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Can BCG vaccination at first health-facility contact reduce early infant mortality? Study protocol for a cluster-randomised trial (CS-BCG)

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ABSTRACT

Introduction Increasing evidence suggests that the BCG vaccine has non-specific effects, altering the susceptibility to non-tuberculous infections. Thus, early BCG vaccination may reduce mortality. BCG is recommended at birth but is often delayed. Vaccination opportunities are missed due to multidose vials not being opened for a few children. We will assess the effect of making BCG available at the first health-facility contact on early infant mortality and morbidity in a rural setting in Guinea-Bissau.

Methods and analysis In a cluster-randomised crossover trial, we randomise 23 health centres to two different treatment groups. In half of the health centres, BCG is provided as per current practice; in the remaining health centres, we make BCG available everyday to allow opening a vial of BCG if there is just one eligible child present. The randomisation of centres will be crossed over after 12 months and enrolment will continue for another 12 months.

We will use logistic regression models with adjustment for village to assess the effect of making BCG available at the first health-facility contact. The main outcome is non-accidental mortality between day 1 and day 42 after birth. We will adjust for sex, health centre, period (before/after crossover) and level of surveillance (level 1 or level 2). Further analyses include assessment of the effect on hospital admission and a cost-effectiveness evaluation.

Ethics and dissemination If BCG vaccination reduces early infant mortality, missed opportunities and delays of vaccinations expose infants in several low-income countries to unnecessary excess mortality risk. The present trial will provide information on the effect of implementing a feasible intervention, where all children receive BCG at their first health-facility contact. Consent is obtained from all pregnant women registered as part of the trial. The results of the study will be published and communicated to the National Institute of Public Health in Guinea-Bissau.

Trial registration number NCT04658680; Clinicaltrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial tests an easily implementable and feasible intervention to increase timeliness and coverage of BCG vaccination.
⇒ The trial builds on previous findings, trial experience and close collaboration with local health authorities.
⇒ Provided that we are able to confirm previous findings of the impact of early BCG vaccination, the trial results can be transformed into immediate policy changes.
⇒ As reliable registries of pregnancies, births and early mortality are absent in Guinea-Bissau, the trial requires a setup with pregnancy registration. Only children registered during pregnancy will be included in the analyses.

INTRODUCTION

The WHO recommends BCG vaccine to be given at birth in countries with high tuberculosis (TB) burden.[1] However, BCG is often given with delay in low-income countries.[2–4] In rural Guinea-Bissau, less than half of children receive BCG within the first month of life.[5 6] One of the reasons for delayed BCG vaccination is a local practice of not opening a BCG vial unless 10–12 children are present for vaccination. BCG vaccines contain 20 doses and the local policy aims to reduce vaccine wastage. However, some of the costs apparently saved by reduced vaccine wastage are transferred to the household as extra costs of seeking BCG vaccination.[7] We have estimated that it is cost-saving to disregard the restrictive vial-opening policy for BCG, if, on average, four children are vaccinated per BCG vial.[6]

The BCG vaccine is provided to protect against TB, but increasing evidence suggests that BCG, aside from the specific protection against TB, has non-specific effects (NSEs) protecting against TB-unrelated infections.[8] Several observational studies have found that BCG is associated with beneficial NSEs,[9–11] and that timing of BCG may be important.[12 13]

In the present trial, we aim to study the mortality and morbidity effects of making BCG available at the first health-facility contacts in a rural setting in Guinea-Bissau.

Background and rationale

In 2014, the Strategic Advisory Group of Experts on Immunization reviewed the literature on NSEs for the BCG vaccine, Diphtheria-Tetanus-Pertussis vaccine and measles vaccine. For BCG, they concluded that the evidence was consistent with BCG having beneficial NSEs. Many studies were observational, and evidence from randomised trials was requested.[8] As BCG is recommended at birth, it is difficult to conduct randomised trials of BCG vaccination, as it is not ethical to deprive children of the BCG vaccine. Therefore, most trials of the effect of BCG vaccination on mortality have been conducted among low-weight children, for whom BCG vaccination was previously delayed. Three trials from Guinea-Bissau using BCG-Denmark showed that BCG vaccination at birth reduced neonatal mortality by 38% (95% CI 17 to 54%).[14–16] Two recent trials among low-weight children in India using BCG-Russia found no effect of BCG vaccination at birth (HR: 0.98 (95% CI 0.85 to 1.11).[17] These differences in results have been suggested to be related to differences in BCG strains.[18]

Immunological evidence indicates that BCG induces epigenetic changes in monocytes, which reprogram the innate immune system to increased proinflammatory responses against unrelated pathogens.[19 20] These findings provide biological mechanisms, whereby BCG could exert non-specific beneficial effects, protecting the recipients against non-targeted infectious diseases.[20 21]

Objective and hypothesis

In the present cluster-randomised crossover trial, we will assess the effect of making BCG available everyday at the health facilities on early infant mortality and morbidity in a rural setting in Guinea-Bissau. We hypothesise that increasing the availability of BCG and vaccinating children at the first health-facility contact can reduce early infant non-accidental mortality by 25%.

