf
[12] Ibid.

studies SAGE reviewed found that DTP vaccine killed more children than it saved.[13] For example, one study found that children receiving DTP vaccine were between 154% and 1,219% more likely to die than those that did not receive DTP vaccine.[14] SAGE, however, chose to give virtually no weight to these studies, despite their being conducted by WHO respected vaccine experts, because SAGE stated: (i) these studies were not "randomized" (*i.e.*, children were not randomly assigned to either receive or not receive DTP vaccine, hence potentially introducing bias[15]), (ii) "OPV [Oral Polio Vaccine] was administered concomitantly with DTP in most included studies" and hence it "was not possible to separate any possible effects of DTP from OPV in the available studies," and (iii) these studies were often conducted in communities with existing "herd immunity," which could have introduced further bias.[16]

Dr. Aaby designed the 2017 Study to address these three issues.[17] It rectified the "randomized" issue by comparing children vaccinated solely based on birthdates, thereby creating a random grouping.[18] It corrected the "OPV with DTP" issue by comparing children with no vaccines and those only receiving DTP.[19] And it addressed the "herd immunity" issue by looking at death rates at the time of the introduction of DTP vaccination.[20] As explained in the introduction to the 2017 Study:

> WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recently reviewed the potential NSEs [Non-Specific Effects] of … diphtheria-tetanus-pertussis (DTP) … and recommended further research (Higgins et al., 2014; Strategic Advisory Group of experts on Immunization, 2014).
>
> Though protective against the target diseases, DTP may increase susceptibility to unrelated infections (Aaby et al., 2003b, 2004a, 2012) (Appendix A). The SAGE review noticed that the majority of studies found a detrimental effect of DTP

[13] Ibid.
[14] Ibid.
[15] For example, unvaccinated children often do not receive vaccines because they are very frail, malnourished or sick, and hence more likely to die irrespective of vaccination, hence the unvaccinated group is often sicker than the vaccinated group, thus making the vaccine appear safer. By randomly picking which children receive or do not receive DTP vaccine, a researcher can avoid this type of bias.
[16] See footnote 11.
[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/pdf/main.pdf
[18] Ibid.
[19] Ibid.
[20] Ibid.

> (Higgins et al., 2014). However, SAGE considered the evidence inconsistent because two studies reported beneficial effects (Higgins et al., 2014) and that most studies underestimated the benefit of DTP because studies were conducted in situations with herd immunity. Furthermore, all studies gave DTP and OPV together, making it impossible to separate effects of DTP and OPV (SAGE non-specific effects of vaccines Working Group, 2014).
>
> On the other hand, the "unvaccinated" children in these studies have usually been frail children too sick or malnourish to get vaccinated, and the studies may therefore have underestimated the negative effect of DTP. We therefore examined what happened when DTP and OPV were first introduced, but not always given together, in 1981–1983 in the capital of Guinea-Bissau. In this situation the children were allocated by birthday to receive vaccines early or late and the "unvaccinated" were therefore not frail children. [21]

The 2017 Study also explains why it is the best study and evidence that modern science will likely obtain to determine whether DTP vaccine kills more children than it saves:

> The recently published SAGE review called for randomized trials of DTP (Higgins et al., 2014). However, at the same time the IVIR-AC committee [Immunization and Vaccines Related Implementation Research Advisory Committee] to which SAGE delegated the follow-up studies of the NSEs [Non-Specific Effects] of vaccines has indicated that it will not be possible to examine the effect of DTP in an unbiased way. If that decision by IVIR-AC remains unchallenged, the present study [the 2017 Study] may remain the closest we will ever come to a RCT [Randomized Controlled Trial] of the NSEs of DTP. [22]

The 2017 Study therefore represents the closest and best data UNICEF is likely ever going to have regarding whether DTP kills more children than it saves. And as a reminder, this

[21] Ibid.
[22] Ibid.

study found that children receiving DTP in the first six months of life *died at ten times the rate* of those children that received no vaccines in the first six months of life.[23] And it concluded that "All currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis."[24]

Your letter states that the "wellbeing of children, . . . is central to the mandate of UNICEF and we do not compromise in any way in fulfilling this mandate." If so, the 2017 Study shows why DTP vaccine presents a danger to the "wellbeing of children" receiving it and UNICEF's mandate dictates that you should, at least, pause supporting the use of DTP vaccine until UNICEF has evidence to demonstrate children receiving the vaccine do not die at a greater rate than children not receiving this vaccine.

