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Can earlier BCG-Japan and OPV vaccination reduce early infant mortality? A cluster-randomised trial in Guinea-Bissau

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ABSTRACT

Objective To assess the effect of providing BCG and oral polio vaccine (OPV) at an early home visit after delivery.

Design Cluster-randomised trial, randomising 92 geographically defined clusters 1:1 to intervention/control arms.

Setting Bandim Health Project Health and Demographic Surveillance System, Guinea-Bissau.

Participants 2226 newborns enrolled between July 2016 and August 2019.

Interventions In both arms, newborns received a home visit within 72 hours after birth. In intervention clusters (n=46), BCG and OPV were provided at the home visit.

Main outcome measure Rates of non-accidental mortality were compared in Cox proportional hazards models from (last of) day 1 or enrolment, until (first of) day 60 or registration of non-trial vaccines.

Results A total of 35 deaths (intervention: 7, control: 28) were registered during the trial. Providing BCG and OPV reduced non-accidental early infant mortality by 59% (8–82%). The intervention also reduced non-accidental hospital admissions. The intervention had little impact on growth and BCG scarring and tended to increase the risk of consultations.

Conclusions The trial was stopped early due to lower-than-expected enrolment and event rates when 33% of the planned number of newborns had been enrolled. Despite the small size of the trial, the results support that early BCG and OPV vaccinations are beneficial and reduce early child mortality and morbidity.

Trial registration number ClinicalTrials.gov Registry (NCT02504203).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vaccines play a major role in reducing the risk of infections and mortality worldwide.
⇒ The vaccines scheduled at birth, BCG vaccine and the oral polio vaccine (OPV), may have reduced early infant mortality from causes other than tuberculosis and polio.
⇒ The WHO-recommended home visits are currently not used as an opportunity to provide vaccines at birth, and vaccines scheduled at birth are often delayed.

WHAT THIS STUDY ADDS

⇒ This study demonstrated that providing BCG and OPV shortly after birth reduced early infant non-accidental mortality and hospital admissions considerably.
⇒ The trial also indicated that implementing home visits with vaccination may not be a feasible way to ensure early vaccination in Guinea-Bissau, as a large number of newborns were not reached within 72 hours of delivery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of early vaccination; thus, local practices such as restrictive vial opening should be removed, so vaccines are provided as early as possible.
⇒ The WHO recommendation of providing home visits after birth should be revised to include provision of BCG and OPV wherever possible.

INTRODUCTION

Despite a global child mortality decline of 59% between 1990 and 2019, neonatal mortality remains high.[1] It is estimated that 47% of the 5.2 million under-5 deaths occur within the first month of life.[1] To reduce the high neonatal mortality, the WHO recommends three home visits after birth,[2] including an assessment of the baby, promotion of exclusive breast feeding and cord care.[2] The recommendation is based on nine trials, which found that home visits reduced neonatal mortality by 24% (relative risk (RR)=0.76,

95% CI 0.62 to 0.92).[2] Providing vaccines is not part of the recommendations.[2] Vaccines have contributed significantly to the decline in child mortality. There is accumulating evidence supporting that the impact of vaccines is broader than the anticipated effect from reduction of target diseases. The BCG vaccine is recommended at birth to protect against tuberculosis. Randomised trials[3 4] and immunological studies[5] support that the BCG vaccine has non-specific effects and can reduce mortality from non-tuberculosis infections. Thus, current evidence indicates a broader benefit of giving BCG at birth.

Despite BCG being recommended at birth, BCG vaccination is often delayed in low-income countries.[6] A major reason for this delay is the focus on reducing vaccine wastage. Freeze-dried vaccines like BCG must be used within 6 hours after reconstitution with their diluent. The BCG vaccine contains 20 infant doses, and a vial of BCG vaccine is often not opened unless 10–12 children are present for vaccination. Hence, there are many missed vaccination opportunities. In 2017, only half the children in rural Guinea-Bissau were vaccinated during the first 2 weeks of life.[7] As 73% of neonatal deaths occur in the first week of life,[8] much could potentially be gained by early vaccination of all neonates. In addition to the BCG vaccine, the oral polio vaccine (OPV) is also recommended at birth.[9] OPV at birth (OPV0) is part of the strategy for eradicating polio.[10] As for the BCG vaccine, increasing evidence supports that OPV has beneficial non-specific effects.[11] A trial comparing BCG only versus BCG+OPV0 in neonates found that OPV0 reduced infant mortality by 32% (95% CI: 0% to 55%) before the next OPV campaign.[12]

In the present trial, we aimed to test the impact of combining the WHO-recommended home visits with provision of the vaccines recommended at birth (BCG and OPV0). We hypothesised that a single home visit after birth with provision of BCG and OPV0 could reduce early infant non-accidental mortality by 40%. In the trial, we assessed the effect of BCG and OPV provided at a single home visit within 72 hours after birth on early infant mortality and morbidity. The trial was stopped early for futility due to low recruitment numbers and low mortality.

