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

1 Decision to expand and stop the trial

In 2017, the investigators discussed the lower-than-expected mortality and lower-than-expected enrolment rates with the Data Safety and Monitoring Board. Following this discussion, the investigators decided to expand the trial to include the BHP urban study area. The fieldworkers in the urban HDSS were trained in trial routines and a BHP nurse was trained to conduct home visits. Once the trial routines were in place the trial was expanded to the urban area from September 18, 2017.

In addition to expanding the trial, several efforts were made to increase the enrolment rate:

- Additional village visits with information about the trial and information on who to call
- Posters with trial information was placed in all villages (see supplementary figure 1)
- Community Key Informants were in close contact with the trial supervisor
- Pregnant women, who had consented for trial participation, were reminded of the trial at all subsequent household visits

Despite these efforts to increase enrolment rates, enrolments were progressing much slower than anticipated. The low enrolment rates were mainly due to problems with identifying births in time (before 72 hours after birth). This problem was probably both due to mothers not remembering to contact the BHP team/CKI directly after birth, and that CKIs were not able to/expected to make outreach daily. After renewed discussion with the Data Safety and Monitoring Board, it was decided to discontinue the trial in the urban area: there was only a single death registered in the urban area, which did therefore not add power to the trial. Further, it was decided to discontinue the trial in the Cacheu health region in rural Guinea-Bissau, as enrolments were few and resource demanding, therefore trial resources were focussed on Oio and Biombo health regions. The trial was stopped in the urban area and Cacheu health region on March 15, 2019.

The discussion with the Data Safety and Monitoring Board continued and the investigators decided to end the trial in all regions. The trial was ended on August 31, 2019, due to lower-than-expected mortality and lower-than-expected enrolment rates.

Analyses of the trial was only conducted after the trial was ended, and the results of the trial was therefore unknown at the time of deciding to end the trial. Thus, results did not affect the decision to end the trial.

2 Statistical analyses of secondary outcomes

The complete analysis plan can be found in the published protocol paper[1].

"Non-accidental hospital admission" and "severe morbidity"

The effect of providing BCG and OPV at a single home visit 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 with age as underlying timescale. The analyses were stratified for factors used in the randomisation (region and cluster-level pre-trial mortality (high/low)) and sex. Children entered the analyses 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, hospital admission, migration, or 60 days of life. Proportional hazards 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.

"Consultations"

The effect of providing BCG and OPV at a single home visit on all-cause consultations was assessed in log-binomial regressions. The analysis was adjusted for factors used in the randomisation (region and

cluster-level pre-trial mortality (high/low)) and sex. Robust standard errors were used to account for clustering.

"Mid-upper-arm circumference" and "weight for age z-score"

The effect of providing BCG and OPV at a single home visit on mid-upper-arm circumference and weight for age z-score between enrolment and first follow-up visit within 6 months of age was assessed in linear regressions. The analyses were adjusted for factors used in the randomisation (region and cluster-level pre-trial mortality (high/low)) and sex. Robust standard errors were used to account for clustering.

"BCG scarring"

The effect of providing BCG and OPV at a single home visit on BCG scarring at the first visit after 6 months of age was assessed in log-binomial regressions. The analysis was adjusted for factors used in the randomisation (region and cluster-level pre-trial mortality (high/low)) and sex. Robust standard errors were used to account for clustering.

3 List of health intervention campaigns during the trial targeting trial participants

Dates	Target group	Intervention
24-11-2017 to 27-11-2017	0-59 months of age	Oral polio vaccine*
20-04-2018 to 24-04-2018	0-59 months of age	Oral polio vaccine*

* Children aged 6-11 months were also eligible for Vitamin A, and children aged 12-59 months were eligible for both oral polio vaccine, vitamin A and mebendazole. However, trial participants were all aged less than 6 months.

4 Author reflexivity statement

Study conceptualisation

1. How does this study address local research and policy priorities?

   The trial was made to address a local issue with delay in vaccinations recommended at birth, partly due to restricted vial-opening policies.