B. UNICEF Should Join Every Developed Nation in Stopping Use of DTP Vaccine

There is a lesson in the fact that every single developed country in the world has long-ago phased out using DTP vaccine.[25] The following are just a few examples of the nations that have ceased all use of the DTP vaccine, and the year in which they were phased out:

- Japan in 1981
- South Korea in 1989
- New Zealand in 1994
- Sweden in 1996
- Australia in 1996
- United States in 1997
- Canada in 1998
- China in 2008

Yet, UNICEF continues to promote and distribute this vaccine to developing countries.[26] Given the findings of the 2017 study, UNICEF's continued use of DTP vaccine, in the face of developed nations' shunning of this vaccine, is very troubling.

C. Industrial and Financial Considerations Should Not Stand in the Way of Protecting Children from Harm

We understand that UNICEF has declared that a "healthy industry is vital to ensure uninterrupted and sustainable supply of vaccines" and has extensive financial arrangements and a "long standing relationship with" pharmaceutical companies

[23] Ibid.
[24] Ibid.
[25] http://www.who.int/immunization/monitoring_surveillance/data/en/
[26] Ibid.

producing vaccines.[27] Indeed, in 2016 alone, UNICEF purchased over $1.6 billion dollars of vaccine products from these companies and spent an equally significant sum paying companies for their distribution, in total amounting to over a third of UNICEF's budget.[28] We nonetheless are sure that these political and economic considerations will not cloud UNICEF's judgment when evaluating its clear moral and ethical duty to protect children from death from DTP vaccine.

D. Continued Use of DTP Vaccine Raises Issues Regarding the Basic Human Right of Informed Consent

Also, previously noted, distributing and administering the DTP vaccine without disclosing the dangers of DTP vaccine, as found in the 2017 Study, and that all developed countries have phased out DTP vaccine, would violate the Nuremberg Code, which provides:

> "The voluntary consent of the human subject is absolutely essential. This means that the person … should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision."[29]

The Nuremberg Code thus makes clear no human being should receive a medical procedure and/or product without informed consent. Failing to, at least, advise parents about the increased risk of death from DTP vaccine prior to administering this vaccine to their child would violate this basic human right.

As with our last letter, we again enclose a copy of the 2017 Study. We suggest you review this study carefully. You and every member of the UNICEF staff involved in the procurement, distribution and promotion of DTP vaccine should be aware of its findings, should receive a copy of the 2017 Study and of this correspondence. Continued promotion and distribution of DTP vaccine without any evidence to refute the 2017 Study's unmistakable findings would violate various laws designed to protect children from harm.

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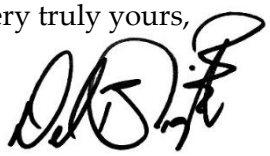
[27] https://www.unicef.org/supply/index_vaccines.html; https://www.unicef.org/supply/index_57476.html
[28] https://www.unicef.org/supply/index_vaccines.html
[29] https://history.nih.gov/research/downloads/nuremberg.pdf

In light of the 2017 Study, we believe an open and frank discussion within UNICEF regarding DTP vaccine will lead the organization to conclude that it must now join the developed world in ceasing to use DTP vaccine. If UNICEF will not take immediate action on this issue, then the countries that are copied on this communication are encouraged to take domestic action based on the 2017 Study, which reflects what is likely the best evidence that can be produced with regard to whether DTP vaccine kills more children than it saves.

Very truly yours,



Del Bigtree

cc: See Appendix A (*Countries Using DTP Vaccine*)

Enclosure: Mogensen S.W., Andersen A., Rodrigues A., Benn C.S., Aaby P., *The Introduction of Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine Among Young Infants in an Urban African Community: A Natural Experiment*, EBioMedicine. 2017;17:192–198.

