# Randomized Trial of BCG Vaccination at Birth to Low-Birth-Weight Children: Beneficial Nonspecific Effects in the Neonatal Period?

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**(See the editorial commentary by Shann, on pages 182–4.)**

***Background.*** Observational studies have suggested that BCG may have nonspecific beneficial effects on survival. Low-birth-weight (LBW) children are not given BCG at birth in Guinea-Bissau; we conducted a randomized trial of BCG at birth (early BCG) vs delayed BCG.

***Methods.*** In the period 2004–2008 we recruited 2320 LBW children in Bissau. The children were visited at home at 2, 6, and 12 months of age. With a pretrial infant mortality of 250 per 1000, we hypothesized a 25% reduction in infant mortality for LBW children.

***Results.*** Infant mortality was only 101 per 1000 during the trial. In the primary analysis, infant mortality was reduced insignificantly by 17% (mortality rate ratio [MRR] = .83 [.63–1.08]). In secondary analyses, early BCG vaccine was safe with an MRR of .49 (.21–1.15) after 3 days and .55 (.34–.89) after 4 weeks. The reduction in neonatal mortality was mainly due to fewer cases of neonatal sepsis, respiratory infection, and fever. The impact of early BCG on infant mortality was marked for children weighing <1.5 kg (MRR = .43 [.21–.85]) who had lower coverage for diphtheria-tetanus-pertussis vaccinations.

***Conclusions.*** Though early BCG did not reduce infant mortality significantly, it may have a beneficial effect in the neonatal period. This could be important for public health because BCG is often delayed in low-income countries.

Several studies from West Africa have shown that vaccinations and micronutrient supplements used routinely in low-income countries have nonspecific effects on mortality [1–3]. Observational studies in low-income countries [4–12] and historical data [13–17] have suggested that the tuberculosis vaccine BCG may have nonspecific beneficial effects on child survival. If BCG has a beneficial nonspecific effect, it would have major implications in low-income countries. BCG is recommended at birth, but it is often delayed. Furthermore, BCG is not administered to low-birth-weight (LBW) children at birth in many countries. Earlier administration of BCG could potentially save many children in infancy. In an observational study, LBW children who had received BCG at birth had 57% lower mortality before they received diphtheria-tetanus-pertussis (DTP) vaccination than BCG-unvaccinated LBW children [4].

We have been interested in testing the effects of BCG and BCG revaccination on child survival [18]. BCG vaccination is postponed in LBW children in

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Potential conflicts of interest: Several of the authors are affiliated with the Statens Serum Institut (SSI) in Copenhagen, which administers their grants. SSI is a producer of BCG. However, SSI did not fund the vaccines, the study, or the researchers.

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Guinea-Bissau [4]. We therefore conducted a randomized trial of early vs delayed BCG to LBW children. Our a priori hypothesis was that early BCG would reduce infant mortality by 25%.

## METHODS

### Setting

The Bandim Health Project (BHP) in Guinea-Bissau runs a health and demographic surveillance system in 6 districts with a population of around 102,000, including 30% of the inhabitants of the capital. About 3000 children are born in the BHP study area each year. All houses in the area are visited every month to register new pregnancies and births. Furthermore, all children <3 years of age are visited at home every 3 months.

### Low-Birth-Weight Cohort

The LBW cohort was started to study the impact of BCG vaccination (ClinicalTrials.gov, NCT00146302). We subsequently extended the cohort to study also the effect of vitamin A supplementation (VAS) in a 2-by-2 factorial design (ClinicalTrials.gov, NCT00168610). The result of VAS has been reported separately [19]; there was no interaction between the 2 interventions.

To obtain a larger group of LBW children, we initiated recruitment of LBW children at the maternity ward of the national hospital in Bissau. We drove the mother home from the hospital. We drew a simple map, registered GPS coordinates, and took photos to facilitate subsequent reidentification. Using this system we have been able to follow all children enrolled in the cohort.

Other routine vaccinations may influence the results of vaccination trials [1, 18, 20, 21] and we therefore collected vaccination information at home visits at 2, 6, and 12 months of age.

