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The introduction of diphtheria-tetanus-pertussis vaccine and child mortality in rural Guinea-Bissau: an observational study

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Background and objective Previous studies from areas with high mortality in West Africa have not found diphtheria-tetanus-pertussis (DTP) vaccine to be associated with the expected reduction in mortality, a few studies suggesting increased mortality. We therefore examined mortality when DTP was first introduced in rural areas of Guinea-Bissau in 1984–1987.

Setting Twenty villages in four regions have been followed with bi-annual examinations since 1979.

Subjects In all, 1657 children aged 2–8 months.

Design Children were weighed when attending the bi-annual examinations and they were vaccinated whenever vaccines were available. DTP was introduced in the beginning of 1984, oral polio vaccine later that year. We examined mortality for children aged 2–8 months who had received DTP and compared them with children who had not been vaccinated because they were absent, vaccines were not available, or they were sick.

Main outcome measure Mortality over the next 6 months from the day of examination for vaccinated and unvaccinated children.

Results Prior to the introduction of vaccines, children who were absent at a village examination had the same mortality as children who were present. During 1984–1987, children receiving DTP at 2–8 months of age had higher mortality over the next 6 months, the mortality rate ratio (MR) being 1.92 (95% CI: 1.04, 3.52) compared with DTP-unvaccinated children, adjusting for age, sex, season, period, BCG, and region. The MR was 1.81 (95% CI: 0.95, 3.45) for the first dose of DTP and 4.36 (95% CI: 1.28, 14.9) for the second and third dose. BCG was associated with slightly lower mortality (MR = 0.63, 95% CI: 0.30, 1.33), the MR for DTP and BCG being significantly inversed. Following subsequent visits and further vaccinations with DTP and measles vaccine, there was no difference in vaccination coverage and subsequent mortality between the DTP-vaccinated group and the initially DTP-unvaccinated group (MR = 1.06, 95% CI: 0.78, 1.44).

Conclusions In low-income countries with high mortality, DTP as the last vaccine received may be associated with slightly increased mortality. Since the pattern was inversed for BCG, the effect is unlikely to be due to higher-risk children having received vaccination. The role of DTP in high mortality areas needs to be clarified.

Keywords BCG, child mortality, DTP, gender differences, non-specific effects of vaccination

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Increasing evidence from areas with high child mortality suggests that vaccines used routinely in infancy are associated with effects on morbidity and mortality that are unrelated to protection against the diseases for which they were designed.[1,2]

Measles vaccine is strongly associated with a reduction in mortality that cannot be explained by the prevention of acute measles or its long-term consequences.[1–3] There are few studies of other routine vaccinations used in developing countries, including BCG, diphtheria-tetanus-pertussis (DTP), and polio vaccine. BCG may be associated with a beneficial stimulation;[2] we have found that BCG promotes a Th1 response in newborns,[4] is associated with less atopy,[5] better response to other vaccines,[6] and lower mortality,[2] particularly for children with a scar or a positive tuberculin response.[7] However, DTP and oral polio vaccines have not been associated with the expected reduced mortality.[1,2,8–11]

To get a better understanding of the impact of these vaccines, we reviewed data from the mid-1980s when we first introduced DTP and oral polio vaccines in rural areas of Guinea-Bissau, one of the poorest countries in the world.[12] Since 1979, we have conducted nutritional surveillance in various regions of the country and, as a service to the communities, we provided vaccinations when possible at the bi-annual visits. Recent observations[2,9] made it important to assess the mortality impact of these routine vaccinations in other studies.