METHODS

Study setting

This cluster-randomised trial was conducted in Guinea-Bissau, where the WHO-recommended home visits have not yet been implemented. It was implemented within the Bandim Health Project's (BHP) urban and rural Health and Demographic Surveillance System (HDSS) sites.[13 14] The HDSS sites follow women and children through regular household visits. In addition to the HDSS set-up, we implemented a platform with community key informants (CKIs) and study nurses. The trial was initiated in the rural health regions in July 2016 before being expanded to the urban study area in September 2017. Due to lower-than-expected enrolment rates, enrolments were suspended in the Cacheu region and in the urban study area in March 2019 and the trial was later stopped in the remaining regions in August 2019. Details on decision to expand and stop can be found in online supplemental file 1. The trial and the HDSS sites are described in further detail in the published trial protocol.[15]

In the rural study area, study nurses were selected among nurses working at a health centre with a catchment area corresponding to the study clusters. Hence, they were able to conduct home visits in addition to their normal routines. For the urban study area, the BHP employed a study nurse full-time.

In the rural areas, CKIs ensured timely information about deliveries. The CKIs were selected among residents in each rural village and collected information about pregnancies and deliveries. In the urban area, we took advantage of the close follow-up by the field assistants, who circulate the area daily.

Randomisation and blinding

The trial was a non-blinded cluster-randomised trial, where 92 clusters were randomised 1:1 to two different treatment groups, stratified by region and pre-trial mortality level (high/low, split at median). Clusters were defined as village clusters in the rural area and as subdistrict zones in the urban area. Clusters were randomised prior to study start using computer-generated random numbers.[15]

In both trial arms, newborns were visited as soon as possible after birth. In intervention clusters, the study nurses provided standard care (umbilical cord and skin care, encourage skin-to-skin contact, examine and weigh the newborn) and vaccines (BCG, OPV0) to children at the home visits; in control clusters, children only received standard care and were informed about vaccination recommendations, but no vaccines were administered.

Safety

The trial is registered at ClinicalTrials.gov (NCT02504203).

A Data Safety and Monitoring Board (DSMB), consisting of a paediatrician (Anja Poulsen, Rigshospitalet, Denmark), a statistician (Morten Frydenberg, Aarhus University, Denmark) and an epidemiologist (Torben Sigsgaard, Aarhus University, Denmark), was overseeing the trial and was involved in the discussions of ending the trial before target sample size was reached.

Participants

Inclusion criteria

All children registered during pregnancy were eligible for the study. Children were only enrolled if they were visited within 72 hours after birth.

Exclusion criteria

Children were excluded if they:

- Were already BCG vaccinated.

- Were moribund (expected to not survive the next 24 hours, as evaluated by the study nurse at the enrolment visit).
- Lived in a rural village where the BHP mobile teams coincidentally visited the same day (and vaccinated all children).

Informed consent

At the registration of a new pregnancy, the trial was explained and oral and written consent was obtained by the BHP nurse at the two monthly household visits in the rural area and by the fieldwork assistant at monthly visits in the urban area.[15] At the time of the home visit, confirmation of the consent was obtained by the study nurse. If women were not able to show the written consent form, a new written consent form was made.

Enrolment

All newborns received a home visit by a study nurse shortly after the birth was reported to the study staff, if possible, on the same day. Newborns born in healthcare facilities were enrolled at home after they had been discharged. At the home visit, the nurse obtained confirmation of consent for participation before revealing the randomisation. For all newborns, the nurse examined and weighed the newborn, encouraged skin-to-skin contact and if necessary performed umbilical cord care.[15]

Procedures

Intervention

For children in the control clusters, the nurse informed about vaccination opportunities (vaccination at closest health centre or vaccination by BHP nurse at subsequent village visit). For children in the intervention clusters, the nurse administered BCG and OPV0.

The BCG vaccine was administered by intradermal injection of 0.05 mL vaccine. All nurses were trained in correct vaccination technique prior to trial start and supervised intensively during the trial. The Tokyo 172 BCG strain from BCG-Japan was used for the study (batch numbers: 1578, 1599, 1621, 1624 and 1630). The vaccine is prequalified by the WHO.

The OPV0 was administered as two oral drops. The OPV was supplied from the national vaccination programme and thus strain, manufacturer and batch varied during the course of the trial (Polio Sabin from GlaxoSmith-Kline, Belgium; BioPolio from Bharat Biotech, India; and Bivalen from Biofarma, Indonesia).

Follow-up

Children were followed up until age 60 days at which age most children in the control group would also be vaccinated. All children enrolled in the trial were visited and an interview was conducted as early as possible after this age. In the rural area, the interviews were carried out in connection with the bimonthly HDSS visits. At follow-up visits, information on vital status, breastfeeding status, supplementary feeding, mid-upper arm circumference (MUAC), vaccinations, hospital admissions and whether the child had received interventions provided in campaigns was collected. For hospital admissions, information on cause, including accidents, was obtained. For all deaths, at a subsequent visit, a verbal autopsy was conducted, where information on cause of death was obtained.

Outcomes

The primary outcome was 'non-accidental mortality' during follow-up. The follow-up began at the time of the home visit or at 24 hours after birth whichever came last, thereby excluding deaths on the day of birth. Follow-up ended at the subsequent follow-up visit by the BHP (at that time point, all unvaccinated children were offered BCG/OPV), the date when the first non-trial vaccine was registered by BHP, migration, death due to accident or 60 days of age, whichever came first. All children living in intervention and control clusters were followed through the HDSS routines with collection of information on vital status for all children (figure 1).