### Objectives and Study Design

The study was designed to measure whether BCG given at birth had a beneficial effect on LBW infant survival. The BCG trial was initiated in November 2002; due to human error the randomization procedures were faulty at the maternity ward during parts of 2003 and 2004, and the first 1309 children had to be excluded. We changed all procedures, emphasizing careful monitoring and supervision of all procedures, and restarted the trial 29 November 2004. Since then the trial has been running correctly. In May 2005, with new funding, we introduced randomization to vitamin A and placebo in a 2-by-2 factorial design [19].

Between November 2004 and March 2008, LBW children (<2,500 g) were identified at discharge from the maternity ward and at the 3 health centers in the study area when children came to receive their first vaccinations. All children were weighed on an electronic Seca scale. Length was measured on a measuring board and arm, and head and abdominal circumferences were measured with a TALC insertion tape or a measuring tape. At the national maternity ward the Ballard score was used to assess gestational age. The children were visited at home after 3 days and at 2, 6, and 12 months of age.

### Primary Outcomes

The primary outcome was infant mortality; the visit at 12 months served to assess survival during the first year of life.

***Secondary Outcomes.*** Adverse events: A subgroup of LBW children was visited at home on days 1 and 2 after enrollment and all children were visited on day 3. We report deaths and morbidity indicators at day 3, which included the largest number of children visited.

***Child Deaths and Tuberculosis.*** Since the BHP area has a tuberculosis (TB) surveillance system [22, 23], we planned to examine whether the effect was modified by control for TB exposure.

***Vaccination Coverage.*** The impact on vaccination coverage was measured using vaccination data obtained at the 2-, 6-, and 12-month visits.

***Other Outcomes.*** We collected information on growth, BCG response, and hospitalizations. These results will be reported elsewhere.

### Sample Size

Prior to the trial (1990–1998), mortality between 2 days and 12 months of age was 250 per 1000 for LBW children born at the national hospital. To detect a 25% difference in infant mortality, we needed to enroll 1600 children in the BCG trial, and to detect a 25% difference in infant mortality due to vitamin A supplementation, we needed to enroll 1600 children in the vitamin A trial. There was no interaction between BCG and vitamin A in the vitamin A trial [19], and since both trials had the same randomization to BCG, we analyzed the effect of BCG on infant mortality in the combined dataset.

### Enrollment

Enrollment took place at the maternity ward and at the 3 health centers in the study area. Prior to enrollment, children were examined by a physician at the maternity ward. Children who had severe malformation and who were too sick to be discharged from the maternity ward were not enrolled in the study. If the child weighed <2.5 kg, the BHP field workers explained the purpose of the study, completed a questionnaire with background factors, and obtained informed consent.

### Informed Consent and Randomization Procedures

The study was explained to the mothers/guardians of LBW children in the local language (Creole), and they received a written explanation in Portuguese. If they wished to participate,

mothers/guardians were asked to sign or fingerprint the consent form. Block randomization procedures have been described in detail elsewhere [19]. Twins were allocated the same treatment to prevent potential confusion regarding who had been vaccinated. The child's study number in the LBW study was indicated on the child's vaccination card.

### Interventions

Children were randomized to receive BCG immediately after birth (herein referred to as "early") or later as is current practice in Guinea-Bissau. Children received a standard dose of .05 mL of State Serum Institute (SSI) BCG by intradermal injection. From May 2005, the children enrolled at the maternity ward were also randomized to receive vitamin A or placebo [19]. Each participant's code was kept secret until all participants had reached 12 months of age.

### Masking

No placebo for BCG was given. Ethics committees in Africa have been reluctant to use a placebo injection in vaccine trials and prefer an irrelevant control vaccine [24]. However, a control vaccine may have a nonspecific impact on mortality [20]. Furthermore, if we had used a placebo, control mothers might have believed that the child had received BCG and might therefore not have sought BCG vaccination. We therefore preferred not to use a placebo. Control mothers were told that their children should receive BCG at a local health center when the child had gained weight or when the child was due to receive DTP and oral polio vaccinations at 6 weeks of age.

### Home Visits and Follow-up

The LBW children were visited at home after 3 days and at 2, 6, and 12 months of age. At each visit weight, length, mid-upper arm circumference, head circumference, and abdominal circumference were measured. We asked to see the vaccination card and all vaccines were noted with the date of vaccination. If the children were missing vaccinations the mothers were encouraged to go to the local health center. When a child's death was identified, a standard verbal autopsy was conducted by a clinician around 3 months after the death. Based on the history, the clinician assigned a probable diagnosis. The 412 children said to be traveling at the 12-month visit were visited again at 15–18 months of age to confirm that the child was indeed alive: 150 were seen, 73 had moved, 162 were still traveling outside Bissau, 18 were absent for the day, and 9 had died but only 3 before 12 months of age (1 BCG, 2 controls).