METHODS AND ANALYSES

Setting and study population

The study will be conducted in Oio, Farim and Biombo regions in Guinea-Bissau. Within these health regions, primary healthcare is managed in 23 health areas, each with a health centre. Bandim Health Project's (BHP) rural Health and Demographic Surveillance System (HDSS) monitors pregnancies, births and child health in 40 BHP village clusters distributed across the regions.

BHP HDSS (level 1): BHP established the rural HDSS in 1990.[22] The BHP teams survey women of fertile age and children below the age of 5 years in randomly selected BHP clusters in all health regions across the country. The 40 rural BHP clusters in the regions where the trial will be implemented are followed through bimonthly visits by the BHP teams. At all visits, the women are asked whether they are pregnant. When a pregnancy is registered, the woman's nutritional status is assessed by measurement of mid-upper arm circumference (MUAC). Information on antenatal care is collected prior to giving birth as well as at the first visit after delivery. Socioeconomic factors (type of roofing, type of bathroom, possession of a mobile phone, radio and generator) are registered. After the delivery, information on the place of delivery (home, health facility) and who assisted the delivery is collected. The annual birth cohort in the 40 BHP clusters is approximately 1200.

Reinforced community health workers (CHWs) monitoring (level 2): in all villages, CHWs, subsidised through national programmes, monitor births and deaths. CHWs report aggregated data on pregnancies, number of births and neonatal deaths (in two categories: 0–7 days and 8–28 days) in their capture area to the health centre at monthly meetings. For the outcome assessment within the framework of the trial, we have developed a reinforced monitoring system based on expanding the existing supervisor system. Each CHW will receive a visit every 1–3 months from a BHP subsidised supervisor, each covering one health area (table 1). At the first visit after the registration of a pregnancy by the CHW, the supervisor will visit the pregnant woman and register information on maternal age, schooling, parity and BCG scar. In villages without a functioning CHW-monitoring system, the supervisor will collect information at the households without a prior visit from a CHW. The supervisor will visit households of children, who, at the prior visit, were aged less than 42 days or not born, and collect individual-level information on vital status, hospital admissions, BCG vaccination status, MUAC and BCG reaction. Each CHW follows 50–100 compounds in a village or a defined area of a large village.

Table 1 Trial design

	Number of clusters	Intervention	Control	Surveillance
Level 1	40 BHP clusters	BCG available at all health-facility contacts	BCG available at weekly contacts as usual practice	HDSS follow-up with bimonthly visits
Level 2	840 villages			Village visit every 1–3 months by a supervisor reinforcing the CHW data collection and monthly CHW data collection

BHP, Bandim Health Project; CHW, community health worker; HDSS, Health and Demographic Surveillance System.

Trial design and randomisation

The present trial is a cluster-randomised crossover trial, randomising health centres (1:1) to two different treatment groups stratified by region. In half of the health centres, the control group, BCG will be provided as per current practice (typically once a week if a sufficient number of children are present for vaccination); in the remaining health centres, the intervention group, we will make BCG available everyday by opening a vial of BCG if there is just one eligible child present. The trial will be implemented stepwise, one region at a time. In each region, the randomisation of centres will be crossed over after 12 months.

Randomisation will be performed prior to study start using computer-generated random numbers. The trial is unblinded.

Sample size considerations

We ran 10 000 simulations with a baseline mortality risk of 2.5% between day 1 and day 42, allowing variation between 1.5% and 3.5% for the individual health centres and using a uniform mortality distribution. Based on the estimated number of births within each health centre area (data provided by the vaccination programme), and assuming that we will obtain information on 85% of pregnancies prior to births, we will include approximately 11 400 children in the analysis per year. The true mortality reduction by the intervention is assumed to be 25%. Using a logistic regression with generalised estimating equation (GEE)-based correction for health area, we will have 90% power to demonstrate an effect of the intervention. In the planned analyses, we will use GEE correction for the smaller unit 'village', and, thus, the sample size estimate is conservative.

Trial methodology

Enrolment

All children registered during pregnancy, enter the trial cohort 1 day after birth (main analysis) or at birth (secondary analysis). A pregnancy can be registered in more than one village, but the child will only enter the trial if the mother gave birth in the village or was discharged to the village after giving birth at a health facility.