Subjects and Methods

Background

Guinea-Bissau became independent in 1974 and little was known about the health situation in the country. In 1979, the present study was initiated to assess malnutrition and to suggest ways of improving child growth in different regions of the country.[13] A mobile team from the Bandim Health Project (BHP) visited selected regions with an interval of 6 months unless there were logistic problems (rainy season, lack of personnel, car problems, etc). In 1979, we selected villages in the regions of Oio, Biombo, and Cacheu. The Gabu region was added in 1984. Most villages in Guinea-Bissau are mono-ethnic and most regions are dominated by one or two ethnic groups; Mandinga in Oio, Pepel in Biombo, Manjaco in Cacheu, and Mandinga and Fula in Gabu. We could examine 100–150 children in one day and with 18–20% of the population being under 5 years old, selected villages were in the range of 400–800 inhabitants. For the present study, we used data from the 1984–1987 period when DTP vaccination was first introduced. We have previously analysed the impact of vaccination status on child mortality in another study from rural Guinea-Bissau of a random sample of 20 clusters of 100 women in each of the five most populous regions and covering the period 1990–1996.[2] There is no overlap in time or children between the two studies.

Village examinations and follow-up

Village committees were advised in the afternoon that the team would be coming the following morning. Mothers and children gathered in a central place in the village and children under 5 years old were weighed and vaccinated. Mothers were asked about pregnant women in their compound and newborn children from these pregnancies were registered at the subsequent village visit. Children were followed to 5 years old and it has always been possible to obtain information on their whereabouts. If a child did not attend an examination, assistants visited the compound to inquire whether the child was travelling, had moved, or died. Over the many years these villages have been followed, we have found no indication that survival or death would be misreported. We believe that we have full information about the survival of the children registered in the system, but there may well have been children who never registered because they were not reported during pregnancy and they died or moved before they had a chance to be seen at one of the mobile team's bi-annual visits.

Vaccinations and vaccination status

In 1979, there was no regular immunization programme in rural areas of Guinea-Bissau. In 1981, following experience with measles epidemics,[14,15] we introduced measles vaccination at village examinations whenever feasible. Since the team only returned every sixth month and the three doses of DTP and oral polio vaccines should be given with intervals of one month, the national vaccination programme did not grant permission to administer these vaccines. However, following severe whooping cough epidemics in two villages in the Oio region in 1982–1983 (authors' unpublished data), we persuaded authorities that one dose was better than none. In January 1984, DTP was introduced and later in 1984–1985 we started using oral polio vaccine as well. During 1984–1985, the mobile team was the only group to administer vaccination in the villages. From 1986 and onwards, the national immunization programme received support from UNICEF and WHO[16] and regional health authorities started more regular vaccination campaigns. We assessed how many children received DTP or measles vaccine from other teams during the 6 months of follow-up among children whose vaccination card was inspected at the subsequent visit.

Children were considered vaccinated if the BHP team had provided the vaccine or the parents presented a card with a date of vaccination. Since children were initially unlikely to have been vaccinated elsewhere, those not present at the initial examination were considered unvaccinated for DTP and polio vaccines. DTP and polio vaccines were provided from 3 months old. However, due to imprecise age assessment, some children aged 2 months were vaccinated, the coverage being 15% and 64%, respectively, among 2 and 3 month old children. We therefore included 2 month old children in the analysis. Children aged ≥9 months would normally receive measles vaccine and have therefore been excluded from the present study. Hence, we examined mortality for children who were 2–8 months old at a village visit. Initially BCG was not provided, but with the accelerated immunization programme, the BCG coverage among children aged 2–8 months increased from 1% (4/385) and 7% (32/461) in 1984 and 1985, respectively, to 26% (130/493) and 29% (144/496) in 1986 and 1987, respectively. We controlled for BCG status in the analysis. The data on vaccinations have not been analysed previously.

In the period 1984–1987, we conducted 28 village examinations in Oio and vaccinations were provided at all visits except 5; in Gabu, we vaccinated on 5 of 34 examination days; and in Cacheu, vaccinations were provided at 20 out of 24 village examinations. In Biombo, which is close to the capital Bissau, it was always possible to get vaccines stored in Bissau and all 48 village examinations were accompanied by vaccination. The lower proportion of vaccination sessions in Gabu was due to regional health authorities being more

proactive in terms of organizing their own vaccination campaigns. Since the provision of vaccinations differed in Gabu we controlled the main estimates for Gabu versus the other regions; this had no effect of the estimate (data not shown).

