



Research Paper

Co-administration of BCG and Diphtheria-tetanus-pertussis (DTP) Vaccinations May Reduce Infant Mortality More Than the WHO-schedule of BCG First and Then DTP. A Re-analysis of Demographic Surveillance Data From Rural Bangladesh



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ABSTRACT

Background: WHO recommends BCG at birth and diphtheria-tetanus-pertussis (DTP)-containing vaccine at 6, 10 and 14 weeks of age. However, BCG and DTP are often co-administered in low-income countries. The health implications have not been examined.

Setting: We reanalysed data from Matlab, Bangladesh, to examine the influence of co-administration on mortality; 37,894 children born 1986–1999 were followed with registration of vaccinations and survival.

Methods: Using Cox models, survival was analysed from 6 weeks to 9 months of age when measles vaccine is given; 712 children died in this age group. We calculated mortality rate ratios (MRR) for children starting the vaccination schedule with BCG-first, BCG + DTP1-first or DTP1-first.

Results: Only 17% followed the WHO-schedule with BCG-first. Mortality was 16/1000 person-years for children who initiated the vaccination schedule with BCG + DTP1 but 32/1000 and 20/1000 for children who received BCG-first or DTP-first, respectively. Compared with BCG + DTP1-first and adjusting for background factors, the BCG-first-schedule was associated with 2-fold higher mortality (MRR = 1.94 (1.42–2.63)). DTP1 administered after BCG-first was associated with higher mortality than receiving DTP1 with BCG (MRR = 1.78 (1.03–3.03)).

Conclusions: Co-administration of BCG and DTP may further reduce mortality. Since all observational studies support this trend, co-administration of BCG and DTP should be tested in randomised trials.

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1. Introduction

Observational studies and randomized trials have shown that vaccines may affect morbidity and mortality unrelated to the vaccine-targeted infections (Aaby et al., 1995, 2003, 2010, 2011, 2012a,b,c). These so-called non-specific or heterologous effects may increase resistance or susceptibility to unrelated infections and may therefore affect child survival beneficially or negatively. These effects are seen most strongly while a vaccine is the most recent vaccination and may be reversed when other vaccines are given. The existence of non-specific effects (NSEs) of vaccines are supported by evidence from human and animal studies that priming with one pathogen may train innate immunity or induce heterologous T-cell immunity and thus reduce or increase susceptibility to subsequent infection with unrelated pathogens (Benn et al., 2013; Kleinnijenhuis et al., 2012; Netea

et al., 2011; Welsh and Selin, 2002). WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recently reviewed the potential NSEs of BCG, diphtheria-tetanus-pertussis (DTP) and measles vaccine (MV). SAGE concluded that BCG and MV might have beneficial NSEs and recommended further research of the NSEs of vaccines (Higgins et al., 2014; Strategic Advisory Group of Experts on Immunization, 2014).

NSEs were not considered when the current immunization schedule and ages of vaccinations were determined in the 1970s and early 1980s (Aaby et al., 2012d). However, if vaccines have NSEs, the way the program is implemented may have major consequences for child health (Aaby et al., 2012a,d). WHO recommends BCG to be administered with oral polio vaccine (OPV) at birth, diphtheria-tetanus-pertussis (DTP) and OPV in three doses at 6, 10 and 14 weeks of age and measles vaccine (MV) at 9 months of age. Vaccines are often delayed in low-income countries (Fisker et al., 2014). If a vaccine is delayed, it is recommended to give the vaccine at the first opportunity even if it means that it will be co-administered with another vaccine (BCG with DTP, DTP with MV) or in the inverse sequence (BCG after DTP, DTP after MV). In

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some countries, the majority of children may receive some vaccines out-of-sequence (Benn and Aaby, 2012; Hornshøj et al., 2012; Welaga et al., 2012). Still there are very few studies of how out-of-sequence vaccinations may affect child survival.

It has been suggested that co-administration of BCG and DTP vaccinations should be better for child survival than following the WHO-recommended schedule of first BCG and then DTP (Aaby et al., 2004, 2011, 2012c; Hirve et al., 2012). This type of out-of-sequence vaccination is common; BCG is often delayed and some institutions have implemented programs which combines BCG with the first dose of DTP (DTP1) (Elguero et al., 2005). We therefore asked the ICDDR,B, Bangladesh, for permission to re-analyse the largest data set on vaccinations and child survival previously published from the Matlab Health and Demographic Surveillance System (HDSS) (Breiman et al., 2004) to test whether the effect of DTP is different when administered after BCG or when DTP and BCG are co-administered.

2. Methods

The study covered vaccinations and survival of all children born within the Matlab HDSS between 1986 and 1999 and with follow-up to December 31, 2001. The previous study analysed the role of vaccination for child survival between 6 weeks and 9 months of age when MV is supposed to be given and between 9 and 60 months of age (Breiman et al., 2004). The present reanalysis focuses on BCG and DTP and is therefore limited to the 6 weeks to 9 months age group.