Informed consent

Within the HDSS (level-1 BHP clusters), we seek consent for surveillance of women and all their children at the first registration (online supplemental appendix 1). In level-2 villages, oral consent for surveillance will be sought at the registration of the pregnancy (online supplemental appendix 2).

InterventionBCG vaccine

BCG vaccination is administered by intradermal injection. After vaccination, most children develop a scar at the injection site. Among BCG-vaccinated children, having a BCG scar is associated with improved survival.[23–25] The proportion of children developing a scar after BCG vaccination depends on the vaccination technique and strain.[26–28] Refresher training on vaccination technique and assessment of lymph glands will be conducted at all health centres prior to trial start and prior to revealing the randomisation to the health facility personnel. During the pilot phase, the ability of the health facilities to provide BCG according to the trial randomisation will be evaluated. If the number of staff capable of providing BCG is not sufficient to be able to vaccinate everyday (intervention arm) or according to routine schedule (control arm), further staff will be trained in BCG vaccination technique.

BCG vaccination is part of the recommended vaccination programme in Guinea-Bissau, and we will use vaccines provided by the national vaccination programme through UNICEF. The strain supplied through the national vaccination programme varies, and different strains are used interchangeably. We will supply additional BCG vaccines to make BCG available at all health-facility contacts at the intervention health centres and, in case of national stock out, as per usual quantity at the control centres. In collaboration with the national vaccination programme, we will coordinate the BCG supply to make sure that, during the same period, the same strain will be used in both randomisation arms. We will only supply WHO-prequalified BCG vaccines. In case of BCG vaccine shortages, we will supply a quantity corresponding to what is usually supplied by the national vaccination programme to control health centres and continue to supply BCG vaccines to be able to open a vial for each child in the intervention health centres.

Other routine vaccines will be available as usual through the national Expanded Programme on Immunization in all health centres irrespective of randomisation allocation.

Follow-up

All children entering the trial in Oio, Farim and Biombo are followed up individually through level 1 and/or level 2 follow-up as explained in 'settings and study population'. At home visits after 42 days of age, individual-level information on vital status, hospital admissions, BCG vaccination status, MUAC and BCG reaction will be collected for all children in the trial. For all registered deaths, a specially trained field worker will visit the household of the deceased child to conduct a verbal autopsy. Furthermore, passive case detection for suspected adverse events (admissions and consultations) will take place at the health centres.

Data management

The CHWs deliver data to the health centres at monthly meetings. The summary data reported by the CHWs will be recorded by the supervisors. Data collected by supervisors (level 2) will be collected on password-protected tablets and backed up to a password-protected encrypted server. Every 6th month data on children who completed follow-up will be moved to an encrypted server only accessible to investigators. Data collected through the HDSS

(level 1) will be copied to the study data table. Following data entry, data are checked for consistency using standardised procedures. Main outcome events are reviewed individually.

Inclusion criteria

All children registered by the supervisors during pregnancy are eligible for the trial, provided that:

- the child is born in the village or
- the child is born in a health facility and discharged directly to the village.

Exclusion criteria

As the trial is expected to answer a pragmatic question about the effect of making the BCG vaccine available at the first health-facility contact, there are few exclusion criteria:

- the child died within 1 day after birth (except in the analysis of neonatal mortality (secondary outcome)).
- the child is born outside Oio, Farim and Biombo health regions.

Box 1 Outcomes

Primary outcome

⇒ · Early infant non-accidental mortality*.

Potential effect modifiers

⇒ Sex.
⇒ Maternal BCG scarring.
⇒ Season.
⇒ Oral polio vaccine campaigns.
⇒ BCG strain.

Secondary outcomes

⇒ Neonatal non-accidental mortality*.
⇒ Non-accidental hospital admission*.
⇒ Incremental cost-effectiveness of making BCG available at the first health-facility contact.

*Analysed using logistic regression models with generalised estimating equation-based correction for cluster effect. All children registered prior to birth are included in the analyses. Further details are provided in online supplemental appendix 3.

Outcomes

Primary outcome

The primary outcome is non-accidental mortality between 1 and 42 days after birth based on individual-level data. As other vaccines are scheduled to be given at 42 days, we have chosen this cut-off to avoid interference from other vaccines. Non-accidental mortality is defined as all deaths not classified as caused by accidents based on the verbal autopsies. As accidents are rare in this age group, deaths will be classified as non-accidental if it is not possible to conduct a verbal autopsy. Follow-up will be censored at migration.

