Appendix 3 - Planned analyses

1 Baseline

Descriptive statistics:

We will describe participant flow and reasons for non-participation by group allocation in a flowchart. For children included in the analysis, we will describe background factors. Distribution of background factors will be presented by group allocation overall and by sex and region. Background factors will be summarised by counts (percentages), means (standard deviation) or medians (interquartile range) as appropriate. Information on the proportion with missing information will be provided.

Table 1: Summary of background factors by intervention and control group

• Sex • Region • Place of birth (hospital, health centre or home) • Maternal factors (age, education, parity and BCG scar) • Level 1/level 2 surveillance • Trial period before/after crossover

2 Primary analysis of primary outcome

The primary analysis of early infant non-accidental mortality will be assessed in an intention-to-treat (TT) analysis. We will use logistic regression models with generalised estimating equation (GEE) correction for village, thus a smaller cluster size than used in our sample size calculation. Analyses will be adjusted for health centre, period (before/after crossover), level of surveillance and sex. The primary analysis of the primary outcome is described in more detail in table 2.

Table 2: Primary analysis of primary outcome

Population	Children are eligible for the analysis if they are registered before birth in a village of a health centre capture area and either born in the same village or born in a health facility and discharged to the same village. Exclusion criteria: - Children, who have died within 1 day after birth

	- Children born outside the Oio, Farim and Biombo health regions
Observation period	From: 1 day after birth. To first of: - 42 days of life - Migration - Crossover of intervention at health centres - End of intervention at health centres - Last date of follow-up, if lost to follow-up
Failure definition	Death classified as not caused by accident during the observation period. Deaths due to accidents will be identified through verbal autopsies. Accidents are rare in this age group. If no verbal autopsy is possible, we will therefore classify a death as not caused by accident.
Statistical tool	Logistic regression
Clustering	We will use GEE-based correction for village
Outline stata code For analysis:	xtset village xtgee dead random sex b1.hc b1.level b0.period, family(binomial) /// link(logit) corr(exchangeable) robust eform *Village =The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

3 Effect-modifier analyses of primary outcome

We will assess whether the effect of the intervention on the primary effect measure is modified by the following potential effect modifiers.

Table 3. Sex as a potential effect modifier of the primary outcome

Potential effect modifier	Sex
Design	We will perform the analysis as describe above (for the primary analysis) allowing the effect of the intervention to differ between the sexes.
Reasoning	Previous studies have found sex-differential non-specific effects[1 2], therefore, we will assess the sex-differential effects.
Outline stata code: For analysis:	xtset village

	xtgee dead random#sex sex b1.hc b1.level b0.period, /// family(binomial) link(logit) corr(exchangeable) robust eform *Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Table 4. Maternal BCG scar as a potential effect modifier of the primary outcome

Potential effect modifier	Maternal BCG scar (yes/no)
Design	We will perform the analysis as described above (for the primary analysis) allowing the effect of the intervention to differ by maternal BCG-scar status
Reasoning	Recent studies suggest that the effect of BCG varies by whether the mother has received BCG or not[3 4]. Since BCG scar is a life-long marker of a successful BCG-vaccination, we will assess whether the effect of making BCG available differs by maternal BCG-scar status
Outline stata code: For analysis:	xtset village xtgee dead random#mBCGscar mBCGscar sex b1.hc b1.level /// b0.period, family(binomial) link(logit) corr(exchangeable) /// robust eform * Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; mBCGscar= maternal BCG scar; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Table 5. Season as a potential effect modifier of the primary outcome

Potential effect modifier	Season of birth (Dry: December-May/Rainy: June-November)
Design	We will perform the analysis as described above (for the primary analysis) allowing the effect of the intervention to differ by season of birth
Reasoning	Previous studies have found that the effect of some vaccines is stronger in the dry season[5]. Therefore, we would like to assess if the effect of making BCG available differs according to season.