2.1. Study Population

In the 1986–1999 cohort, 37,894 children were followed between 6 weeks (>42 days) and 9 months of age; 712 children died in this age group. The data collection with regard to study population, vaccinations, socio-economic background factors and survival analysis has been described in detail previously (Breiman et al., 2004).

2.2. Health and Demographic Surveillance and Collection of Vaccination Data

Data was collected by two systems: Health and demographic data have been collected through regular household visits every 2 weeks between 1986 and 1997 and with intervals of one month thereafter. Children for whom no information was available were assumed to be unvaccinated. In the Matlab area, community health workers (CHW) are assigned about 25 households to visit every day for surveillance purposes. The CHW invited mothers to attend vaccinations sessions on the monthly vaccination day in the area and noted all the vaccinations next to the child's name in the record-keeping book (Breiman et al., 2004).

2.3. Deaths and Verbal Autopsies

Causes of death were ascertained by verbal autopsy as part of the routine HDSS (Breiman et al., 2004). Twenty of the 712 deaths in the age group 6 weeks to 9 months were due to accidents; these deaths have been excluded from the analysis of the impact of vaccination policy on child survival. One death occurred after measles vaccination and has been censored in the main analysis. Hence, the main analysis had 691 deaths.

2.4. Registration of Vaccinations and Survival Analyses

The previous analysis (Breiman et al., 2004) compared the survival of different vaccine groups with the unvaccinated group. No children were excluded for lack of information and “unvaccinated” was therefore the default category of children for whom no vaccination had been identified; in other words, it was not actively determined that a child was unvaccinated by inspecting the vaccination card or interviewing the

mother as done elsewhere (Kristensen et al., 2000). Hence, there may have been underreporting of early vaccinations among children categorized as “unvaccinated” and there were several indications that early vaccinations were underreported; for example, children who moved had significantly lower vaccination coverage than other children. Hence, children who were vaccinated and died could end up in the unvaccinated group if the vaccination was not registered before the death; this might happen if some mothers were travelling, e.g. to give birth elsewhere, or there were delays in registering the vaccinations as happened for those who moved.

With advancing age through infancy, completely unvaccinated children will be an increasingly selected group of frail children whom the mothers have considered too weak to vaccinate. As a consequence the mortality rate ratio (MRR) between unvaccinated and vaccinated children should increase with age (Aaby et al., 2009; Chan et al., 2007). However, in the Matlab data set the MRR for unvaccinated compared with vaccinated declined from 3.43 (2.42–4.86) at 1.5 to 3 months to 1.82 (1.08–3.05) at 6–8 months of age. In a review of DTP and child survival, we found that the MRR of unvaccinated versus vaccinated children was below 2.0 in all studies with documentation of vaccination status and subsequent follow-up (Aaby et al., 2016a). Hence, early mortality was probably too high in the unvaccinated group in the Matlab data set, potentially due to misclassification of dead children as ‘unvaccinated’ because there was no information. With follow-up to a higher age more misclassified “unvaccinated” children would have been registered with vaccination and the MRR for unvaccinated and vaccinated children should go down as happened in the Matlab data set. Given these uncertainties about the status of “unvaccinated”, we have not compared the mortality of unvaccinated and vaccinated children in the present study but instead compared different vaccine groups, which had in common that they have been registered to have received at least one vaccination.

There are three ways of starting the vaccination schedule: first, BCG-first possibly followed by DTP1–3 vaccinations as currently recommended by WHO; second, BCG + DTP1-first possibly followed by DTP2–3 vaccinations; and third, DTP1-first possibly followed by DTP2–3 vaccinations and BCG. If subsequent vaccinations were not always registered immediately, some children who died after having received the second or third dose may not have had these vaccinations registered and therefore ended up as a death in the initial group; in other words, mortality would be too high in the initial group and too low in the subsequent vaccine dose groups. That something similar might have happened is suggested by an analysis of mortality in relation to vaccination status and distance from the hospital (Supplementary Table 1). Mortality of unvaccinated children did not differ by distance from the hospital but mortality for the BCG-only group was much higher with distance from the hospital and even tended to be higher than mortality in the unvaccinated groups. With such potential registration problems comparisons of the subsequent vaccinations might be biased, e.g. DTP1 (after BCG-first) versus BCG-first or DTP2 (after BCG + DTP1) versus BCG + DTP1. Due to the potential registration problems in the present data set, the main analyses in Tables 1–3 and Fig. 1 are comparing the three ways of starting the vaccination schedule. The mortality following subsequent vaccinations within each of these three groups is depicted in Fig. 2 and analyzed in Table 3.