If a LBW child had moved, field workers attempted to obtain contact information and visit the new residence. In many cases it was possible to identify the new residence.

### Exclusions

Children were enrolled based on their weight at the time of enrollment. However, 16 children with a birth weight of $<2.5$ kg were erroneously included though they weighed $\geq 2.5$ kg at discharge from hospital. These children were excluded. One pair of twins was erroneously randomized individually and was therefore excluded. One LBW child was erroneously randomized to a normal-birth-weight study and was therefore excluded. Due to lack of communication between staff, 3 children with malformations were enrolled. The mother of 1 child who had been randomized refused follow-up. These children were also excluded. Of the 23 children excluded, 14 had been randomized to BCG (1 died) and 9 to the control group (1 died).

### Statistical Analyses

The primary outcome was infant mortality, but survival was also assessed in relation to the other visits. Mortality rates were compared for children randomized to early BCG or the usual delayed BCG in a Cox proportional hazards model with age as the underlying time variable and delayed entry at randomization. Hence, we adjusted precisely for age in all analyses. The proportional hazard assumption was tested for infant mortality using Schoenfeld residuals ($P = .126$). As 21% of the children were twins, we adjusted for dependence of lifetimes of twins using robust 95% confidence intervals. Kaplan-Meier estimates with time since randomization as time variable were used to display the cumulative mortality in the randomization groups.

### Ethics

The protocol was approved by the Danish Central Ethical Committee, The Gambia/MRC Scientific and Ethics committees, and the Guinean Ministry of Health's Research Coordination Committee. Study participants had access to free consultations and essential drugs at the local health centers.

## RESULTS

### LBW Cohort and Study Population

Of the 2343 children enrolled in the LBW cohort between November 2004 and March 2008, 23 were excluded (Figure 1). The remaining 2320 children were included in the main analysis. There were few differences in anthropometric measurements, gestational age, or background factors between children who received BCG and controls. The BCG group had more twins and tended to have more mothers who had died before enrollment (Table 1).

### Follow-up Status

At the 2-month follow-up visit, 124 children had died (5.3%), and 1855 (80.0%) were seen at home; 99% (1830) of these children had their vaccination card seen (Figure 1). At the 6-month follow-up visit, 182 children had died (7.8%), and 1607 (69.3%) were seen at home; 97% (1565) of these children had their vaccination card seen (Figure 1). At the first visit after 12 months of age, 229 of these had died before reaching

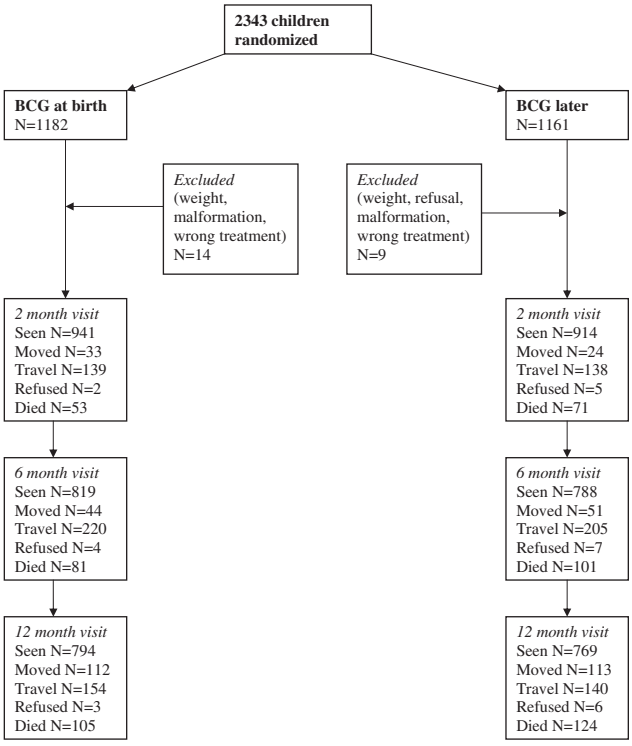


**Figure 1.** Diagrammatic representation of the trial. Numbers of moved and dead children are accumulated at a specific visit. Numbers of seen, travel, and refused to participate are the numbers specific for that visit.