Secondary outcomes

Prespecified secondary outcomes were 'non-accidental hospital admission', 'severe morbidity' (composite outcome of non-accidental mortality and non-accidental hospital admissions) and 'consultations' during the same follow-up period. Furthermore, secondary outcomes were 'MUAC' and 'weight-for-age z-score' (measured at the first follow-up visit), and 'BCG scarring' (measured at 6–12 months of age).

Sample size

The target sample size for the trial was based on previous data from the rural HDSS with an estimated proportion of events of 2.4%. The trial was sized to obtain 80% power to detect a reduction in early infant severe morbidity if the true effect of the intervention was larger than 40%. The target sample size was 6666 children. Details on sample size calculation can be found in the published protocol.[15] The trial was stopped before the target sample size was reached due to low recruitment and low mortality, and the trial population corresponds to only 33% of the target sample size.

Statistical analyses

General analysis principles can be found in online supplemental file 2. In Cox proportional hazards models with age as underlying time scale, we assessed the effect of providing BCG and OPV at a single home visit in a per-protocol analysis. We stratified for factors used in the randomisation (region and cluster-level pre-trial mortality (high/low)) and sex. To account for within-village clustering, cluster-robust variance estimates were employed on all analyses. Children entered the analysis on the date of enrolment or 24 hours of age, whichever came last, and remained in the analysis until whatever came first: the first subsequent visit by the BHP team, date of registering first non-trial vaccine after enrolment, death, migration or 60 days of life. Proportional hazards

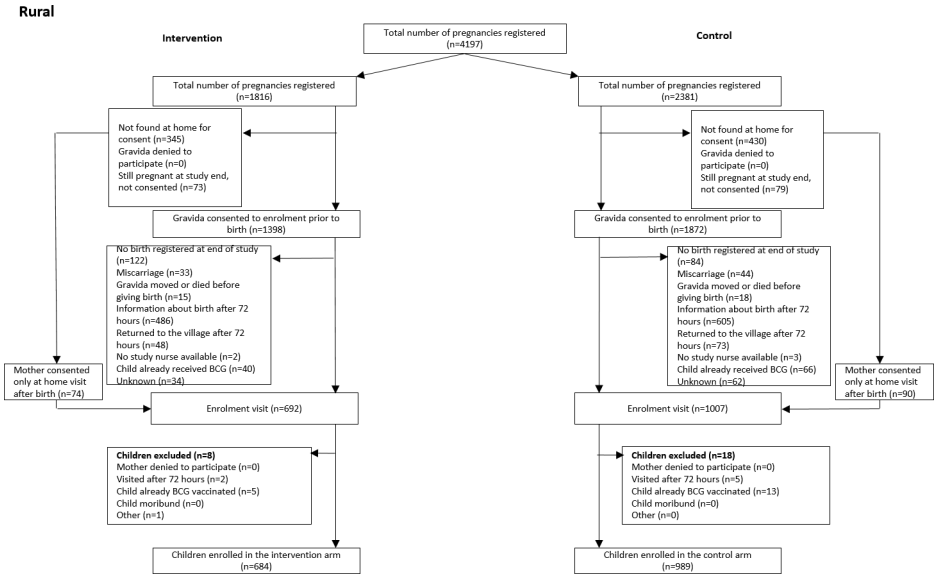

Figure 1 Flow chart of participants in the rural area.

assumptions were evaluated using Schoenfeld residuals significance test, log–log survival curves and by checking whether the effect interacted with the underlying time scale using the time-varying covariates (tvc) options. Further details are provided in the prespecified analysis plan (online supplemental file 3).[15]

Analyses of secondary outcomes are described in more detail in online supplemental file 3. In brief, the effect of providing BCG and OPV on non-accidental hospital admissions and severe morbidity (composite outcome of non-accidental mortality and non-accidental hospital admissions) was assessed in Cox proportional hazards models. The effect of providing BCG and OPV on all-cause consultations and BCG scarring was assessed in log-binomial regression models. The effect of providing BCG and OPV on MUAC and weight-for-age z-score between enrolment and first follow-up visit within 6 months of age was assessed in linear regression models.

In the analysis plan, a cost-effectiveness analysis was specified. As the trial was stopped prematurely, we did not perform a cost-effectiveness analysis.

Sensitivity analyses

In planned sensitivity analyses, we assessed the robustness of the main results by (1) censoring follow-up at general health intervention campaigns (a list of all health intervention campaigns in the period can be found in the online supplemental file 1), and (2) using an intention-to-treat approach, including all children, who had a home visit by a study nurse. We furthermore assessed the effect of the intervention on repeated hospital admissions.

Exploratory analyses

In an exploratory analysis, we assessed whether censoring follow-up time at deaths, hospital admissions and registration of non-trial vaccines affected the risk of consultations by further adjusting the consultation analysis for the length of follow-up time in the main analysis.

Patient and public involvement

The communities were involved in locating households, when the HDSS was set up and contributed information allowing tracing of internal migrants between villages throughout the study period. No participants were involved in setting the research question or the outcome measure, nor were they involved in developing plans for recruitment, design or implementation of the study. Local CKIs were selected to ensure timely information about birth. Nurses from local health centres were involved in the trial, which ensured a close collaboration with the local health system. No participant was asked to advise on interpretation or writing up the results. The results were disseminated to the national public health institute. There are no plans to directly disseminate the results of the research to study participants. However, all women in the HDSS are informed about the importance of early vaccinations during BHP village visits. Study results will be disseminated to local nurses involved in the study. The collaboration between local and international researchers is described in the author reflexivity statement (online supplemental file 1).