2.5. Socio-economic and Cultural Background Factors

Several background factors were shown in the previous analyses to relate to the likelihood of receiving three doses of DTP by 9 months of age: Religion (Muslim vs non-Muslim), maternal age, maternal education, birth order, asset score (indicator of socio-economic standing), and distance from hospital. Though all variables were significant in a data set of this size, it was only maternal education which was associated with large differential effects, the DTP3 coverage being 75% for children of mothers with no education and 93% for children of mother with higher education. These factors were also associated with

Table 1

The relative distribution of first vaccination by 9 months of age, the median age of vaccination in days, and mortality between 6 weeks and 9 months of age.

	Period	BCG first	BCG + DTP1 first	DTP1 first	No vaccine #	Total
First vaccine	1986–89	28% (3451)	10% (1270)	49% (5987)	12% (1482)	12190
% (N)	1990–94	13% (1723)	62% (8112)	21% (2725)	4% (500)	13060
	1995–99	10% (1244)	79% (10040)	8% (1006)	3% (354)	12644
	Total	17% (6418)	51% (19422)	26% (9718)	6% (2336)	37894
First vaccine	1986–89	77 (57–115)	76 (61–115)	84 (63–124)		
Median age	1990–94	61 (49–78)	67 (55–85)	64 (52–81)		
	1995–99	62 (51–77)	64 (53–80)	62 (52–80)		
	Total	67 (53–97)	66 (54–84)	74 (58–107)		
Mortality	1986–89	26 (43/598147)	18 (11/220831)	20 (56/1010842)	69 (167/885981)	37 (277/2715801)
Rate/1000 years (deaths/days at risk)	1990–94	43 (40/337432)	19 (81/1559040)	21 (31/533259)	72 (95/483758)	31 (247/2913489)
	1995–99	28 (19/244744)	13 (72/1974584)	17 (9/198542)	59 (67/413912)	22 (167/2831782)
	Total	32 (102/1180323)	16 (164/3754455)	20 (96/1742643)	67 (329/1783651)	30 (691/8461072)

Notes: The period is birth year periods. In all periods the median ages of first vaccination differed significantly between the three groups. # 30 children have measles vaccine as their first vaccine.

mortality between 6 weeks and 9 months of age. Maternal education and asset score were associated with the largest differentials in mortality. Higher education was associated with 87% lower under-9-month mortality and the highest asset score was associated with 30% lower mortality (Breiman et al., 2004).

2.6. Statistical Methods

Different socio-economic and health service related factors may have influenced how a given child started the vaccination schedule. Multiple logistic regression was used to examine possible determinants

Table 2

Odds ratios (OR) comparing the frequency of BCG + DTP1 as first vaccine versus BCG or DTP1 as first vaccine in relation to background factors.

	Percentage with BCG + DTP1 (number of/total)	1986-99 N = 35 558		1986-89 N = 10 708		1990-94 N = 12 560		1995-99 N = 12 290	
		OR	(95%-CI)	OR	(95%-CI)	OR	(95%-CI)	OR	(95%-CI)
Sex									
Male	54.5 (9790/17964)	(ref)							
Female	54.8 (9632/17594)	1.02	(0.96–1.07)	1.10	(0.98–1.24)	1.00	(0.93–1.08)	0.98	(0.90–1.08)
Religion									
Non-muslim	51.2 (2786/5438)	(ref)							
Muslim	55.2 (16636/30120)	1.06	(0.98–1.14)	1.47	(1.22–1.77)	1.15	(1.03–1.27)	0.78	(0.68–0.90)
Maternal age (at birth of infant)									
14–31 years	53.3 (4703/8820)	(ref)	P = 0.184		P = 0.185		P = 0.476		P = 0.279
22–30 years	55.0 (10785/19616)	1.06	(0.98–1.15)	1.17	(0.98–1.40)	1.04	(0.92–1.16)	1.05	(0.91–1.21)
>30 years	55.2 (3934/7122)	1.02	(0.91–1.13)	1.22	(0.97–1.55)	0.98	(0.84–1.14)	0.95	(0.79–1.14)
Maternal education									
None	51.6 (8711/16881)	(ref)	P = 0.013		P = 0.007		P < 0.001		P = 0.412
Primary	55.2 (5684/10307)	1.01	(0.94–1.07)	1.20	(1.04–1.39)	0.94	(0.86–1.03)	1.02	(0.91–1.15)
Secondary	64.0 (3766/5888)	1.12	(1.03–1.22)	1.31	(1.05–1.63)	1.14	(1.01–1.29)	1.04	(0.90–1.20)
Higher	72.0 (525/729)	1.31	(1.07–1.61)	0.70	(0.33–1.48)	1.69	(1.21–2.35)	1.18	(0.87–1.60)
No info	42.0 (736/1753)	1.07	(0.94–1.22)	1.31	(1.06–1.62)	0.90	(0.75–1.08)	1.32	(0.97–1.81)
Birth order									
First	58.8 (5798/9858)	(ref)	P = 0.090		P = 0.044		P = 0.189		P = 0.640
Second	56.9 (4714/8281)	0.95	(0.87–1.03)	0.85	(0.71–1.03)	0.98	(0.87–1.11)	0.97	(0.84–1.13)
Third	51.2 (8910/17419)	0.91	(0.83–0.99)	0.78	(0.64–0.95)	0.91	(0.80–1.02)	1.04	(0.89–1.22)
Asset score									
1 (poorest)	53.6 (3905/7285)	(ref)	P = 0.386		P < 0.001		P = 0.076		P = 0.404
2	53.3 (3571/6706)	1.03	(0.95–1.12)	0.90	(0.75–1.08)	1.03	(0.92–1.16)	1.11	(0.95–1.29)
3	54.7 (3951/7223)	1.06	(0.98–1.15)	0.79	(0.66–0.95)	1.14	(1.02–1.28)	1.11	(0.96–1.29)
4	54.6 (4150/7604)	1.00	(0.92–1.09)	0.71	(0.59–0.86)	1.12	(0.99–1.26)	1.05	(0.90–1.22)
5	57.1 (3845/6740)	0.97	(0.89–1.07)	0.66	(0.53–0.81)	1.00	(0.88–1.14)	1.15	(0.97–1.35)
Distance from hospital									
<3000 m	59.1 (4932/8340)	(ref)	P < 0.001		P < 0.001		P < 0.001		P < 0.001
3001–6000 m	56.5 (6732/11917)	0.94	(0.87–1.01)	1.02	(0.88–1.19)	0.97	(0.88–1.07)	0.84	(0.74–0.96)
6001–9000 m	53.1 (4698/8852)	0.81	(0.75–0.87)	0.71	(0.60–0.84)	0.88	(0.79–0.98)	0.78	(0.68–0.89)
>9000 m	47.5 (3060/6449)	0.59	(0.54–0.64)	0.39	(0.31–0.48)	0.61	(0.54–0.68)	0.65	(0.57–0.76)
Period (year of birth)									
1986–89	11.9 (1270/10708)	(ref)	P < 0.001	–	–	–	–	–	–
1990–94	64.6 (8112/12560)	13.56	(12.65–14.54)	–	–	–	–	–	–
1995–99	81.7 (10040/12290)	32.81	(30.41–35.41)	–	–	–	–	–	–