The national immunization programme provided the vaccines we used. It has not been possible to identify the vaccine producers since all records of the immunization programme were destroyed during the recent war in Guinea-Bissau (1998–1999). It is likely that several producers provided vaccines since all vaccines were obtained through UNICEF; UNICEF, Copenhagen, does not keep records of vaccines distributed before 1990.

Comparisons and statistical methods

The impact of vaccinations was assessed for children aged 2–8 months at the initial visit by comparing the mortality rates over the next 6 months for vaccinated and unvaccinated children. In the main analysis, the unvaccinated infants were: firstly, children examined on days when the team had no vaccines; secondly, absent and travelling children; thirdly, children examined but considered too sick to be vaccinated; and fourthly, children who were 2 months old.

We examined mortality over a 6-month period. If the next visit occurred within 6 months of the initial visit, follow-up was censored at the new examination day if more than 8 months old at this visit and therefore eligible for measles vaccination. Intervals between visits were usually 5–7 months but sometimes longer due to logistic problems. If children were still less than 9 months old at the next visit they were included with the next 6-month follow-up period. If unvaccinated children were vaccinated with DTP at the revisit they changed to the vaccinated group from this date. Children were censored before 6 months of follow-up due to death (3.8%), migration (1.2%), or a new examination (39.6%). The proportion of children with censoring would not differ noticeably between villages within the same region since the main cause of censoring was a new visit to the region by the BHP team; the interval between visits would be similar for all villages in a given region.

Vaccinations given during the follow-up period are not taken into account in the survival analysis as these were only recorded for children surviving and remaining in the area until next visit and who had their vaccination card examined. Inclusion of these initially unvaccinated children in the DTP vaccinated group would have implied a survival bias in the estimate of mortality ratios (MR) since only survival time but no death would have been moved from the unvaccinated to the vaccinated group. As emphasized previously,[2] in the analysis we used, some initially unvaccinated were subsequently vaccinated and would therefore have been 'misclassified' in the last part of follow-up period; this would tend to reduce the MR between vaccinated and unvaccinated groups.

To exclude accidents, we reviewed the information on causes of death collected by the mobile team, which was limited to main symptoms like 'fever', 'diarrhoea', 'vomiting', 'measles', 'whooping cough', or 'chest pain'. Two children dying of burns and drowning were censored at date of death. Many deaths had no declared symptoms because the child had died outside the community and the mother was not present at the time of the village visit. In the initially DTP-vaccinated group, the main symptoms for the 47 deaths were declared to be diarrhoea and/or vomiting (8), cough and chest pain (3), fever (malaria) (19), measles (1), and unknown (16), whereas the distribution was diarrhoea and/or vomiting (3), cough and chest pain (1), fever and malaria (7), and unknown (9) for the 20 deaths in DTP-unvaccinated group.

To examine possible long-term effects on mortality, we conducted additional analyses beyond 6 months after the initial inclusion following the vaccinated and initially unvaccinated children from the censoring date (next visit or 6 months later) and until 5 years of age.

We used a Cox proportional hazards model[17] with days of follow-up as underlying time and adjusting by stratification for initial age (in months) and region (Oio, Biombo, Gabu, Cacheu) if not stated otherwise. Results are shown as MR with Wald-based 95% CI. Other possible confounders such as period (1984–1985, 1986–1987), season, sex, and BCG vaccination status were introduced as covariates in the Cox model. A total of 178 children contributed with two follow-up periods, being examined twice in the 2–8 months age range. As the Cox model was stratified for initial age in months, no child was used more than once in a stratum. Children could only change vaccination status at the following visit when we could vaccinate the child or inspect his or her vaccination card. Most 6-month periods covered both the rainy and the dry season; season at examination had no effect on mortality estimates for vaccination (data available upon request). All dates of death are only known to lie within a month, i.e. we have interval censored data, and we have used the 15th of the month as the day of death in the Cox analyses. In supplementary analyses we used a parametric survival model using an exponential distribution and taking into account the interval censoring. The results were very similar to the Cox analyses and are not shown (data available upon request). Several other models, including a random effect model using village as random intercept were examined but provided similar results and have therefore not been presented.[18] Weight-for-age (w/a) z-scores were calculated with the Anthro-program and analysed with a normal regression model.