RESULTS

During the trial period (between 28 July 2016 and 31 August 2019), a total of 8811 pregnancies were registered in the BHP HDSS, of these 48% (4197) were registered in the rural HDSS, while 52% (4614) were registered in the urban HDSS.

In the rural area, 78% of pregnant women provided consent prior to giving birth (77% in intervention clusters/79% in control clusters). The main reason for not giving consent was that the pregnant woman was not found at home during village visits before delivery. Of those giving consent, 52% (49% in intervention clusters/54% in control clusters) received a home visit by a study nurse. Of the 1699 newborns receiving a home

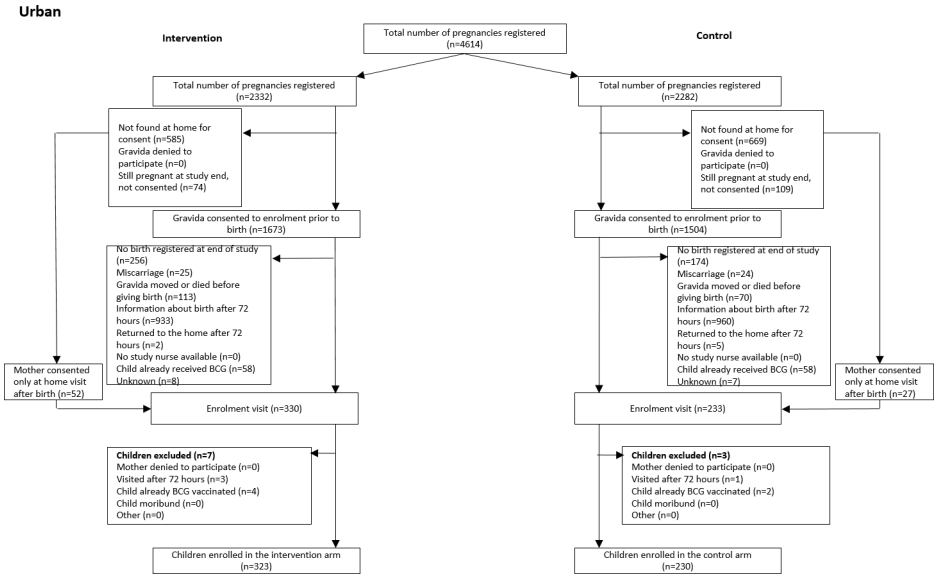

Figure 2 Flow chart of participants in the urban area.

visit, 1673 newborns were enrolled. In total, 26 newborns were excluded (7 newborns were visited later than 72 hours after birth, 18 newborns had already received BCG vaccine, 1 newborn was excluded by mistake, no newborns were excluded because the mother denied participation or because the newborn was considered moribund) (figure 1).

In the urban area, 69% (72% in intervention clusters/66% in control clusters) of pregnant women provided consent prior to giving birth. Again, the main reason for not giving consent was that the pregnant woman was not found at home during visits before delivery. In the urban area, more children were born at the national hospital, where BHP provides BCG and OPV0 vaccination before discharge[16] and were therefore not eligible for enrolment. Consequently, only 18% (20% in intervention clusters/15% in control clusters) received a home visit by a study nurse. Of the 563 newborns receiving a home visit, 553 newborns were enrolled. In total, 10 newborns were excluded (4 newborns were visited later than 72 hours after birth, 6 newborns had already received BCG vaccine, no newborns were excluded because the mother denied participation or because the newborn was considered moribund) (figure 2). Thus, the resulting sample size was 2226 newborns.

Most newborns were enrolled within 24 hours after birth (54% in intervention clusters and 57% in control clusters). Newborns from intervention and control clusters had similar distribution of background characteristics and most statistically significant differences reflected small absolute differences (table 1). However, in the Oio health region, more newborns were enrolled in control clusters. This was mainly driven by few large clusters with many enrolments. In the urban area, more newborns in the intervention group were born at health centres, whereas more children in the control group were born either at home or in the hospital (table 1).

Main outcome: non-accidental mortality

Among the 2226 newborns, 2212 entered the analyses (13 were visited by the mobile team on/before enrolment and 1 moved at the date of enrolment before being 24 hours old). In total, 35 children died during follow-up and the mortality rate was 66.5/1000 person-years (PYRS) (7 deaths during 105 PYRS) in the intervention group and 276.5/1000 PYRS (28 deaths/101 PYRS) in the control group. The resulting HR was 0.41 (95% CI: 0.18 to 0.92) stratified for region, cluster-level pre-trial mortality and sex (table 2). Thus, providing BCG and OPV reduced non-accidental early infant mortality by 59% (95% CI: 8% to 82%). The Schoenfeld residuals test did not indicate a violation of the proportional hazard assumptions (p=0.16) nor did the log–log curves, but the HR was not constant over time when tested with the tvc options (p=0.02). Inspecting follow-up of events revealed that all events in the intervention group occurred before age 10 days. Before day 10, the HR was 0.66 (95% CI: 0.26 to 1.66); after day 10, the HR was undefined but the rates were significantly different (online supplemental table 1).