Notes: (ref) indicates the reference group in each analysis. The overall estimates are obtained from a multiple logistic regression model including all background factors. The dataset was split in the three separate periods to obtain the period specific estimates. P-values are for testing equal distribution per factor using a Wald test.

Table 3
Mortality rate ratios (MRR) comparing different vaccination groups.

First	Most recent vaccination	Mortality per 1000 years (deaths/days)	MRR Most recent vaccination	MRR Most recent vaccination vs BCG + DTP1 as reference	MRR First vaccination ^a vs BCG + DTP1 first as reference
BCG	BCG	57 (51/328026)	(ref)	3.44 (2.17–5.45)	1.94 (1.42–2.63)
BCG	DTP1	31 (26/308022)	0.52 (0.31–0.87)	1.78 (1.03–3.06)	
BCG	DTP2/3	17 (25/544275)	0.25 (0.14–0.43)		
BCG + DTP1	BCG + DTP1	19 (50/980027)	(ref)	(ref)	(ref)
BCG + DTP1	DTP2/3	15 (114/2774428)	0.82 (0.54–1.25)		
DTP1	DTP1	25 (29/419906)	(ref)	1.47 (0.86–2.52)	1.25 (0.91–1.73)
DTP1	DTP2/3	17 (43/930320)	0.64 (0.37–1.10)		
DTP1	BCG	27 (17/228228)	1.07 (0.56–2.03)	1.57 (0.84–2.95)	
DTP1	BCG + DTP	16 (7/164189)	0.54 (0.22–1.32)	0.80 (0.34–1.85)	

Notes: (ref) indicates the reference group in each analysis. The estimates are obtained from a single Cox model adjusted for age (time-scale in the model), sex, birth order, religion, maternal age, maternal education, asset-score, and stratified for year of birth and community health worker (Breiman et al., 2004). The MMR between BCG-first and BCG + DTP1-first was 2.24 (1.51–3.31) from 6 weeks to 6 months of age and 1.52 (0.93–2.50) from 6 to 9 months of age ($P = 0.23$).

^a First vaccination refers to the first vaccination received. In this analysis, the child stays in the same category regardless of the subsequent vaccinations.

of receiving BCG + DTP1-first versus BCG-first or DTP1-first (Table 2). Results are shown as odds ratios (ORs) with corresponding 95% confidence intervals.