Secondary outcomes and potential effect modifiers

We will evaluate the effect of increased availability of BCG on neonatal non-accidental mortality and early infant non-accidental hospital admission, defined as an overnight stay in a health facility, or arrival at the health facility and death within the first day, due to all other causes than accident.

We will assess potential effect modifiers (sex, maternal BCG scarring, season, oral polio vaccine (OPV) campaigns, and BCG strain) to gain a better knowledge of the potential effect modifiers (a list of all outcomes is found in box 1).

Provided that we find support for our hypothesis, we will study the cost-effectiveness of making BCG available at the first health-facility contact using the effects on mortality and hospital admission from the present trial. Furthermore, we will assess number of births and neonatal deaths reported by CHWs, and whether they differ from the numbers recorded by supervisors.

Statistical analyses

General analysis principles applied in all analyses are found in online supplemental appendix 4. A list of all planned analyses are provided in online supplemental appendix 3. In brief, in logistic regression models with GEE-based correction for village, we will assess the effect of making BCG available at the first health-facility contact. We will adjust for sex, health centre, period (date of birth of child before vs on/after crossover) and level of surveillance. In the main analysis, children are under observation from day 1 after birth until death or migration within the first 42 days of life. In secondary analyses, we will investigate whether the effect of making BCG available at the first health-facility contact differs by the following potential effect modifiers, which in prior trials have been important determinants of the effect: sex, maternal BCG-scarring, season, OPV campaigns and strain of BCG. In sensitivity analyses, we will assess the robustness of the effect by (1) restricting the outcome definition to particular causes of death, (2) excluding children, who have been eligible for OPV campaigns within the first 42 days of life and (3) stratifying the analysis by before/after cross-over.

Secondary outcomes are non-accidental hospital admissions, neonatal mortality and BCG scarring. In the planned cost-effectiveness analysis, we will assess the cost per death averted using a societal perspective, contrasting the costs of vaccine provision in the present programme and a scenario where BCG is available at the first health-facility contact for all children.

In addition to assessing the effect of making BCG available at all health facility contacts, we will compare data (number of births and neonatal deaths) reported by CHWs and supervisors.

Time schedule

The trial will be implemented stepwise in the three health regions. A pilot phase of the trial, initially implementing the field data collection with subsequent addition of health centre intervention, was started in February 2021 in Biombo. Trial start was December 2021 in Biombo and

is anticipated to be August 2022 in Oio and Farim, with pilot phases preceding each regional start. The crossover of randomisation groups of the health centres will occur 12 months after trial starts in each region. We anticipate that the last enrolments will be conducted in July 2024, and that follow-up will end in October 2024.

Patient and public involvement

We use the infrastructure of the health system in Oio, Biombo and Farim health regions in Guinea-Bissau. The community health workers and supervisors from the local health centres were involved in locating households of pregnant women and obtaining information. 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. Nurses and midwives from local health centres were trained on BCG vaccination technique. The trial will be conducted in close collaboration with the local health facilities and local health authorities. We do not plan to include participants in the interpretation or writing up the results. The results will be disseminated to the local health facilities, local health authorities and to the National Institute of Public Health. There are no plans to disseminate the results to study participants.

DISCUSSION

Despite BCG being recommended at birth in countries with high TB burden, less than half of children in rural Guinea-Bissau are vaccinated by 1 month of age.[6] Several studies have found that BCG vaccination is important,[9 23 29 30] and that timing of BCG may also be important.[12 13] Previous randomised trials of early BCG vaccination to low birth weight (LBW) children in Guinea-Bissau showed that early BCG vaccination had major impact.[14–16] Trials among LBW children in intensive care units in India did, however, not demonstrate similar effects.[17] The conflicting results may be explained by different strains of BCG[18 31] and the causes of death may be different before and after discharge from the hospital, fatal infectious diseases playing a limited role before discharge.[32] In the present trial, we will, therefore, in collaboration with local health authorities, ensure that the same strain of BCG is used in both the intervention and the control clusters at the same time.