Results

Using data from the same age groups and the same villages in 1981–1983, we examined the mortality pattern of travelling children. In the 1981–1983 period, the mortality rate for children aged 2–8 months in the three regions, which had been followed, was 210/1000 person-years (pyrs) in Oio (31 deaths/154.0 pyrs), 130/1000 in Biombo (26/199.6 pyrs), and 116/1000 in Cacheu (14/120.6 pyrs). Adjusting for age and region, 6-month mortality for absent children was not different from the mortality of children who had been present at a specific examination (MR = 1.08, 95% CI: 0.53, 2.21).

In the period 1984–1987, we identified 1657 children who took part in 1835 examinations between 2 and 8 months of age; 178 children being seen twice within this age interval. Of these children, 67 (4.0%) died within the next 6 months (Table 1). The mortality rate for children aged 2–8 months differed by region being 87/1000 in Oio (17 deaths/195.4 pyrs), 110/1000 in Biombo (31/282.7 pyrs), 60/1000 in Gabu (12/201.0 pyrs), and 56/1000 in Cacheu (7/125.2 pyrs). The mortality rate tended to be higher for children examined in 1984–1985

Table 1 Deaths and person years (pyrs) according to age, vaccination status, and year. Guinea-Bissau, 1984–1987

	Mortality per 100 person years (deaths/pyrs) (No. of children)					
Initial age (months)	1984–1985[a] DTP and polio +	1986–1987[a] DTP and polio −	1984–1987 DTP and polio +	DTP and polio −	DTP and polio +	DTP and polio −
2	0 (0/6.2) (14)	4.2 (2/47.5) (104)	0 (0/8.9) (21)	5.0 (3/59.9) (136)	0 (0/15.1) (35)	4.7 (5/107.4) (240)
3	24.2 (6/24.8) (57)	7.8 (2/25.5) (55)	6.3 (2/31.8) (74)	10.5 (3/28.5) (62)	14.1 (8/56.7) (131)	9.3 (5/54.0) (117)
4	13.8 (4/28.9) (66)	5.3 (1/18.9) (42)	10.3 (3/29.1) (67)	0 (0/29.6) (64)	12.1 (7/58.0) (133)	2.1 (1/48.5) (106)
5	15.8 (6/38.0) (88)	4.3 (1/23.1) (51)	2.6 (1/38.0) (89)	0 (0/27.9) (64)	9.2 (7/75.9) (177)	2.0 (1/51.0) (115)
6	13.8 (6/43.5) (102)	8.6 (2/23.3) (53)	15.9 (6/37.6) (88)	13.1 (4/30.5) (70)	14.8 (12/81.1) (190)	11.1 (6/53.8) (123)
7	9.5 (3/31.7) (76)	0 (0/23.3) (52)	11.6 (5/43.2) (100)	0 (0/22.0) (49)	10.7 (8/74.9) (176)	0 (0/45.3) (101)
8	8.0 (2/24.9) (60)	9.3 (1/10.7) (26)	10.3 (3/29.1) (65)	5.6 (1/17.8) (40)	9.3 (5/54.0) (125)	7.0 (2/28.5) (66)
Total[b]	13.6(27/198.0) (463)	5.2 (9/172.3) (383)	9.2 (20/217.7) (504)	5.1 (11/216.4) (485)	11.3 (47/415.7) (967)	5.1 (20/388.6) (868)
MR (95% CI)[c]	2.38 (1.10, 5.15)		1.70 (0.80, 3.64)		2.03 (1.17, 3.52)	

[a] The period when the children were recruited.