To assess the relative impact of different vaccination categories we used the Cox proportional hazards model, with age as underlying time-scale. Children entered the analyses at the maximum age of first vaccination (BCG-first, BCG + DTP1-first and DTP1-first) or 6 weeks of age; for example, if a child was BCG-first vaccinated on day 30 of life, its follow-up in the BCG-first group started at 6 weeks of age (42 days), but if it was only BCG-first vaccinated on day 55 of life, its follow-up in the BCG-first group started at 55 days. Children were followed until the minimum age of death, out-migration, and 9 months of age. Results reported are mortality rate ratios (MMRs) with corresponding 95% confidence intervals. All vaccination dates were assumed to be known at the date and subsequent vaccines (e.g.

DTP1 after BCG-first) were entered as time-dependent covariates changing status at the age of vaccination. In the comparison of different schedule groups we censored follow-up at the time of MV if given before 9 months of age as done in the original presentation of data (Breiman et al., 2004); it had no impact on estimates whether children with MV before 9 months of age were censored or not. All estimates were adjusted for the background factors described above. Furthermore, we stratified for year of birth and community health worker ($N = 117$) and all comparisons of the three vaccination schedule groups are therefore conducted within a small subarea. The assumption of proportional hazards was tested using Schoenfeld residuals. When comparing the BCG-first, BCG + DTP1-first and DTP1-first schedules from 6 weeks to 9 months of age the mortality rate ratios decreased over age; we have therefore also presented estimates for the two age intervals 42–180 and 181–270 days of age (Table 3).

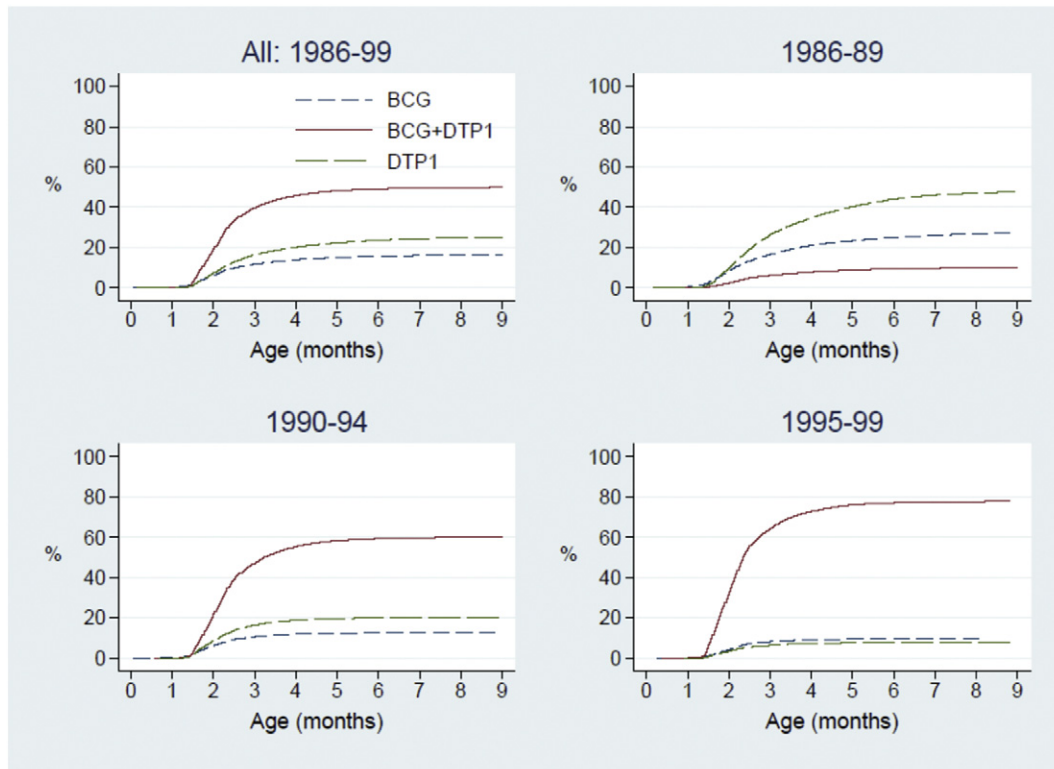


Fig. 1. The coverage for starting first with BCG alone, BCG + DTP1 or with DTP1 alone in the three periods.