We previously conducted a cluster-randomised trial in rural Guinea-Bissau, assessing the effect of providing BCG and OPV vaccination at home visits within 72 hours after birth.[33] The trial was ended prematurely due to lower than expected enrolment rates. Providing BCG and OPV vaccines at home visits reduced mortality in rural Guinea-Bissau (authors' unpublished data), but the setup was resource demanding, and unlikely to be introduced in a resource-constrained health system as in Guinea-Bissau. In the present trial, we assess the effect of providing BCG at the first health facility contact, thus the intervention could easily be implemented in the health system in Guinea-Bissau. Providing BCG at the first health-facility contact for all children will ensure that no mother walks to a health centre in vain to obtain BCG vaccination for her child. We have previously demonstrated that mothers in rural Guinea-Bissau, on average, use US$1.89 to bring their children for BCG vaccination with the current restrictive vial-opening policy.[7] We recently estimated that disregarding the restrictive vial opening policy in rural Guinea-Bissau would increase 1-month BCG coverage from 42% to 60% and reduce all-cause deaths before 5 years by 8.4% (uncertainty range: 3.3%–13.5%) per birth cohort. The incremental cost-effectiveness ratio was estimated at US$8 (uncertainty range: 4–20) per discounted life-year gained.[6] Thus, the estimated impact of disregarding the restrictive vial-opening policy of BCG is major, and with the present trial, we will assess the impact of the intervention in a cluster-randomised crossover trial. Some villages are located with similar distance to two health centres, which could make mothers seek another health centre than the target health centre to obtain BCG vaccines. However, as most villages only have one health centre nearby, we expect most mothers to seek the target health centre. Monitoring BCG vaccination ages will allow us to assess the extend of a potential contamination.

The trial builds on previous findings, trial experience, and close collaboration with local health authorities. The intervention assessed is easily implementable. Thus, provided that we are able to confirm previous findings of the impact of early BCG vaccination, the trial results can be transformed into immediate policy changes. Vaccine delays are not only present in Guinea-Bissau[4] and trial results are likely to be relevant in other settings with vaccine delays.

ETHICS AND DISSEMINATION

Ethical considerations

BCG is recommended at birth, but vaccination is often delayed.[5] Evidence suggests that BCG may have beneficial NSEs.[8 34 35] The proposal compares the current situation in rural Guinea-Bissau, where less than half of all infants get BCG during the first month of life[5] with a scenario where BCG would be available at the first health-facility contact for every child. Hence, no child receives BCG later than it would have done, had the trial not been carried out. The trial protocol was approved by the Guinean Ethical Committee on 3 January 2020 and the Danish National Ethical Committee provided consultative approval on 17 March 2020.

Trial registration

The trial was first registered at clinicaltrials.gov on 19 November 2020 (Clinicaltrials.gov ID). Secondary identifiers 062/CNES/INASA/2020 (Guinean Ethical Committee) and CS-BCG (sponsor). The trial is researcher initiated and the sponsor is the BHP (www.bandim.org).

Advisory board

An advisory board has been formed consisting of a paediatrician (Anja Poulsen, Rigshospitalet, Denmark), an

epidemiologist (Torben Sigsgaard, Aarhus University, Denmark) and a statistician (Theis Lange, University of Copenhagen, Denmark). The members have been appointed on their experience, reputation for objectivity, absence of conflicts of interest and knowledge on clinical trial methodology.

Safety monitoring

The vaccines used for the trial are prequalified and recommended by WHO to be given at birth. The trial participants will possibly get the vaccine earlier than usual, but no child will be vaccinated later. Adverse reactions are rare for BCG. Within the HDSS, at the village visits, a trained study assistant examines the BCG vaccination site and the axillary lymph glands of all children to assess suppurative lymphadenitis as an adverse reaction to the BCG vaccination. Prior to study start and reveal of randomisation, staff at all health centres will receive refresher training on vaccination technique and assessment of lymph glands and be requested to report cases of suppurative lymphadenitis to the study team. Other serious adverse events are captured through primary and/or secondary outcomes (mortality and hospitalisations).

As a public financed Danish research institution, University of Southern Denmark is self-insured and cannot take out a liability insurance through a private company. As an investigator-initiated trial by investigators affiliated with University of Southern Denmark, any harm to study participants due to their participation in the trial is, thus, covered by the University of Southern Denmark.

Dissemination of results

The results of the study will be published in international peer-reviewed journals and results will be communicated to the National Institute of Public Health in Guinea-Bissau. We will, furthermore, prepare a policy brief to ensure that our results are easily accessible to policymakers, civil society and BCG vaccine manufacturers. After publication of the main results on completion of the trial, data will be available on a collaborative basis. Please contact a.fisker@health.sdu.dk.

Protocol amendments

Any protocol modifications including amendments to the analysis plan will be discussed with the advisory board, and changes will be added to the trial registration.

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Contributors SMT and ABF conceived the idea for the trial. SMT and ABF designed the study in collaboration with CSB and PA. SMT, AMJ, JOV, AKGJ and ABF planned the analyses with input from Theis Lange. AMJ, JOV and ABF set up the study with help from SMT. AMJ, JOV, IdSB and ABF supervised data collection. SMT drafted the manuscript and data analysis plan with help from AMJ, JOV and ABF. All authors read and approved the final manuscript and data analysis plan.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

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