12 months of age (9.9%), and 1563 (67.4%) were seen at home; 94% (1475) of these children had their vaccination card seen (Figure 1).

**Table 1. Differences in Background Factors for BCG-Vaccinated and Control Children at Enrollment**

| Risk factors at enrollment | BCG | Controls |
|---|---|---|
| | (n = 1168) | (n = 1152) |
| Median maternal MUAC | 238 mm | 232 mm |
| Median Ballard score | 38 (n = 1048) | 38 (n = 1042) |
| Median age at enrollment | 2 days | 2 days |
| Median weight | 2.160 kg | 2.160 kg |
| Median length | 45.0 cm | 45.0 cm |
| Median MUAC | 76 mm | 78 mm |
| Median head circumference | 310 mm | 310 mm |
| Median abdominal circumference | 255 mm | 260 mm |
| Boys | 495/1168 (42%) | 495/1152 (43%) |
| Twins | 270/1168 (23%) | 225/1152 (20%) |
| Mother dead at enrollment | 5/1168 (0.4%) | 1/1152 (0.1%) |
| From BHP study area | 354/1168 (30%) | 353/1152 (31%) |
| Recruited at main maternity ward | 1054/1168 (90%) | 1046/1152 (91%) |
| Randomized to vitamin A | 431/862 (50%) | 423/855 (49%) |
| Risk factors during follow-up | | |
| Mother died | 13/1163 (1%) | 12/1151 (1%) |

**NOTE.** BHP, Bandim Health Project; MUAC, mid-upper arm circumference.

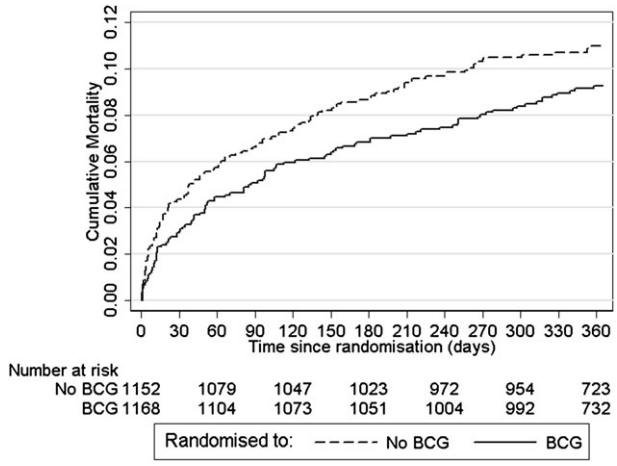


**Figure 2.** Cumulative mortality curves during the first year of life according to randomization group.

### Primary Outcome

***Infant Mortality.*** The accumulated infant mortality among LBW controls was 101 per 1000, which is less than half the level observed prior to the trial. At age 12 months, the mortality rate ratio (MRR) for early BCG vs controls was .83 (.63–1.08). The mortality curves for the 2 groups are depicted in Figure 2. The effect of BCG on infant mortality was the same among children who had received vitamin A (MRR = .81 [.52–1.25]) and those who had not (MRR = .83 [.60–1.17]).

### Secondary Outcomes

***Adverse Events.*** The children were visited at day 3 after enrollment (Table 2). There were no significant differences in morbidity indicators except for the specific reactions expected following BCG vaccination. BCG-vaccinated children tended to have lower mortality in the first 3 days after enrollment, the MRR being .49 (.21–1.15).

***Mortality by Age Group.*** At 1, 2, and 6 months of age, the MRR for early BCG vs controls was .55 (.34–.89), .73 (.50–1.05), and .78 (.58–1.06), respectively (Table 3). Early BCG had a beneficial effect only in the neonatal period while few children had received other vaccines (Table 1; online only); the MRR was .51 (.25–1.06) for girls and .59 (.32–1.11) for boys.

***TB Exposure.*** Of the 707 LBW children from the study area, only 25 were exposed to TB at home between birth and the end of the study, and only 2 were exposed in the first 4 weeks of life. None of the exposed LBW children died and it was not possible to examine whether TB exposure at home modified the effect of early BCG.