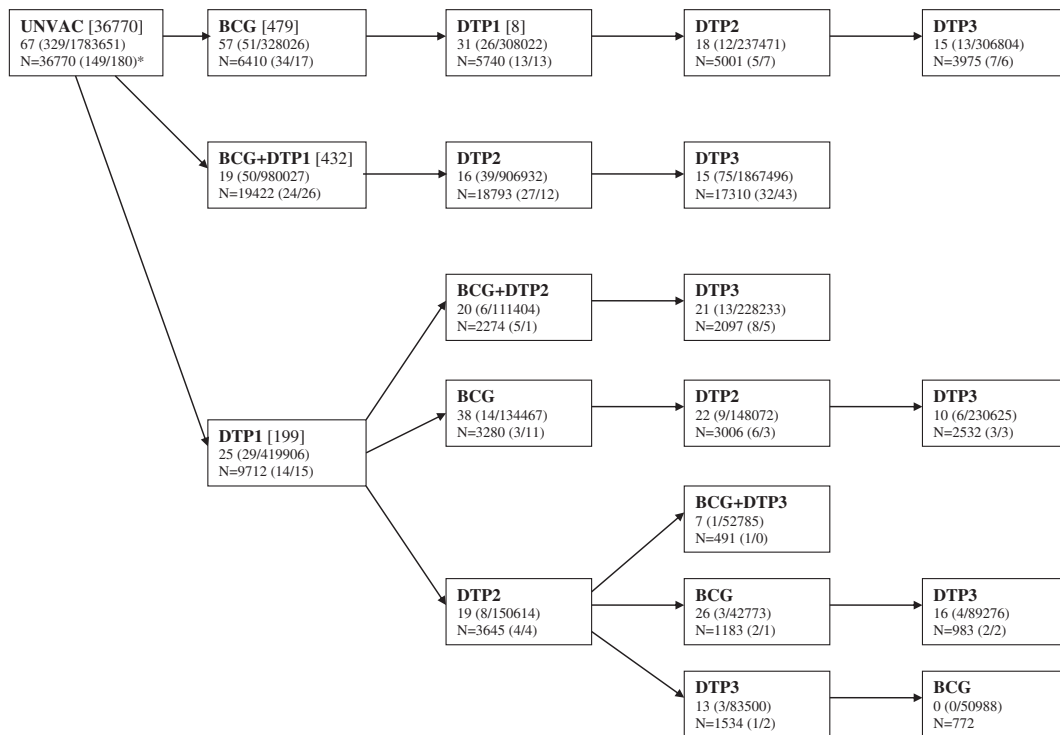


Fig. 2. Vaccination status and mortality between 6 weeks and 9 months of age. The figure shows the vaccination statuses the 37,894 children between 6 weeks and 9 months of age. For each status is indicated in [] the number of children who were in this category when the study started at 6 weeks of age; the mortality rate per 1000 person-years (death/person-days of follow-up); N the total number of children who spent some time in the category and the number of female/male deaths between 6 weeks and 9 months of age. Some children had been vaccinated before 6 weeks of age and there are therefore less than 37894 children in the unvaccinated at the start of the study. Note that this diagram has 691 deaths as accidental deaths have been excluded.

3. Results

3.1. Vaccination Coverage and Changes in Vaccination Policy

As seen in Table 1, the proportion of children receiving at least one vaccination before 9 months of age changed from 88% to 97% over the three periods: 1986–89, 1990–94, and 1995–99. The relative distribution of how children started in the vaccination program changed dramatically (Fig. 1). When the universal infant immunization program began in Matlab (January 1, 1986), the majority of children started with either BCG-first or DTP1-first. From 1990 onwards, the majority of children started by receiving BCG + DTP1 simultaneously; 79% received co-administered BCG + DTP1 vaccinations in the last period from 1995–1999. The median age of first vaccination was roughly the same for the three schedule groups; if anything the BCG-first group had a younger age of vaccination (Table 1). The children in the three groups had received at least one vaccine and most likely several more subsequent vaccines (Fig. 2); children with no vaccine registered were classified in the “no vaccine” group (Table 1). As seen in Table 1 and Fig. 1, the first vaccines were not received at a uniform age and very few children were vaccinated in the first month of life; so even when children received BCG first they did not follow the WHO recommendation of receiving BCG at birth.

The 6-week-to-9-month mortality rate declined significantly over the three periods (Table 1).

In the multiple logistic regression analysis, the determinants for receiving BCG and DTP1 simultaneously were distance from the hospital and maternal education: children living less than 6 km from a hospital and children of mothers with secondary or higher education were more likely to receive simultaneous BCG + DTP1 vaccinations (Table 2).

3.2. Mortality in Relation to Sequence of BCG and DTP Vaccinations

The sequential vaccinations of all children between 6 weeks and 9 months of age are depicted in Fig. 2. There was a considerable

difference in mortality between 6 weeks to 9 months of age depending on how the vaccination schedule was started (Table 3). The MMR between BCG-first and BCG + DTP1-first (regardless of subsequent vaccinations) was 1.94 (1.42–2.62) (Table 3); the difference was slightly stronger for girls than for boys (Supplementary Table 2). The MRR between BCG-first and BCG + DTP1-first was 1.30 (0.62–2.72) in 1986–89, 2.60 (1.67–4.06) in 1990–94, and 1.64 (0.92–2.91) in 1995–99 (P = 0.21) (data not shown). The DTP1-first group had a MRR of 1.25 (0.91–1.73) compared with BCG + DTP1-first.