Almost all deaths (34) occurred in the rural area. Stratifying on study area resulted in an HR of 0.37 (0.15 to 0.87) in the rural area, while it was not possible to calculate an HR for the urban area, as there was only one death in the intervention group and no deaths in the control group.

The effect of providing BCG and OPV at home visits was not modified by sex (p=0.40), maternal BCG scar (p=0.81), birth weight (p=0.97) or season (p=0.18) (table 2). One-third of the deaths were classified as due to sepsis, and effects were similar across all categories (online supplemental table 2). Sensitivity analyses did not alter conclusion (online supplemental tables 3–6).

Table 1 Baseline characteristics of trial participants in the intervention and control clusters

	All		Rural		Urban	
	Intervention	Control	Intervention	Control	Intervention	Control
n (%)	1007 (45)	1219 (55)	684 (41)	989 (59)	323 (58)	230 (42)
Males, n (%)	514 (51)	612 (50)	344 (50)	485 (49)	170 (53)	127 (55)
Age at enrolment, n (%)						
<24 hours	541 (54)	689 (57)	403 (59)	598 (60)	138 (43)	91 (40)
24–47 hours	237 (24)	274 (22)	73 (11)	147 (15)	164 (51)	127 (55)
48–71 hours	229 (23)	256 (21)	208 (30)	244 (25)	21 (7)	12 (5)
Region, n (%)						
Oio	346 (34)	619 (51)	346 (51)	619 (63)	–	–
Biombo	178 (18)	206 (17)	178 (26)	206 (21)	–	–
Cacheu	160 (16)	164 (13)	160 (23)	164 (17)	–	–
Bissau	323 (32)	230 (19)	–	–	323 (100)	230 (100)
Weight at enrolment*, mean (SD)/kg	2.94 (0.45)	2.88 (0.46)	2.92 (0.45)	2.85 (0.45)	2.99 (0.44)	2.98 (0.45)
Low birth weight, n (%)						
Yes	145 (14)	220 (18)	105 (15)	185 (19)	40 (12)	35 (15)
No	859 (85)	988 (81)	576 (84)	793 (80)	283 (88)	195 (85)
Temperature at enrolment†, mean (SD)/°C	36.7 (0.8)	36.7 (0.8)	36.6 (0.8)	36.7 (0.8)	36.8 (0.6)	36.7 (0.6)
Mid-upper arm circumference at enrolment‡, mean (SD)/mm	98 (9)	97 (10)	97 (9)	97 (10)	98 (8)	99 (11)
Head circumference at enrolment§, mean (SD)/cm	34 (1)	34 (2)	34 (1)	34 (2)	34 (1)	34 (1)
Place of birth¶, n (%)						
Home	571 (57)	801 (66)	474 (69)	694 (70)	97 (30)	107 (47)
Health centre	306 (30)	247 (20)	144 (21)	204 (21)	162 (50)	43 (19)
Hospital	80 (8)	122 (10)	46 (7)	75 (8)	34 (11)	47 (20)
Other	48 (5)	47 (4)	19 (3)	15 (2)	29 (9)	32 (14)
Season, n (%)						
Rainy	490 (49)	482 (40)	319 (47)	381 (39)	171 (53)	101 (44)
Dry	516 (51)	737 (60)	365 (53)	608 (61)	151 (47)	129 (56)
Maternal education**, n (%)						
No schooling	357 (35)	503 (41)	255 (37)	428 (43)	102 (32)	75 (33)
1–4 years	206 (20)	291 (24)	178 (26)	272 (28)	28 (9)	19 (8)
5–7 years	213 (21)	215 (18)	158 (23)	161 (16)	55 (17)	54 (23)
>7 years	165 (16)	123 (10)	34 (5)	46 (5)	131 (41)	77 (33)
Maternal BCG scar††, n (%)						
Yes	606 (60)	705 (58)	388 (57)	572 (58)	218 (67)	133 (58)
No	304 (30)	377 (31)	221 (32)	309 (31)	83 (26)	68 (30)
Toilet‡‡, n (%)						
No toilet	224 (22)	202 (17)	221 (32)	202 (20)	3 (1)	0 (0)
Latrine	736 (73)	974 (80)	457 (67)	778 (79)	279 (86)	196 (85)
Inside the house	38 (4)	37 (3)	0 (0)	5 (1)	38 (12)	32 (14)
Roof§§, n (%)						
Straw	130 (13)	138 (11)	130 (19)	138 (14)	320 (99)	229 (100)
Hard	870 (86)	1075 (88)	550 (80)	846 (86)	–	–
Electricity¶¶, n (%)						

Continued

Table 1 Continued

	All		Rural		Urban	
	Intervention	Control	Intervention	Control	Intervention	Control
Yes	527 (52)	594 (49)	340 (50)	477 (48)	187 (58)	117 (51)
No	468 (46)	613 (50)	336 (49)	501 (51)	132 (41)	112 (49)

*14 newborns have missing information on weight.
†13 newborns have missing information on temperature.
‡2 newborns have missing information on mid-upper arm circumference.
§6 newborns have missing information on head circumference.
¶4 newborns have missing information on place of birth.
**153 newborns have missing information on maternal education.
††234 newborns have missing information on maternal BCG scar.
‡‡15 newborns have missing information on toilet.
§§13 newborns have missing information on roofing.
¶¶24 newborns have missing information on electricity.