[b] Total number of examinations as 178 children contributed with two examinations (see text).

[c] Mortality rate ratio (95% CI) from a Cox proportional hazards model with stratification for initial age in months.

(97/1000 pyrs) than in the next 2 years (71/1000) (MR = 1.36, 95% CI: 0.84, 2.21). During 1984–1985, the team provided 93% (405/436) of the first DTP vaccinations; in 1986–1987, more children received vaccines in campaigns organized by regional health authorities and only 64% (299/468) received their first vaccination from our mobile team. Due to other campaigns some children received additional doses of DTP during the 6 months of follow-up; among children taking part in the subsequent examination, the percentage with DTP vaccinations during the 6 months of follow-up increased from 13.6% (68/500) in 1984–1985 to 39.8% (231/580) in 1986–1987. Controlling for period and region, the likelihood of new or additional DTP vaccinations during the period of follow-up was lower for those initially DTP-unvaccinated (relative risk [RR] = 0.80, 95% CI: 0.67, 0.95). The percentage with measles vaccination during the 6 months of follow-up increased from 2.0% (10/500) in 1984–1985 to 18.1% (105/580) in 1986–1987. Controlling for period and region, the likelihood of measles vaccination during the period of follow-up was equal for DTP-vaccinated and DTP-unvaccinated children (RR = 0.89, 95% CI: 0.61, 1.30).

After the introduction of DTP and later polio vaccine (Table 1), the mortality adjusted for age was higher among children who had received DTP vaccine (MR = 2.03, 95% CI: 1.17, 3.52), the effect being slightly stronger in 1984–1985 than in 1986–1987. For children who had received DTP but no polio vaccine during the first campaigns in 1984, the MR was 5.09 (95% CI: 0.65, 39.9). Mortality per follow-up period for DTP vaccinated children was 4.9% (47/967). In unvaccinated children, mortality was 7 (2.1%) of 338 children examined on days when there were no vaccinations in the village; 11 (3.3%) of 332 children not present at the examination; and 2 (1.0%) of 198 children examined but not vaccinated. Adjustment for region (MR = 1.81, 95% CI: 1.01, 3.25), BCG (MR = 1.99, 95% CI: 1.08, 3.65), season (MR = 1.82, 95% CI: 1.02, 3.25), or limiting the analysis to children age ≥3 months (MR = 1.92, 95% CI: 1.05, 3.52) had little effect on the overall estimate. Adjusting for village, the estimate of mortality associated with DTP and polio vaccines was 1.91 (95% CI: 1.04, 3.51). Controlling simultaneously for period, season, sex, BCG, and region, the effect was 1.92 (95% CI: 1.04, 3.52); the estimate being 2.34 (95% CI: 1.04, 5.27) for girls and 1.56 (95% CI: 0.70, 3.48) for boys. If we included only children vaccinated on the day of examination by the mobile team, the MR was 1.98 (95% CI: 1.03, 3.79) controlling for the same factors (Figure). Compared with the DTP-unvaccinated children, the differential effect of DTP was as strong for 73 children who received their second or third dose (MR = 4.36, 95% CI: 1.28, 14.9) as for the 705 children receiving their first dose of DTP (MR = 1.81, 95% CI: 0.95, 3.45).

In an analysis of mortality for children aged 0–8 months, BCG vaccinated children had an MR of 0.63 (95% CI: 0.30, 1.33) compared with BCG unvaccinated children, adjusting for age, sex, region, DTP vaccine status, season, and period. In this same data set including children aged 0–8 months, the MR between DTP-vaccinated and DTP-unvaccinated was 1.95 (95% CI: 1.07, 3.57). The MR for BCG and DTP vaccinated children compared with unvaccinated children were significantly inversed (test of homogeneity, $P = 0.038$).