Bangladesh has usually had higher female than male mortality in the post-neonatal period (Breiman et al., 2004). We therefore tested whether the different ways of starting the vaccination affected the female-male MRR. Among children in the “no vaccine” (Fig. 2), the female-male MRR was 0.83 (0.68–1.06). Among children who had received BCG + DTP1-first, the female-male MRR was 1.05 (0.76–1.45) between the first vaccination and 9 months of age. In the DTP1-first group where the children typically got BCG after DTP, the female-male MRR was 0.96 (0.64–1.45). In the BCG-first group, the ratio was 1.30 (0.86–1.96) (data not shown). Hence, the BCG-first group tended to be associated with a higher F/M MRR than the “no vaccine” group.

Comparing only the first dose of DTP (DTP1), mortality was significantly higher for children who received DTP1 after BCG-first compared with those who had received DTP1 + BCG simultaneously, the MRR being 1.78 (1.03–3.03) (Table 3).

4. Discussion

4.1. Main Observations

First, the BCG + DTP1-first group had only half the mortality of the WHO recommended policy of BCG-first and then DTP. In the period after 1990 when co-administration of BCG and DTP became common, the BCG-first group was vaccinated at a younger age than other groups. All data suggest that children with better nutritional status are

vaccinated first (Aaby et al., 2016a) and inherently the BCG–first group might therefore have been healthier. Since we controlled for year of birth and major determinants of vaccination coverage and child mortality, this result is unlikely to be explained solely by confounding. Furthermore, as we stratified for community health worker (Breiman et al., 2004), the comparison between different vaccination groups would be within distinct areas where environmental conditions and epidemics would be similar for those compared. Second, receiving DTP1 after BCG–first was associated with significantly higher mortality than receiving DTP1 together with BCG.

4.2. Strengths and Weaknesses

This is by far the largest data set of routine infant vaccinations from a low-income country and there were good possibilities of analyzing whether the variation in administration of vaccinations had any impact on child survival. The people who compiled the data were not aware of the hypotheses about out-of-sequence vaccinations which we tested in this data set.

Data sets from low-income countries are unlikely to have complete information on all vaccinations. In the present study, data was collected by both the record-keeping system and the HDSS and the data was analyzed as if it was complete. However, there is always the possibility that mothers go to deliver in their natal home and that mothers and children are travelling and receive vaccinations elsewhere; this may not be recorded if the child dies or moves. If the child dies administrative information on vaccinations may not be recorded because it is no longer of direct relevance for vaccine delivery. For example, in the present data set, the children who moved during infancy had significantly lower vaccination coverage before they moved than other children in the community. To circumvent these problems we emphasized the comparison of groups which had at least received one vaccine and therefore been exposed to similar data collection procedures. This strategy suggested that BCG + DTP1 administered simultaneously reduced infant mortality substantially compared with the official WHO strategy of receiving BCG–first and then DTP.

Due to lack of vaccine information some dead vaccinated children may have been misclassified as unvaccinated. It seems unlikely that such misclassified vaccinated deaths have come particularly from the BCG–DTP1–group and have inflated the comparison of the BCG–first and the BCG–DTP1–first schedules. Since the underreporting of vaccinations was strongest among the youngest children and the BCG–first group was vaccinated at a younger age than other groups (Table 1), misclassified vaccinated death may have been slightly more common in the BCG–first group.

4.3. Consistency With Previous Observations

We tested the potential impact of simultaneous vaccination with BCG and DTP1 on mortality because previous studies have suggested that this combination may reduce infant mortality. In rural India, children who received BCG + DTP1 first had four-fold lower mortality up to 9 months of age than children who started the vaccination schedule with BCG–first or DTP1–first (Hirve et al., 2012). In Senegal, we conducted two studies (Aaby et al., 2015, 2016b). In the first period from 1989–1996 all children received BCG and DTP1 simultaneously; BCG + DTP1 was associated with 28% lower mortality than unvaccinated children but comparison could not be made with other vaccine groups since all vaccinated children had received BCG + DTP1 (Aaby et al., 2016b). In the second period from 1997–1999, 73% of the children received BCG + DTP1 simultaneously and they had lower mortality than those who had started with either BCG–first or DTP1–first (Aaby et al., 2015). In these studies the group receiving BCG–first was vaccinated at a younger age and they would normally have been the healthier and more compliant group.

In Guinea-Bissau, we conducted a randomized trial of BCG at birth to low birth weight (LBW) children who normally do not get BCG at birth but delayed BCG; LBW children will often get BCG with DTP around 6 weeks of age. As a result of the randomization, the children in the control group tended to get DTP1 at the same time as BCG. In a study of mortality between 2 and 6 months of age for DTP–vaccinated versus DTP–unvaccinated children, the MRR for DTP–vaccination was 4.33 (1.54–12.2) in the group having received BCG at birth, who therefore had BCG well before DTP1, as currently recommended. The negative association was reduced being “only” 1.71 (0.73–4.01) among the children in the control group receiving BCG and DTP more or less simultaneously (Aaby et al., 2011, 2012c).