Non-accidental hospital admission

The rate of hospital admission was 66.8 (7 hospital admissions during 105 PYRS) in the intervention group and 149.2 (15 hospital admissions during 101 PYRS) in the control group. The intervention group thus had 67% fewer hospital admissions (HR: 0.33 (95% CI: 0.13 to 0.84)) (table 3). Schoenfeld residuals (p=0.005), log–log plots and the tvc option (p=0.04) all indicated that the proportional hazards assumption was violated. Splitting follow-up after day 10 resulted in an HR of 0.06 (95% CI: 0.01 to 0.39) for the early period and 1.60 (95% CI: 0.28 to 9.11) in the late period (data not shown). In the rural area, the intervention resulted in an HR of 0.49 (95% CI: 0.15 to 1.59), while the corresponding estimate in the urban area was 0.21 (95% CI: 0.05 to 0.86). There were no repeated hospital admissions during follow-up.

Severe morbidity

Combining mortality and hospital admissions in a composite outcome of severe morbidity resulted in an event rate of 133.6/1000 PYRS (14 events during 105 PYRS) in the intervention group and 358.0/1000 PYRS (36 events during 101 PYRS) in the control group. Thus, the intervention resulted in 58% fewer events (HR: 0.42 (95% CI: 0.22 to 0.81)). The intervention tended to reduce the risk of events in both the rural (HR: 0.49 (95% CI: 0.23 to 1.04)) and the urban area (HR: 0.28 (95% CI: 0.08 to 0.94)) (table 3).

Outpatient consultations

Among the 2208 newborns entering the main analysis, 177 (101 in intervention and 76 in control clusters) received a consultation during follow-up. Providing BCG and OPV0 at home visits tended to increase the risk of consultation by 32% (RR=1.32 (95% CI: 0.92 to 1.88), adjusted for sex, region and cluster-level pre-trial mortality). Newborns in the urban area were more likely to have a consultation during follow-up, but the effect of BCG and OPV0 was similar in the rural (RR=1.29 (95% CI: 0.73 to 2.26)) and the urban areas (RR=1.42 (95% CI: 0.94 to 2.15)) (table 4). In a post hoc analysis, adjusting for the (differential) length of follow-up, the RR was 1.08 (95% CI: 0.74 to 1.58).

BCG scarring

Among the 2208 newborns, 1753 children were present at an HDSS visit between 6 and 12 months of age and had their arm inspected for a BCG scar. Most of these children had developed a BCG scar (95% in the intervention group and 92% in the control group). In the rural area, the intervention had little impact on BCG scarring (RR=1.03 (95% CI: 0.99 to 1.07)) (table 4). Only three children had not developed a scar in the urban area.

Growth

The intervention had no effect on growth (difference in MUAC was 0.82 mm (95% CI: −0.39 to 2.03) and difference in weight z-score was 0.04 (95% CI: −0.06 to 0.13)) (online supplemental table 7).

Adverse events

During the trial, three cases of lymphadenitis were identified in the intervention group and no adverse events in the control group (online supplemental table 8).

DISCUSSION

Providing BCG and OPV0 vaccinations at a single home visit within 72 hours after birth reduced early infant mortality (HR: 0.41 (95% CI: 0.18 to 0.92)), hospital admissions (HR: 0.33 (95% CI: 0.13 to 0.84)) and event-free survival for either of the outcomes (HR: 0.42 (95% CI: 0.22 to 0.81)). The intervention was not associated with growth and BCG scarring and tended to increase the risk of consultations during follow-up. The trial was stopped early due to low enrolment rates and low mortality.

We conducted the trial in a setting where the WHO-recommended home visits are not yet implemented. We created new vaccination opportunities at birth to be able to test the effect of providing vaccines recommended at birth with the home visits as this is not currently

Table 2 Effect of providing BCG and OPV at a home visit on non-accidental mortality and potential effect modifiers

	n	MR/1000 PYRS (deaths/PYRS)	HR (95% CI)
Main outcome: non-accidental mortality			
Intervention	1006	66.5 (7/105)	0.41 (0.18 to 0.92)
Control	1206	276.5 (28/101)	Reference
Rural			
Intervention	683	95.3 (6/63)	0.37 (0.15 to 0.87)
Control	976	328.9 (28/85)	Reference
Urban			
Intervention	323	23.7 (1/42)	NA
Control	230	0.0 (0/16)	Reference
Effect modifiers			
Sex			
Male, intervention	514	76.1 (4/53)	0.59 (0.20 to 1.76)
Male, control	603	233.0 (12/51)	Reference
Female, intervention	492	57.0 (3/53)	0.28 (0.08 to 0.98)
Female, control	603	321.5 (16/50)	Reference
Maternal BCG scar			
Maternal BCG scar, intervention	605	61.7 (4/65)	0.45 (0.15 to 1.36)
Maternal BCG scar, control	702	234.7 (14/60)	Reference
No maternal BCG scar, intervention	304	63.1 (2/32)	0.35 (0.08 to 1.57)
No maternal BCG scar, control	371	284.5 (9/32)	Reference
Birth weight			
Low birth weight, intervention	145	211.8 (3/14)	0.44 (0.11 to 1.78)
Low birth weight, control	216	811.1 (15/18)	Reference
Normal birth weight, intervention	858	44.1 (4/91)	0.46 (0.16 to 1.32)
Normal birth weight, control	979	159.0 (13/82)	Reference
Season			
Rainy season, intervention	490	77.5 (4/52)	0.85 (0.22 to 3.30)
Rainy season, control	476	148.7 (6/40)	Reference
Dry season, intervention	516	56.0 (3/54)	0.26 (0.08 to 0.80)
Dry season, control	730	361.2 (22/61)	Reference