***Mortality According to Birth Weight.*** Seven percent of the children had a birth weight <1.5 kg, and infant mortality was significantly better for children who received early BCG in this group (MRR = .43 [.21–.85]) (Table 3). Children with the lowest weight at enrollment had the same beneficial effect in the

**Table 2. Differences in Morbidity Indicators and Mortality 3 Days After Enrollment**

| Morbidity indicators | BCG (n = 1067) | Controls (n = 1055) | *P* Value[a] |
|---|---|---|---|
| Doing well | 1052/1065 (99%) | 1033/1050 (98%) | $P = .140$ |
| Vaccination pustule | 5/1056 (.5%) | 0/1047 (0%) | $P = .062$ |
| Vaccination mark | 157/1051 (15%) | 1/1047 (0%) | $P < .001$ |
| Crying frequently | 410/1058 (39%) | 427/1043 (41%) | $P = .325$ |
| Went for consultations | 11/1060 (1%) | 14/1055 (1%) | $P = .529$ |
| Hospitalized | 1/1063 (.1%) | 5/1055 (.5%) | $P = .139$ |
| Mean (SD) respiratory frequency | 37.6 (7.3) | 38.0 (7.7) | $P = .872$ |
| Mean (SD) temperature | 35.9 (0.81) | 35.8 (.83) | $P = .859$ |
| **Mortality** | | | Mortality rate ratio |
| Deaths before or at day 3 visit | 8 | 16 | .49 (.21–1.15) |

**NOTE.** [a] *P* values are adjusted for possible dependence within twin pairs using robust standard errors.

first month but were much less likely to receive vaccinations during follow-up (Table 3).

***Causes of Death.*** Of the 229 infant deaths, a verbal autopsy was conducted for 210; 19 families had moved. In the neonatal period there were 27 and 48 deaths in the BCG group and the control group, respectively (Table 3); neonatal sepsis (13 vs 22), respiratory infections/breathing problems (3 vs 7), and fever (3 vs 5) accounted for most excess deaths among controls. There were no differences in the main categories of death later in infancy (data not shown).

***Vaccination Coverage.*** Due to the study design, children in the BCG group received BCG first and then DTP, whereas a majority (448 of 755) in the control group received DTP before or simultaneously with BCG when the children were examined at 2 months of age. Despite the encouragement at the home visits to seek vaccinations, 19% of children in the control group

**Table 3. Mortality and Vaccination Coverage at 1, 2, 6, and 12 Months According to Birth Weight and Randomization Status**

| Age and weight at enrollment | Mortality per 100 person-years (deaths/person-days) | | MRR (BCG/Control) | Vaccination coverage[a] | | |
|---|---|---|---|---|---|---|
| | BCG group (n = 1168) | Control group (n = 1152) | | BCG coverage in control group | DTP coverage in BCG group | DTP coverage in control group |
| At 4 weeks | | | | | | |
| .690–1.490 | 154 (6/1427) | 328 (11/1225) | .47 (.17–1.30) | 0% (0/58) | 0% (0/59) | 0% (0/58) |
| 1.500–1.990 | 45.1 (8/6481) | 82.7 (14/6179) | .54 (.23–1.27) | 4% (8/219) | 0% (0/247) | 0% (1/219) |
| 2.000–2.490 | 24.2 (13/19,602) | 42.6 (23/19,724) | .56 (.29–1.11) | 15% (95/644) | 0% (2/650) | 0% (1/644) |
| Total | 35.8 (27/27,510) | 64.6 (48/27,128) | .55 (.34–.89) | 11% (104/916) | 0% (2/952) | 0% (2/916) |
| At 2 months | | | | | | |
| .690–1.490 | 105 (12/4165) | 177 (18/3706) | .60 (.28–1.29) | 28% (16/58) | 31% (18/59) | 14% (8/58) |
| 1.500–1.990 | 32.5 (16/17,975) | 45.8 (21/16,718) | .71 (.37–1.35) | 58% (126/219) | 56% (138/247) | 52% (114/219) |
| 2.000–2.490 | 18.1 (25/50,344) | 23.2 (32/50,250) | .77 (.46–1.31) | 60% (389/644) | 71% (460/650) | 70% (454/644) |
| Total | 26.7 (53/72,484) | 36.7 (71/70,674) | .73 (.50–1.05) | 58% (531/921) | 64% (616/956) | 63% (576/921) |
| At 6 months | | | | | | |
| .690–1.490 | 34.8 (12/12,572) | 80.9 (22/9921) | .44 (.21–.94) | 85% (34/40) | 48% (20/42) | 50% (20/40) |
| 1.500–1.990 | 18.8 (26/50,526) | 22.2 (29/47,763) | .85 (.49–1.45) | 79% (153/193) | 55% (115/211) | 62% (119/193) |
| 2.000–2.490 | 11.1 (43/140,900) | 13.0 (50/140,507) | .86 (.57–1.29) | 75% (407/544) | 66% (367/558) | 68% (371/544) |
| Total | 14.5 (81/203,998) | 18.6 (101/198,191) | .78 (.58–1.06) | 76% (594/777) | 62% (502/811) | 66% (510/777) |
| At 12 months | | | | | | |
| .690–1.490 | 21.6 (14/23,667) | 52.4 (26/18,118) | .43 (.21–.85) | 88% (35/40) | 64% (28/44) | 80% (32/40) |
| 1.500–1.990 | 14.1 (36/93,260) | 15.9 (38/87,319) | .89 (.56–1.42) | 82% (147/179) | 76% (145/192) | 78% (140/179) |
| 2.000–2.490 | 7.7 (55/260,574) | 8.4 (60/261,005) | .92 (.64–1.32) | 80% (408/511) | 79% (418/532) | 83% (423/511) |
| Total | 10.2 (105/377,511) | 12.4 (124/366,442) | .83 (.63–1.08) | 81% (590/730) | 77% (591/768) | 82% (595/730) |