Adjusting for age, sex, BCG, season, region, and period, 197 children taking part in a village examination but not DTP-vaccinated tended to have lower mean weight-for-age z-scores (−0.66, 95% CI: −0.87, −0.44) than 698 children vaccinated with DTP (−0.52, 95% CI: −0.67, −0.37), though the difference was not statistically significant ($P = 0.149$). Children with low weight-for-age had higher mortality but it was not possible to adjust the mortality estimate for nutritional status since many unvaccinated children had not been weighed because they were travelling. Unvaccinated children tended to grow better than vaccinated children but this was not a significant difference.

Of the 1657 children included in the analysis of DTP, 67 died, 22 moved, and 2 were censored due to accidental death during the follow-up period. The 1566 children who remained in their village beyond the first 6 months were followed for mortality to 5 years old, 97 dying among the 720 children not vaccinated

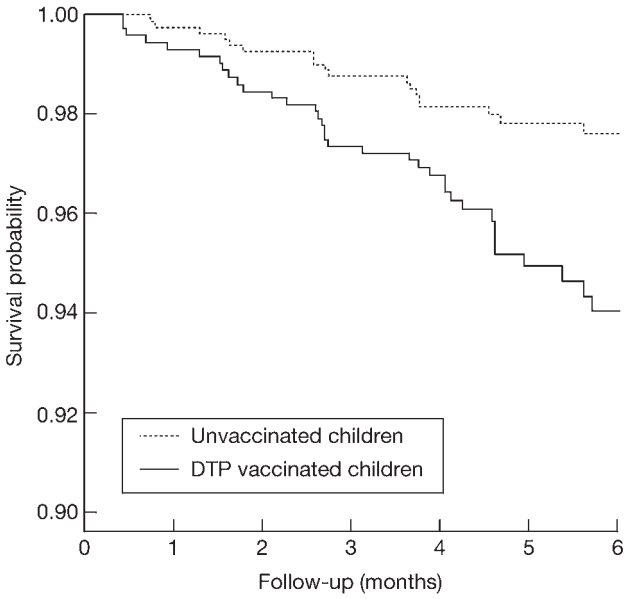

Figure Kaplan–Meier survival curves for unvaccinated children, and recipients of diphtheria-tetanus-pertussis. Guinea-Bissau, 1984–1987

with DTP before 9 months of age and 117 among the 846 DTP-vaccinated children. The MR following the initial 6-month period was 1.04 (95% CI: 0.74, 1.47) to 3 years old and 1.06 (95% CI: 0.78, 1.44) to 5 years old for the DTP vaccinated children compared with the initially unvaccinated children. Hence, the initial difference in mortality was not compensated by subsequent lower mortality rate among the children who had received DTP initially. Among children examined after 3 years old, there was no difference in vaccination coverage for measles vaccine (87%) or BCG (67%) but children who had not initially received DTP had lower mean number of DTP doses (N = 2.7) than children who had received DTP before 9 months old (N = 3.1) ($P < 0.001$) (data not shown).

Discussion

Studies from Guinea-Bissau (MR = 1.84, 95% CI: 1.10, 3.10),[2] Senegal (MR = 1.59, 95% CI: 0.76, 3.33),[1] Benin (odds ratio = 2.20, 95% CI: 0.93, 5.22),[8] and wartime Guinea-Bissau (MR = 1.58, 95% CI: 0.36, 7.02)[9] have suggested somewhat higher mortality associated with DTP and oral polio vaccines. Though obviously not planned as a randomized study, the present study supports a similar tendency. The observed effect is likely to be associated with DTP and not polio vaccine. During most of 1984, we administered DTP only and the effect was at least as strong for these children as for those who received DTP and polio vaccines simultaneously. Furthermore, we have observed lower mortality after national polio immunization days when only oral polio vaccine was provided to young children,[19] and lower case fatality at the hospital when children had received oral polio vaccine (OPV) only compared with children having received both DTP and OPV.[20]

In previous studies,[1,2,8–11] most DTP and polio vaccinated children had received BCG first and it has been suggested that the negative effect of DTP might better be described in terms of reducing the survival advantage associated with BCG vaccine.[21] However, in the present study, few children had received BCG first, the proportion increasing from 1% to 29% between 1984 and 1987, and the negative effect of DTP was stronger in the first period when virtually none of the children had received BCG (Table 1).