Outline stata code: For analysis:	xtset village xtgee dead random#season season sex b1.hc b1.level b0.period, /// family(binomial) link(logit) corr(exchangeable) robust eform * Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Table 6. OPV campaigns as a potential effect modifier of the primary outcome

Potential effect modifier	OPV campaign
Design	We will perform the analysis as described above (for the primary analysis) allowing the effect of the intervention to differ among children exposed and not exposed to OPV campaigns
Reasoning	Previous studies have found that OPV campaigns may affect the impact of other vaccines. Therefore, we would like to assess if the effect of making BCG available differs before and after eligibility to OPV campaigns.
Outline stata code: For analysis:	xtset village xtgee dead random#OPVcamp OPVcamp sex b1.hc b1.level b0.period, /// family(binomial) link(logit) corr(exchangeable) robust eform * Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Table 7. Strain of BCG as a potential effect modifier of the primary outcome

Potential effect modifier	Strain in use (i.e. a range of weeks of birth during which different strains were in use)
Design	We will perform the analysis as described above (for the primary analysis) allowing the effect of the intervention to differ by time of birth
Reasoning	Different BCG vaccine strains vary in ability to cause BCG scarring[6 7]. Their immune modulatory effects, and presumably effects on child mortality[8] may therefore be associated with varying effects. Therefore,

	we will assess if the intervention effect vary over time (as a proxy for strain of BCG).
Outline stata code: For analysis:	xtset village xtgee dead random#strain strain sex b1.hc b1.level b0.period, /// family(binomial) link(logit) corr(exchangeable) robust eform *Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

4 Primary analyses of secondary outcomes

Neonatal non-accidental mortality

We will assess the effect of BCG availability on non-accidental neonatal mortality. The rate of neonatal mortality will be compared using a logistic regression model with GEE-based correction for village.

Table 8: Non-accidental neonatal mortality between day 1 and 28

Population	Children are eligible for the analysis if they are registered before birth in a village of a health centre capture area and either born in the same village or born in a health facility and discharged to the same village. Exclusion criteria: - Children, who have died within 1 day after birth - Children born outside the Oio, Farim and Biombo health regions
Observation period	From: 1 day after birth To first of: - 28 days of life - Migration - Death - Crossover of intervention at health centres - End of intervention at health centres - Last date of follow-up, if lost to follow-up
Failure definition	Death classified as not caused by accident during the observation period. Deaths due to accidents will be identified through verbal autopsies. Accidents are rare in this age group. If no verbal autopsy is possible, we will therefore classify a death as not caused by accident.
Statistical tool	Logistic regression

Clustering	We will use GEE-based correction for village
Stata code	xtset village xtgee neodead random sex b1.hc b1.level b0.period, /// family(binomial) link(logit) corr(exchangeable) robust eform * Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

The analysis of non-accidental neonatal mortality will be repeated with a slightly altered population, including children who died within the first day of life. This is to ensure that the results of the trial will be included in future meta-analyses investigating neonatal death.

Table 9: Non-accidental neonatal mortality between day 0 and 28

Population	Children are eligible for the analysis if they are registered before birth in a village of a health centre capture area and either born in the same village or born in a health facility and discharged to the same village. Exclusion criteria: - Stillborn children - Children born outside the Oio, Farim and Biombo health regions
Observation period	From: Birth To first of: - 28 days of life - Migration - Crossover of intervention at health centres - End of intervention at health centres - Last date of follow-up, if lost to follow-up
Failure definition	Death classified as not caused by accident during the observation period. Deaths due to accidents will be identified through verbal autopsies. Accidents are rare in this age group. If no verbal autopsy is possible, we will therefore classify a death as not caused by accident.
Statistical tool	Logistic regression
Clustering	We will use GEE-based correction for village
Stata code	xtset village xtgee neodead random sex b1.hc b1.level b0.period, /// family(binomial) link(logit) corr(exchangeable) robust eform

	* Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Early infant non-accidental hospital admission

Since it can be difficult to distinguish between hospital admissions and outpatient contacts through interviews, we have defined hospital admission as at least one overnight stay in a health facility or death in a health facility on the day of arrival at the facility. The potential effect modifiers for the primary outcome specified in tables 3-6 will also be assessed for non-accidental hospitalisation.