Exhibit F

ICAN
Informed Consent Action Network

VIA FEDEX

July 26, 2018

UNICEF House
Henrietta H. Fore, Executive Director
Dr. Stefan Peterson, Associate Director, Health
3 United Nations Plaza
New York, NY 10017
Telephone: (212) 326-7490
Facsimile: (212) 326-7477

Re: *DTP Vaccine is Killing More Children Than it Saves*

Dear Ms. Fore and Dr. Peterson,

Our opening letter of December 5, 2017 detailed the disturbing results of a rigorous and seminal study, published February 1, 2017, which again found that DTP vaccine[1] is killing more children than it is saving (the "**2017 Study**"). A copy of the 2017 Study is attached as **Exhibit A** and a copy of our opening letter of December 5, 2017 letter is attached as **Exhibit B**.

You responded to our opening letter on February 6, 2018, a copy of which is attached as **Exhibit C**. We responded to this letter on March 15, 2018 noting that, amazingly, your response did not address the 2017 Study and that the information it did provide in fact supported the conclusion of the 2017 Study. Hence, we urged UNICEF to quickly join all developed nations and cease administration of DTP vaccine. A copy of our March 15, 2018 response letter is attached as **Exhibit D**.

Despite the passage of over four months, UNICEF has failed to respond to our March 15, 2018 letter and it has now been over eight months since we brought to your attention the fact that UNICEF is purchasing, distributing and widely promoting a vaccine for which, as is plain from our letter exchange, the best available evidence clearly demonstrates it is killing far more children than it is saving.

As you are likely also already acutely aware, on the heels of our last letter, Dr. Aaby and his renown vaccine advocate colleagues published an article on March 19, 2018, in the journal Frontiers in Publish Health, entitled *Evidence of Increase in Mortality After the Introduction of Diphtheria–Tetanus–Pertussis Vaccine to Children Aged 6–35 Months in Guinea-Bissau: A Time for Reflection?* (the "**2018 Study**"). A copy of this article is attached as **Exhibit E**.

[1] "DTP vaccine" is also commonly referred to as "DTwP vaccine" or so-called "whole cell pertussis vaccine," as opposed to "DTaP vaccine" or so-called "acellular pertussis vaccine."

As you will recall, the 2017 Study found that babies younger than six months of age receiving DTP vaccine died at ten times the rate as babies in the same age range that did not receive any vaccines. (Exhibit A.) The 2018 Study looked at children between six and thirty-five months of age and compared DTP-vaccinated children that were generally healthier and had better nutritional status with non-DTP-vaccinated children who generally were unhealthier and had worse nutritional status. (Exhibit E.) The incredible result:

> Although having better nutritional status and being protected against three infections, 6-35 months old DTP-vaccinated children tended to have higher mortality than DTP-unvaccinated children. All studies of the introduction of DTP have found increased overall mortality.

(Exhibit E.) The children in developing countries which still use DTP vaccine would be better served if UNICEF and the WHO took the following advice from the 2018 Study:

> Given the threat from diphtheria, tetanus, and pertussis and the less-effective acellular pertussis vaccine used in many countries, it is understandable that there has been reluctance in accepting that DTP could have negative effects for overall health in low-income countries. However, the studies from low-income countries have been consistent in showing deleterious effect of DTP. …
>
> In the current global immunization system, the coverage for the third dose of DTP (DTP3) is used as the main performance indicator for national immunization programs. This will clearly lead to an emphasis on increasing the coverage for DTP3 more than the coverage for other vaccines. Given that all studies, including the present one, suggest that DTP is associated with increased female mortality, this is really an illogical position. We need to use program performance indicators which are positively associated with better child survival.

(Exhibit E.)

In our letter from March 2018, we stated that you and every member of the UNICEF staff involved in the procurement, distribution and promotion of DTP vaccine should be aware of the 2017 Study's findings as well as receive a copy of the 2017 Study and of our prior correspondence. We also asserted that continued promotion and distribution of DTP vaccine without any evidence to refute the 2017 Study's unmistakable findings would violate various laws designed to protect children from harm.

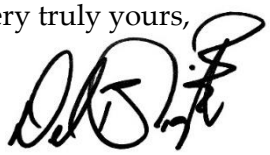
It has now been over eight months since we provided you, on two occasions, a copy of the 2017 Study. Yet, despite your verbose response in February 2018, you have failed to provide even a single argument to contest the 2017 Study's methodology or conclusions. In fact, you have failed

to address this study altogether. And you have also failed to indicate that UNICEF will, at the least, as required by the Nuremberg Code, assure that parents are being advised of the increased risk of death from DTP vaccine prior to administering this vaccine to their child.