2. How were local researchers involved in study design?

   AR conceived the idea for the study together with PA and CB. The study was designed by SMT, PA, CB, and ABF, who have all worked in Guinea-Bissau for at least 10 years. The study design was made in close communication with local health authorities, and AR was consulted during this process.

Research management

1. How has funding been used to support the local research team(s)?

   The funding has been used to support the Health and Demographic Surveillance System, which has been in place in Guinea-Bissau since 1978, and was established by PA. Thus, the funding was primarily used for salaries for local staff.

Data acquisition and analysis

1. How are research staff who conducted data collection acknowledged?

   Supervisors of the data collection, both local (IdSB, JaM, and LMVdS) and international (SMT, ADS, JHS, and ABF) are co-authors of the paper. However, further field assistants and nurses were involved in the trial. As they do not fulfill the ICMJE criteria for authorship, they have been acknowledged in the acknowledgement section.

2. How have members of the research partnership been provided with access to study data?

The original data is stored on local servers in Guinea-Bissau and local and international researchers have had access to the trial data.

3. How were data used to develop analytical skills within the partnership?

   The trial has been used to build competencies on data management for IdSB, JaM, and LMVdS. During the trial period JuM initiated a master in public health and development, although this was not based on the present work.

Data interpretation

1. How have research partners collaborated in interpreting study data?

   The results have been discussed with the whole research team, and both local and international researchers have contributed to the interpretation of study data. As not all local researchers are able to read and write English, the paper have been discussed in the local language, and a summary of trial results have been made in Portuguese. Local researchers have adapted the Portuguese summary for communication of trial results to the Ethical Committee in Guinea-Bissau, and to inform local health authorities.

Drafting and revising for intellectual content

1. How were research partners supported to develop writing skills?

   Writing skills in English have not been prioritized as part of this project. However, this is prioritized in other collaborative projects within the group.

2. How will research products be shared to address local needs?

   Research results are shared with local health authorities in Portuguese, and we are currently conducting a follow-up trial in close collaboration with the local health authorities, where the effect of making BCG vaccine available at the first health-facility visit is investigated.

Authorship

1. How is the leadership, contribution and ownership of this work by LMIC researchers recognised within the authorship?

   Local researchers have been deeply involved with setting up and maintaining the trial routines, and have ownership over the trial. Due to not speaking English or having statistics training, most of the local study team has not been able to participate directly in the analyses and writing of the paper, but have rather commented on results. However, all researchers involved in the project (both local and international) have significantly increased the research skills, and it has been a focus throughout the trial to ensure that local researchers (as well as field assistants and nurses) developed new skills during the trial. All LMIC researchers that could be acknowledged as authors have been included as such.

2. How have early career researchers across the partnership been included within the authorship team?

   Early career researchers have been supported throughout the trial and are included as authors.

3. How has gender balance been addressed within the authorship?

   This has not been a particular focus for the present trial. The author group consists of 4 female authors and 8 male authors.

Training

1. How has the project contributed to training of LMIC researchers?

   The trial has trained CKIs and nurses, most of whom had previously not been involved with research, to be able to participate in data collection for research. Further, the trial has trained trial supervisors to be able to take a more leading position in the trial routines. Most trial supervisors were field assistants prior to the initiation of the present trial. JuM has during the trial been supported in their analytical and interpretation skills by some of the international authors, although this project was not the major focus of JuM's work.

Infrastructure

1. How has the project contributed to improvements in local infrastructure?

   The trial was conducted within the urban and rural HDSS sites, which have been in place since 1978 and 1990. These sites are the most important research infrastructure in Guinea-Bissau. During the trial, the collaboration with local health authorities have been strengthened and the trial, which is now conducted based on the results of the present trial, takes place at the local health facilities in close collaboration with local health authorities.

Governance

1. What safeguarding procedures were used to protect local study participants and researchers?

   Informed consent processes were implemented and staff were trained on GCP during the trial implementation.

Supplementary Figure 1. Kaplan-Meier survival curve for the primary outcome non-accidental mortality