Table 10: Non-accidental hospitalisation

Population	Children are eligible for the analysis if they are registered before birth in a village of a health centre capture area and either born in the same village or born in a health facility and discharged to the same village. Exclusion criteria: - Children, who have died within 1 day after birth - Children born outside the Oio, Farim and Biombo health regions
Observation period	From: Day 1 day after birth To first of: - 42 days of life - Death - Migration - Crossover of intervention at health centres - End of intervention at health centres - Last date of follow-up, if lost to follow-up
Failure definition	A hospital admission during the observation period – only overnight stays or arrival at the hospital and death within the first day will be considered in this analysis. Admission reported to be caused by accidents will be censored.
Statistical tool	Logistic regression
Clustering	We will use GEE-based correction for village
Outline stata code For analysis:	xtset village

	xtgee hosp random sex b1.hc b1.level b0.period, family(binomial) /// link(logit) corr(exchangeable) robust eform *Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Cost-effectiveness of making BCG available at the first health-facility contact

A cost-effectiveness analysis seeking to measure the cost per death averted using a societal perspective will be performed, contrasting the costs of vaccine provision in the present programme to a scenario with BCG available at the first health-facility contact as tested in the trial. The costs/savings associated with different rates of consultations and admissions will also be taken into account.

5 Sensitivity analyses to test for robustness of conclusions

Table 11: Early infant cause-specific mortality

Population	Children are eligible for the analysis if they are registered before birth in a village of a health centre capture area and either born in the same village or born in a health facility and discharged to the same village. Exclusion criteria: - Children, who have died within 1 day after birth - Children born outside the Oio, Farim and Biombo health regions
Observation period	From: 1 day after birth To first of: - 42 days of life - Migration - Crossover of intervention at health centres - End of intervention at health centres - Last date of follow-up, if lost to follow-up
Failure definition	Death during the observation period due to: Malaria, Respiratory Infection, Sepsis, Gastrointestinal disease, Accidents, Other. If no verbal autopsy is possible or the information obtained is insufficient to reach a conclusion, we will classify the cause of death as “no information” and group it with “other” in the analysis. Deaths may be classified as due to more than one cause and can count in more than one analysis.

Statistical tool	Logistic regression
Clustering	We will use GEE-based correction for village
Outline stata code For analysis:	xtset village xtgee event random sex b1.hc b1.level b0.period, family(binomial) /// link(logit) corr(exchangeable) robust eform * Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Table 12: Non-accidental mortality between day 1 and 42, for children followed the complete 42 days

Population	Children are eligible for the analysis if they are registered before birth in a village of a health centre capture area and either born in the same village or born in a health facility and discharged to the same village. Exclusion criteria: - Children, who have died within 1 day after birth - Children born outside the Oio, Farim and Biombo health regions - Migration before 42 days of life - Lost to follow-up before 42 days of life
Observation period	From: 1 day after birth. To first of: - 42 days of life - Crossover of intervention at health centres - End of intervention at health centres
Failure definition	Death classified as not caused by accident during the observation period. Deaths due to accidents will be identified through verbal autopsies. Accidents are rare in this age group. If no verbal autopsy is possible, we will therefore classify a death as not caused by accident.
Statistical tool	Logistic regression
Clustering	We will use GEE-based correction for village
Outline stata code For analysis:	xtset village xtgee dead random sex b1.hc b1.level b0.period, family(binomial) /// link(logit) corr(exchangeable) robust eform

	*Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

Table 13: Non-accidental mortality stratified by before/after cross over

Population	Children are eligible for the analysis if they are registered before birth in a village of a health centre capture area and either born in the same village or born in a health facility and discharged to the same village. Exclusion criteria: - Children, who have died within 1 day after birth - Children born outside the Oio, Farim and Biombo health regions
Observation period	From: 1 day after birth. To first of: - 42 days of life - Migration - Crossover of intervention at health centres - End of intervention at health centres - Last date of follow-up, if lost to follow-up
Failure definition	Death classified as not caused by accident during the observation period. Deaths due to accidents will be identified through verbal autopsies. Accidents are rare in this age group. If no verbal autopsy is possible, we will therefore classify a death as not caused by accident.
Statistical tool	Logistic regression
Clustering	We will use GEE-based correction for village
Outline stata code For analysis:	xtset village xtgee dead random#b0.period b0.period sex b1.hc b1.level, family(binomial) /// link(logit) corr(exchangeable) robust eform * Village=The geographical village boundaries are defined by the supervisors prior to initiating data collection and may comprise th capture area of one or more CHW; hc=health centre id; level=level of surveillance; period=0 (before crossover) / 1(after)

In sensitivity analyses, we will furthermore, assess whether the conclusions are robust to

- Excluding children who during the first 42 days of life were exposed to general health intervention campaigns targeting children <42 days (e.g. OPV campaigns)
- Censoring deaths, where a verbal autopsy have not been conducted.

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