The importance of the present observation depends on whether it is reasonable to compare the vaccinated and unvaccinated infants. All children were followed prospectively having been registered at a previous village visit or during pregnancy. Survival information was available for all children. Prior to the introduction of vaccines there was no mortality difference between attending and travelling children. DTP and polio vaccines were not given at certain visits for logistic reasons and some children were absent or travelling on the day of vaccination. Some children were considered too sick to be vaccinated. It seems unlikely that these groups should have lower mortality, higher mortality being more plausible as the unvaccinated children tended to have lower weight-for-age z-scores than vaccinated children. Sick children may have benefited from chloroquine, aspirin, and oral rehydration advice, the only treatment provided by our field assistants. It seems unlikely that such treatment would have a lasting effect, and the fact that lower mortality was observed in the following 6 months for all children examined on days without vaccination would contradict the idea that treatment of sick children could be the reason for differences in mortality between unvaccinated and vaccinated children. DTP vaccinated children had higher mortality than all of the unvaccinated groups (travel, sick, no vaccine). It should also be noted that vaccinated children generally did not have higher mortality, as BCG vaccination was associated with slightly lower mortality and the estimates for DTP and BCG were significantly inversed.[2] Furthermore, after the initial difference between the unvaccinated and vaccinated groups, there was no difference in vaccination coverage and mortality; hence, the initially DTP vaccinated group was not a particular high-risk group. These observations would also suggest that the possible negative effect of early DTP vaccination is limited to the period when DTP is the last vaccine received. On the other hand, the initial difference in mortality between DTP-vaccinated and DTP-unvaccinated children was not subsequently compensated by lower mortality in the initial DTP-vaccinated group.

Different batches of DTP vaccine would have been used over the 4 years of the present study. Had some form of contamination or adverse reaction specific to DTP been implicated, DTP vaccinated children should have died more rapidly than the unvaccinated children; however, as will be seen from the Figure, the children in the DTP group did not die immediately after vaccination, the median time to death being 95 days for 40 DTP vaccinated children and 82 days for 20 unvaccinated children. Hence, there was no tendency within the 6-month follow-up period for the MR to be reduced with time since vaccination.

The present study provided essentially the same tendencies as in our previous study,[2] BCG being associated with lower mortality and DTP with higher mortality compared with unvaccinated children, the inversion of the MR being significant.

Since the team provided most of the initial vaccinations, at least in the period 1984–1985, the information on vaccination status is more complete than in our previous study.[2] For methodological reasons, estimates may still be conservative. The categories of children included in the unvaccinated group are likely to have higher mortality than the vaccinated group. Furthermore, some children received vaccination elsewhere after the initial visit, particularly in 1986–1987. Provision of additional vaccinations to both groups during the follow-up period would tend to equalize the mortality rates in the two groups and therefore to reduce the MR between the initially DTP-vaccinated and DTP-unvaccinated children.[2] It should be noted that the mortality difference between DTP-vaccinated and DTP-unvaccinated children was most pronounced in 1984–1985 when there was little interference from other vaccination campaigns (Table 1). The difference between DTP-vaccinated and DTP-unvaccinated children declined in the second period (Table 1) at the same time as the number of vaccinations by other teams increased. For most children, we assessed the effect of the first dose of DTP and polio vaccine as less than 30% received additional DTP vaccinations during follow-up and subsequent doses would usually be received together with measles vaccination at the subsequent visit. In our previous study,[2] we found the first dose of DTP to be associated with a significant increase in mortality whereas subsequent doses were associated with a somewhat lower and not significant increase in mortality (MR = 1.38, 95% CI: 0.73, 2.61). However, this effect was due to the study design[2] where children with two or three doses of DTP would be more likely to be measles vaccinated during the 6-month follow-up period; when follow-up was censored before measles vaccination, estimates were essentially identical for one dose and two to three doses.[22] Hence, the effect is unlikely to be special to the first dose of DTP and in the present study the effect of the second and third doses were as strong as the effect of the first dose.