Copies of this letter with all exhibits will be distributed directly to all members of UNICEF that we can identify that are involved in the purchase, distribution and promotion of DTP vaccine. For all UNICEF individuals receiving this letter, please take notice that your continued distribution of this for-profit product violates various laws, including various international human rights law. Furthermore, absent forthwith confirmation from UNICEF that it has either ceased distribution of DTP vaccine or has evidentiary support for why the 2017 Study and 2018 Study are incorrect, we intend to take appropriate remedial action, including referral to the International Criminal Court, against all individuals at UNICEF involved in continued purchase, distribution and promotion of a product that the best available evidence makes clear is killing far more children than it is saving.

We also hereby repeat the call to all countries that are copied on this communication to take domestic actions based on the 2017 Study and 2018 Study to protect babies in their country from increased rates of death from a for-profit product that all developed countries have long ago ceased using due to its serious adverse reactions.

Very truly yours,



Del Bigtree

cc: See Appendix A (*Countries Using DTP Vaccine*)

Enclosures

APPENDIX

Permanent Mission of Afghanistan to the United Nations
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Permanent Mission of the Republic of Albania to the United Nations
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albania.un@albania-un.org

Permanent Mission of Algeria to the United Nations
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Permanent Mission of the Republic of Azerbaijan to the United Nations
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Exhibit G

VACCINE SCIENCE FOUNDATION

UNICEF House
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Dear Dr. Lake,

Please find enclosed an expert report by Peter C. Gøtzsche, Professor, DrMedSci, MSc on the effect of the DTP vaccine on total mortality in low-income countries. Gøtzsche analyzed the WHO's 2014 systematic review of the non-specific effects of BCG, DTP, and measles related vaccines. He then conducted a review of the literature and analyzed any studies published after the WHO report which assessed the effect of DTP vaccine on total mortality. According to the available evidence, Gøtzsche came to the conclusion that "it is likely that the DTP vaccine increases total mortality in low-income countries." [1]

This echoes the conclusion by Peter Aaby – the scientist credited for the discovery of non-specific effects of vaccines - that "all currently available evidence suggests that DTP vaccine may kill more children from other causes than it saves from diphtheria, tetanus or pertussis. Though a vaccine protects children against the target disease it may simultaneously increase susceptibility to unrelated infections."[2] Dr. Aaby's recent study, the first ever naturally randomized comparison of mortality between children receiving DTP and those that are unvaccinated, found that children vaccinated with DTP were 10 times more likely to die in the first 6 months of life than the unvaccinated.[2]

As a leading agency for vaccine procurement, UNICEF plays a vital role in increasing the accessibility of vaccinations worldwide, and provides crucial support for the WHO's Global Vaccine Action Plan (GVAP). Among other targets, the GVAP calls for nations to reach 90 percent or greater coverage of the DTP3 vaccine.[3] If Gøtzsche's conclusion is correct, this is a counterproductive strategy to reduce child mortality rates in low-income countries.

The Vaccine Science Foundation proudly supports UNICEF's goal of reducing child mortality worldwide. For this reason, the Vaccine Science Foundation urges you to read the expert report *Effect of DTP Vaccines on Mortality in Children in Low-Income Countries*, to ensure that UNICEF can productively engage in its goal of reducing child mortality.

The Vaccine Science Foundation respectfully requests that UNICEF explain whether it accepts the conclusion of the attached expert report. If it does, please explain the actions it intends to take. If it does not, please explain the basis for rejecting the conclusion of this report. The Vaccine Science Foundation welcomes publishing on its website any evidence or response that UNICEF believes is relevant to addressing the concern raised by the enclosed expert report, and any actions it intends given the findings in this report.

Please send a response to info@vaccinescience.org within sixty days so that the Vaccine Science Foundation can post it publicly on the vaccinescience.org website next to the paper *Effect of DTP Vaccines on Mortality in Children in Low-Income Countries.*

We look forward to hearing from you.

Vaccine Science Foundation

References:

1. https://vaccinescience.org/expert-report-effect-of-dtp-vaccines-on-mortality-in-children-in-low-income-countries/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5360569/
3. https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/