MR, mortality rate; NA, not applicable; OPV, oral polio vaccine; PYRS, person-years.

part of the WHO recommendation. To do so, we set up a CKI system to allow for timely information about births. This mimics the community health worker system implemented in many low-income countries, and thus strengthens the ability to transfer trial results to future policy. The close collaboration with the national health system was also reflected in the recruitment of study nurses, whom we trained on home visit routines and vaccination technique. In addition to the close collaboration with the national health system, the trial set-up benefited from the implementation within a research platform with extensive trial experience. By nesting the trial within an HDSS, it became feasible to identify pregnancies and ensure that all pregnant women in a defined area were invited to participate in the trial, and that no trial participants were lost to follow-up. Furthermore, nurses and data collectors were intensively supervised. A major limitation was that the trial was ended early as there were lower-than-expected enrolment rates and few deaths and hospital admissions. This was mainly due to difficulties in obtaining timely information about births. Thus, the trial only included 33% of the planned sample size. However, no interim analyses were performed: analyses of the trial were only conducted after the trial had ended, and the results of the trial were therefore unknown when deciding to end the trial. The decision to end the trial was made in collaboration with the DSMB based on enrolment rates and the overall event rates. As the trial was stopped early, the results of the trial are likely to be more imprecise leading to an increased risk

Table 3 Effect of providing BCG and OPV at a home visit on non-accidental hospital admission and severe morbidity (composite outcome of non-accidental mortality and non-accidental hospital admission)

	n	MR/1000 PYRS (deaths/PYRS)	HR (95% CI)
Non-accidental hospitalisation			
Intervention	1006	66.8 (7/105)	0.33 (0.13 to 0.84)
Control	1206	149.2 (15/101)	Reference
Rural			
Intervention	683	63.7 (4/63)	0.49 (0.15 to 1.59)
Control	976	106.0 (9/85)	Reference
Urban			
Intervention	323	71.4 (3/42)	0.21 (0.05 to 0.86)
Control	230	384.2 (6/16)	Reference
Composite outcome: non-accidental hospitalisation and non-accidental mortality*			
Intervention	1006	133.6 (14/105)	0.42 (0.22 to 0.81)
Control	1206	358.0 (36/101)	Reference
Rural			
Intervention	683	159.2 (10/63)	0.49 (0.23 to 1.04)
Control	976	353.2 (30/85)	Reference
Urban			
Intervention	323	95.3 (4/42)	0.28 (0.08 to 0.94)
Control	230	384.2 (6/16)	Reference

Two newborns with missing information on whether hospital admission was caused by accident.
*In the intervention group, there was no overlap between events (death and hospital admission), whereas seven newborns in the control group were first admitted to hospital and later died.
MR, mortality rate; OPV, oral polio vaccine; PYRS, person-years.

of dismissing a beneficial or harmful effect of the intervention. The trial set-up was very resource demanding in a setting where the WHO-recommended home visits are not implemented.

Historically, low birthweight infants were recommended delayed BCG vaccination. This made it possible and ethically justified to study the impact of early BCG vaccination in randomised trials among low birthweight infants. Therefore, most randomised trials assessing the impact of BCG vaccination on mortality early in life have been done in low birthweight infants. Three trials from Guinea-Bissau in low birthweight infants found that BCG+OPV versus just receiving OPV reduced neonatal mortality by 38% (95% CI: 17% to 54%).[3]

In the present trial, we took advantage of the common delays in vaccination,[7 17] and were therefore able to enrol normal birthweight newborns, still ensuring that no newborn received the BCG and OPV0 vaccines later than had the trial not been carried out. Since we found a similar benefit of BCG and OPV0 in newborns with low and normal birth weight, the benefits do not appear to be limited to children with low birth weight.

Since the Guinean low birthweight BCG trials, two trials have been conducted in India. These trials provided BCG alone or BCG+OPV0 versus no vaccines to neonates weighing <2000 g. Neither of the trials found any effect on neonatal mortality.[18] It has been proposed that the discrepancy between the trial results may be explained by different BCG strains.[19] The three trials from Guinea-Bissau in low birthweight infants all used BCG-Denmark,[3] whereas the two trials from India used BCG-Russia.[18] The hypothesis on different non-specific effects of different BCG strains was tested in a randomised trial comparing the effect of BCG-Denmark and BCG-Japan with BCG-Russia on hospital admissions (primary outcome) and mortality. The trial found no difference between BCG-Denmark and BCG-Russia for either admission (HR: 1.08 (95% CI: 0.84 to 1.37)) or mortality (HR: 1.15 (95% CI: 0.74 to 1.81)),[16] while the BCG-Japan strain tended to increase hospital admissions compared with BCG-Russia (HR: 1.15 (95% CI: 0.93 to 1.43)) but not mortality (HR: 0.71 (95% CI: 0.43 to 1.19)).[16] In the present trial, BCG-Japan was used in combination with OPV0 vaccines and reduced early infant mortality and the risk of non-accidental hospital admission. The effect of BCG-Denmark on hospital admissions was also assessed in a trial in Denmark, which also found no effect of BCG on hospital admission,[20] but a protective effect against atopic dermatitis,[21] as seen in other high-income settings.[22] A trial from Uganda found BCG-Denmark at birth to be associated with 29% (95% CI: 5% to 47%) lower infectious disease incidence, most pronounced in low birthweight