Available data from West Africa consistently suggest a negative effect of DTP vaccine[1,2,8–11] and this effect may be stronger for girls, as in the present study.[9–11] If these observations are repeatable, it should be investigated whether the pattern is related to the age at vaccination or due to interaction with specific infections. In the present study, there was no indication that the effect of DTP varied by age at vaccination (Table 1). In other studies, a negative effect of DTP has been found for children vaccinated before 3 months old[9] or after 8 months old.[11] There was no marked difference in causes of deaths between vaccinated and unvaccinated children suggesting that the non-specific effects might be related to a general immune stimulation affecting the response to several infections. Further epidemiological and immunological studies should clarify the impact of DTP and polio vaccinations. BCG stimulates a Th1 type immune response[4] and is associated with reduced mortality.[2,8] However, DTP promotes a Th2 type immune response[23] and we have found DTP vaccinated children to be more atopic.[5] It may be important that the adjuvant of DTP vaccine, aluminium hydroxide, is a strong promoter of a Th2 type immune profile in mice and has enhanced susceptibility to tuberculosis rather than prevented infection in animal experiments.[24] In animal studies of respiratory syncytial virus (RSV) and measles virus, live vaccine promotes a Th1 cytokine response and the animals have mild disease upon challenge. However, inactivated RSV or measles vaccine as well as pertussis toxin and DTP induce a Th2 cytokine profile and increase mortality after challenge with RSV or measles virus.[25–27]

Results from the present study must be interpreted with caution. Our study did not replicate the routines of the immunization programme as it is not the policy to provide only one dose of DTP during the first months of life. However, it should still be a concern if any dose is associated with increased mortality as many children may only receive one dose. Furthermore, the effect appeared to be similar for children receiving the second or third dose of DTP. While DTP vaccine appears to be associated with increased mortality, general infant mortality did decline over the period examined from 1979 to 1987. This decline was undoubtedly related to expansion in primary health care, increased availability of drugs, and better control of measles and whooping cough epidemics, both associated with very high mortality in 1979–1983.[13–15] Since mortality declined over the period, MR were controlled for 'period'. DTP undoubtedly protects against whooping cough deaths; previous pertussis epidemics may have contributed to herd immunity and in periods with little whooping cough infection, DTP vaccine may contribute little to reducing infant deaths. The decline in whooping cough epidemics and mortality may have permitted us to observe, unexpectedly, that DTP vaccination might also be associated with increased mortality from non-targeted diseases. The effect in the present study may have been unusually large because very few had received BCG; in the current immunization programme in developing countries virtually all DTP vaccinated children would have received BCG earlier or at the same time as DTP.

There is little doubt that the combined effect of all routine immunizations is strongly beneficial for childhood survival.[2] However, so far, all studies including the present one have found increased mortality associated with DTP vaccination,[1,2,8,9] though only two of these studies were large enough to be significant in their own right. It should also be noted that studies including the present one have found the effect to be worse for girls than for boys.[9–11,28] Should the isolated effect of DTP on survival turn out to be negative in spite of protection against specific diseases, it would have major implications for our understanding of child mortality. New vaccine formulations might improve the vaccination programme and contribute significantly to infant survival in low-income countries.

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KEY MESSAGES

- Previous studies from West Africa have found diphtheria-tetanus-pertussis (DTP) vaccine to be associated with slightly increased infant mortality.
- We therefore examined the impact on survival when we introduced DTP in rural communities in Guinea-Bissau in the mid-1980s.
- Compared with children who had not been vaccinated because they had been travelling, no vaccine was available, or they were too sick to get vaccinated, mortality was twofold increased over the next 6 months for the children who had received DTP, the negative effect being stronger for girls.
- Mortality was lower for children who had received BCG making it unlikely that vaccine had been given mainly to high-risk children.

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