**NOTE.** DTP, diphtheria-tetanus-pertussis; MRR, mortality rate ratio.

[a] Vaccination coverage is based on the vaccination cards seen at the home visits. The expected DTP coverage is the first dose of DTP at 2 months of age and the third dose of DTP at 6 and 12 months of age.

had not received BCG at 12 months of age (Table 3). The children had obviously visited the health centers, since 96% had received at least 1 DTP vaccination. Many health centers only administer BCG once a week not to waste doses and therefore, some children do not receive BCG even though they have visited the health center. The DTP3 coverage tended to be higher at 6 and 12 months of age in the control group, the prevalence ratio being 1.06 (.98–1.14) and 1.06 (1.01–1.12), respectively.

## DISCUSSION

### Main Observations

Administration of BCG to LBW children was safe; there was a tendency for lower mortality already during the first 3 days after BCG vaccination. Instead of the hypothesized 25% reduction, we observed a 17% reduction in infant mortality, which was not statistically significant; the mortality level halved during the trial compared with the pretrial level. BCG had only a beneficial effect in the first month of life before controls received BCG and all children received DTP; the reduction in neonatal mortality was linked to less neonatal sepsis and fewer respiratory infections. BCG had a significant beneficial effect on infant mortality among the smallest children weighing <1.5 kg, who received fewer vaccinations during follow-up.

### Strengths and Weaknesses

This is one of the first randomized trials to test a nonspecific beneficial effect of vaccination on child survival rather than protection against a specific disease [25].

The study had few imbalances between the 2 interventions groups; the early BCG group had more twins, who usually have higher mortality. The follow-up was good for an urban mobile population and there is little reason to think that deaths might have been underreported.

It should be noted that the study could not be double-blind. It seems unlikely, however, that this would have affected outcomes. The trial staff was not involved in providing health care apart from encouraging mothers to bring their children for missing vaccinations. Doctors and nurses at the pediatric ward and the health centers were unaware of the study and would normally not inspect the vaccination card of a child coming for consultations.

The effect on infant mortality was less than hypothesized, but the effect of BCG compared with BCG-unvaccinated controls on neonatal mortality was stronger than expected. The study was not planned to observe an effect only in the first months of life before controls received other vaccines. Instead we believed there would be some benefits from early BCG also when other vaccines were received and therefore planned to observe a 25% reduction in infant mortality. This belief was partly based on the observation that children with a BCG scar and a positive PPD reaction continued to have better survival even when other vaccines had been given [10–12]. However, in the present randomized trial the beneficial effect associated with receiving BCG at birth disappeared once other vaccines were given.