Table 4 Effect of providing BCG and OPV at a home visit on all-cause outpatient consultations and BCG scarring

		Consultations	Adjusted for region, cluster-level pre-trial mortality and sex	Further adjusted for FU time
	n	n (%)	RR (95% CI)	RR (95% CI)
All-cause consultations				
Intervention	1006	101 (10)	1.32 (0.92 to 1.88)	1.08 (0.74 to 1.58)
Control	1206	76 (6)	Reference	Reference
Rural				
Intervention	683	47 (7)	1.29 (0.73 to 2.26)	1.25 (0.71 to 2.19)
Control	976	50 (5)	Reference	Reference
Urban				
Intervention	323	54 (17)	1.42 (0.94 to 2.15)	0.98 (0.64 to 1.51)
Control	230	26 (11)	Reference	Reference
BCG scarring				
	n	BCG scar n (%)	RR (95% CI)	
Intervention	771	734 (95)	NA	
Control	982	907 (92)	Reference	
Rural				
Intervention	575	539 (94)	1.03 (0.99 to 1.07)	
Control	826	753 (91)	Reference	
Urban				
Intervention	196	195 (99)	NA*	
Control	156	154 (99)	Reference	

*The model could not converge as only three children had no scar in the urban area.
FU, follow-up; NA, not applicable; OPV, oral polio vaccine; RR, risk ratio.

newborns.[4] In our trial, BCG-Japan and OPV0 tended to increase the risk of consultation. However, this could at least partly be ascribed to the longer follow-up period, as the effect disappeared in the urban area when adjusting for follow-up time.

In the Danish trial, stratified analyses suggested that maternal BCG vaccination status modified the effect of BCG vaccination. Among children of BCG-vaccinated mothers, BCG vaccination was associated with 35% (95% CI: 6% to 55%) fewer infectious disease hospital admissions.[23] This was supported by a study from Guinea-Bissau,[24] which also found stronger effects of BCG among infants when the mother had a BCG scar (an indicator of a successful BCG vaccination). Other studies have found maternal BCG scar to be beneficial on its own.[25 26] In the present trial, BCG and OPV were beneficial for both children of mothers with and without a BCG scar.

The trial is to our knowledge the only trial assessing the effect of BCG and OPV vaccination versus no vaccination on early infant mortality in both low birthweight and normal birthweight newborns.

Prior trials conducted in low birthweight infants found that BCG did not reduce the risk of hospital admission, but it reduced the case fatality among hospitalised children, indicating that BCG might not reduce the incidence, but rather the severity of infection.[27] In contrast, the present trial indicates a protective effect of BCG and OPV0 against hospital admissions. We speculate that a potential explanation for this could be different thresholds for hospital admission among children born at the national hospital (previous trials) and families with children who were unvaccinated, when met at home by the study nurse (the present trial). The latter group will likely have a higher threshold for hospitalisation, which would mean that only the most severely ill children would be hospitalised.

The trial was stopped due to low enrolment rates and low mortality. Obtaining information on births within 72 hours was far from always possible, and among those who were registered and consented during pregnancy, 33% provided information on delivery more than 72 hours after birth. Though the vaccine delivery set-up employed in the present trial was not likely to be effective at scale in a setting like the Guinean, vaccine delivery could relatively easily be implemented in settings where the WHO-recommended home visits are implemented or by implementing BCG vaccination at birth facilities. The WHO recommendation of providing home visits after birth should be revised to include provision of BCG and OPV wherever possible. Previous research has shown that

the BCG vaccine is often delayed due to local practices of not opening a vial of BCG for few children. The results of the present trial stress the importance of removing such barriers. With the strong effect indicated in the present trial and in a number of other trials,[3 12 28 29] providing BCG and OPV at birth could be an important contributor to lowering neonatal mortality.

CONCLUSION

Despite of its small size, our trial supports that early vaccination with BCG and OPV0, as recommended in low-income countries, has the potential to lower early child mortality and morbidity. Early vaccination should therefore be of highest priority.

Transparency statement

Sanne Marie Thysen is the guarantor of the trial and affirms that the manuscript is an honest, accurate, and transparent account of the trial; no important aspects of the trial have been omitted; any discrepancies from the original trial protocol have been explained.

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Contributors AR, PA and CSB conceived the idea for the trial. SMT, PA, CSB and ABF designed the study. SMT set up the study with help from IdSB, JSH, ADS and ABF. SMT, IdSB, JM, ADS, JSH, LMVdS and ABF supervised data collection. JSDM diagnosed the verbal autopsies. SMT, AJ and ABF planned the data analyses. SMT analysed the data and drafted the manuscript with input from ABF. ABF verified the data analyses. All authors read and approved the final manuscript. SMT is the guarantor of the trial and affirms that the manuscript is an honest, accurate, and transparent account of the trial; no important aspects of the trial have been omitted; any discrepancies from the original trial protocol have been explained.

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