As suggested by a non-significant tendency in the present study, BCG + DTP simultaneously may reduce the increased female mortality which has been associated with DTP–vaccinations administered after BCG (Aaby et al., 2004, 2015, 2016c; Chan et al., 2007). In the study from Senegal the female–male MRR was 0.64 (0.38–1.05) after BCG + DTP1 vaccinations but increased significantly to 1.42 (0.92–2.18) after DTP2 and DTP3. This again would suggest that BCG + DTP1 is beneficial particularly for girls (Aaby et al., 2016b).

Hence, the present study is consistent with several other studies in indicating a more beneficial effect of co-administered BCG + DTP than of BCG–first followed by DTP and that the beneficial effect might be stronger for females.

4.4. Inconsistencies With Previous Observations

Fig. 2 suggests a surprisingly high (female) mortality in the group having received only BCG–first. Mortality was also higher for children who received BCG alone after DTP1–first and lower for children who received BCG + DTP after DTP1–first. The higher mortality of BCG–first cannot be explained by a particular selection bias for children entering the BCG–first group since we controlled for potential confounding factors. BCG scarring is associated with better child survival and it is known to depend on the strain of BCG and the mode it has been administered (Storgaard et al., 2015). Hence, one could imagine that the BCG strain used in Matlab had been of poor quality. The strain used in Matlab is unfortunately not known.

The mortality level for BCG–first varied by distance from the center being higher than the mortality of unvaccinated children in distant areas (Supplementary Table 1) and the proportion of BCG–first or DTP–first children increased with distance from a hospital (Table 2). Hence, registration problems may also have played a role for the surprisingly high mortality in the BCG–first group. However, we have no simple explanation for the high mortality for the children who had received only BCG–first.

4.5. Interpretation

The simultaneous BCG and DTP vaccinations which became common practice around 1990 in the Matlab area could account for a considerable part of the reduction in infant mortality seen in recent years (Table 1). The immunological effect of combining the initial BCG and DTP has not been studied. Recent studies have indicated that BCG induces epigenetic changes which reprogram monocytes to non-specific protection against unrelated infections (Jensen et al., 2015; Kleinnijenhuis et al., 2012). It has not been studied what happens when these children get DTP. The reprogramming could be different if the initial priming took place in the presence of DTP or if BCG was given at a later age, but this has not been studied.

It cannot be excluded that the excess mortality among infants following the WHO recommended schedule is partly related to some uncontrolled selection biases. However, the analysis adjusted for year and community health worker area, and all comparisons between vaccination groups are therefore within a small area. Since these observations speak against selection bias being a major explanation, it would seem worthwhile to test the potential beneficial effect of BCG + DTP1 in randomized trials.

4.6. Implications

All studies with prospective follow-up have found DTP-vaccinated children compared with DTP-unvaccinated children to have higher mortality (Aaby et al., 2012b,c, 2016a; Kristensen et al., 2000; Mogensen et al., 2017). The excess mortality has been particularly marked for girls (Aaby et al., 2015, 2016b,c). These observations have been around for more than 15 years (Kristensen et al., 2000) and still no prospective study has shown DTP to be associated with a beneficial effect for child survival. Hence, there are good reasons to consider strategies that might reduce the negative non-specific effects of DTP.

Given the consistency with previous studies, the potential impact on child survival of co-administration of BCG and DTP vaccinations deserves to be tested in randomized trials. This could potentially happen by giving an early DTP with BCG or a second dose of BCG with the current schedule for DTP vaccinations. In areas where the first vaccinations are provided late as has been the case in Matlab, it should be possible to randomise to BCG + DTP1 or BCG-first-then-DTP. None of the studies mentioned above (Aaby et al., 2015, 2016b; Breiman et al., 2004; Chan et al., 2007) provided co-administered BCG and DTP1 vaccinations at birth but only around 6–12 weeks of age. Since several studies have suggested that BCG at birth has a beneficial effect on the neonatal mortality (Aaby et al., 2011; Biering-Sørensen et al., 2012), it is essential that a possible early combination of BCG and DTP does not reduce the beneficial effect of BCG on neonatal mortality. It might be more feasible to give a later second dose of BCG together with DTP3 to examine whether this would reduce the negative effects of DTP. In any case, randomized trials measuring the overall effect of vaccinations on child morbidity and mortality are urgently needed to establish evidence-based policies to improve child survival.

Ethical Approval

See Breiman et al., 2004.

Role of the Funding Source

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

Data Sharing

The data belongs to ICDDR,B, Bangladesh. This manuscript has been reviewed by ICDDR,B for scientific content and consistency of data interpretation with previous ICDDR,B publications and significant comments have been incorporated prior to submission for publication.

Conflict of Interest

Nothing to declare.

Contributions

HR and PA designed the study; HR and AA were responsible for the statistical analyses; the first draft was written by PA, HR and MK; all authors contributed to the final version of the paper. HR and PA will act as guarantor of the study.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ebiom.2017.07.012>.

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