### Consistency With Previous Findings

The effect of BCG in the first month of life in this randomized trial is consistent with the 40%–60% reduction in mortality shown for BCG-vaccinated children compared with BCG-unvaccinated children in previous observational studies [4–12]. Most of these studies have been for normal-birth-weight children but we also conducted 1 study of LBW children. As in the previous observational studies, the effect of BCG was equally good or better in the children with the lowest birth weight [4]. Previous studies have suggested that the beneficial effect was stronger for girls than for boys [12, 26]; the present trial had limited power to find a difference because mortality had declined. In line with the previous observational study, we also showed that failing to vaccinate children with BCG at birth lowers the coverage for BCG among LBW children [4].

### Interpretation

The estimate of 3–4 weeks of age may be the best estimate of the effect of BCG compared with BCG-unvaccinated children since few controls had received BCG (Table 1; online only). The beneficial effect of BCG vaccination is unlikely to be related to protection against TB as few children were exposed to TB in the first month of life. As children grow older, more of them have received other vaccines, and the difference between the 2 groups is reduced. Consistent with this perspective, the beneficial effect of BCG at birth was strongest among the lowest birth weight children, who were much less likely to receive other vaccinations (Table 3).

Since this trial was initiated, we have observed in several studies that children receiving BCG and DTP vaccines simultaneously may have better survival after the neonatal period than children following the official policy of receiving BCG first and then DTP [27, 28] (unpublished data). Within the present trial, having received DTP at 2 months of age was associated with higher mortality between 2 and 6 months of age compared with not having received DTP at 2 months of age (Aaby P, Ravn H, Roth A, et al, unpublished data). The negative effect of having received DTP at 2 months of age was significantly increased in the early BCG group (4.3-fold) but not in the control group (1.7-fold), which had mostly received DTP before or simultaneously with BCG (Aaby P, Ravn H, Roth A, et al, unpublished data). Hence, the differences in timing and sequence of vaccinations in the 2 groups that resulted from the study design may have contributed to reducing the initial benefit of BCG vaccination.

### Biological Mechanisms

The verbal autopsy data suggested that BCG nonspecifically enhanced protection against important infections killing

neonates. Immunological studies support that BCG may alter the immune response to unrelated pathogens [29–32]. Considering the early effect on neonatal sepsis in particular, an effect on innate immune mechanisms may be likely. Neonates suffer from many deficits in innate immune function [33, 34], and BCG has been shown to stimulate Toll-like receptor 4, among others [35]. Hence, BCG might prepare the immune system to mount an effective response to infectious pathogens and therefore enhance survival. BCG may also help control excessive inflammation [36]; among hospitalized Malawians no case of sepsis was seen in infants with a BCG scar [37]. Further studies to elucidate the immunological mechanisms behind the nonspecific effects of BCG are needed.

### Implications

Though we did not find a significant effect on infant mortality, the study suggested that early BCG is associated with beneficial effects on survival in early infancy. It has recently been recommended not to use the BCG vaccine with HIV-infected children [38] because the 4-per-1000 risk of disseminated BCG disease [39] is assumed to outweigh the risk of TB in HIV-infected children [38]. If BCG protects against other causes of mortality, this could easily change the risk-benefit ratio; among LBW children BCG reduced infant mortality by 22 per 1000 (Table 3). If our observations are reproducible, there are several implications for vaccination policies in low-income countries. First, LBW children should receive BCG at birth. Second, if the effect is similar in normal-birth-weight children, BCG should also be given at birth in this group. BCG is very often delayed in low-income countries [40, 41]; the mean age of BCG vaccination is $>1$ month in many parts of Africa. Third, if a new TB vaccine is introduced, its effect on total mortality should be tested against BCG in areas with high mortality [42]. Fourth, there is a need to investigate the probable negative effect of DTP vaccination Aaby P, Ravn H, Roth A, et al. Early diphtheria-tetanus-pertussis vaccination associated with increased female mortality in a cohort of low-birth-weight children. An observational study within a randomized trial (submitted).

The vaccination schedule in the WHO immunization program is currently being reconsidered [43]. Taking the nonspecific effects into consideration could help reduce child mortality considerably in low-income countries [44].

## Supplementary Data

Supplementary data table is available at The *Journal of Infectious Diseases* online.

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