Version 3.1
16th Jan 2023

INSPIRING Jigawa Trial Analysis Plan

Primary outcome:

Primary analysis question*:* What is the impact of a package of gender sensitive group-based problem solving interventions at community and community-facility levels to improve protection, prevention, diagnosis and treatment of childhood pneumonia and infectious diseases on mortality of children under-5 years old in Kiyawa LGA, Nigeria?

Eligible population: All children aged 7 days to 59 months inclusive, reported as residing in a randomly sampled compound, during the endline survey or prospective cohort follow-up visits by any member of the compound are considered eligible for the primary analysis.

Exposure*:* The primary analysis will take an intention-to-treat approach, meaning that a participant will be defined as "exposed" if they reside in a compound within the catchment area of one of the 16 intervention primary healthcare facilities at the time of the endline survey. Women and children residing in a control cluster at the time of the endline survey will be categorised as "unexposed".

Primary outcome: All-cause mortality of children aged 7 days – 59 months inclusive during the intervention period. The intervention period is defined as from when the interventions have had sufficient time to start working (1st October 2021, which is 9 months after the interventions started as per related community mobilisation interventions [1]) and ends at the end of the endline survey (last data collection): 20th December 2022. We will assess our primary outcome via survival analysis of an open cohort (see page 2).

> *Mortality outcome*: Any verified deaths of eligible children, who were residing in the compound at the time of their death. Deaths will be verified by study staff during verbal autopsy interviews. Suspected neonatal deaths (deaths within 28 days of birth) without a date of birth or date of death will be excluded as we will be unable to determine the exact age of death and most (~70-80%) neonatal deaths occur in the first 7 days, and so are not part of our primary outcome measure. We expect very few verbal autopsies to not record dates of birth or death. For deaths missing dates in children aged 1-59 months, the WHO VA tool records an age category, and these deaths will be included, with an assumed date of death (needed for our survival analysis, see below) as the midpoint between the last interview where they were alive and the one where they were reported as died.
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> *Time at risk*: Time at risk will be calculated in days, for all eligible children. Children will start contributing survival time from: i) 1st October 2021, ii) the date they are 7 days old for children born between the 24th September 2021 and the endline survey; iii) the date of the prospective follow-up when they are first reported as residing in the compound. Children will have their time at risk censored at the following times: i) their verified date of death (or approximated date for those with missing date information); ii) their 5th birthday; iii) the date of the last follow-up interview where their residence and/or survival status was known. Please note this has changed from livebirths (reported in our published protocol paper: [2]) to enable individual level analysis (see page 2) and because of the nature of our data collection and primary outcome – we need to consider all children aged 7 days to 59 months old during our baseline and intervention periods as captured in our five rounds of data collection (baseline, three follow-ups and endline survey).

Baseline period: 1st Jan 2021 to 30th June 2021

Intervention period: 1st Oct 2021 to 20th December 2022

Clustering: Clustering will be adjusted for at the trial cluster level and treated as random effects. Clustering at the compound level will be explored, however its possible that there won't be much clustering as there are few eligible children in each compound and adding random effects by compound may result in the model being unable to converge due to there being thousands of compounds. If this is the case we will not include random effects by compound. If we are not able to estimated random effects we will explore use of robust standard error or marginal models (General Estimating Equations, GEE). We will not adjust for woman-level clustering, as there are unlikely to be many instances where the same woman will contribute more than child to the cohort (i.e. experiencing two deaths amongst children under-five in 12 months) and it is impractical to do in our survival analysis as the model is even less likely to converge than a model with compound level clustering.

Analysis: **Our primary analysis of our primary outcome will be done on an individual level, as a survival analysis using a Cox proportional hazards model** (stcox in Stata) with the unit of time being days, and where trial (and potentially compound – see above) clusters are treated as random effects and the trial exposure as a fixed effect. Child's age will be treated as a time-varying variable [3] to account for changes in the age profile (hazard of death) of cases over the duration of the study period. Providing there is balance between study arms at baseline (see *Imbalance between trial arms* below) we will assume proportional hazards in each study arm at baseline. An indication of departure from proportional hazards will be further investigated using (Royston-Parmar) flexible parametric survival models. During the intervention period, consequent to any difference in mortality between study arms especially at younger ages when deaths are more likely, it is possible the two study arms will have different hazards. This would be part of the intervention effect though so we would not adjust for it. The intervention effect will be presented as a hazard ratio, with 95% confidence interval.

Our **secondary analysis of our primary outcome will be at cluster level as a T-Test** (weighted by cluster size – number of children) of the difference in deaths/livebirths between intervention and control arms.

Sensitivity analyses: We will explore four sensitivity analyses:

Imbalance between trial arms: We will describe the distribution of the following potential confounders between intervention and control clusters from the baseline data (trial baseline period is 1st Jan 2021 to 30th June 2021, also see protocol paper: [2]): age of children, follow-up (exposure) time (in-migration, out-migration, loss-to-follow-up), flooding, dates of data collection, cholera outbreaks, verbal autopsy verification of deaths, wealth quintile (defined through PCA of household assets); monthly income; education; occupation. If any differ between trial arms (intervention and control) by >5% we will present these to the Trial Steering Committee (TSC) for a recommendation of whether an analysis which adjusts for these variables should be conducted.

Missing data: See the section on Missing Data on page 5.

On treatment analysis: A three-category exposure variable will be generated: defined as: intervention-direct: those children for whom any woman or man in their compound directly took part in the intervention; intervention-indirect: those who spent >80% of the intervention period time in intervention areas but did not directly take part in the intervention; control: those who did not take part in the intervention and who spent >80% of the intervention time in control areas so were also not directly exposed to the

intervention. Those who do not fall into these three categories will be excluded from this analysis. We will also explore sub-groups of the intervention-direct exposure category consisting of: care givers, other women in the compound, other men in the compound, head of compound, and combinations of these groups.

Difference in intervention effect over time: It's possible that the intervention effect may differ during the intervention period. Though likely to be underpowered we will repeat our primary and secondary analyses of our primary outcome for the first half and last half of the intervention period, and plot the intervention effect over time to see if it changes during the intervention period.

Secondary outcomes [2]:

The same exposure and clustering approach will be taken for the analysis of secondary outcomes. A summary of the outcome definition and modelling approach is presented in Table 1.

Outcome	Numerator	Denominator	Model	Notes / Sensitivity analysis
Suspected pneumonia mortality rate	Deaths in children aged 7 days – 59 months, as reported the endline / prospective follow-up visits, that have been verified by study staff through a verbal autopsy interview and classified as Neonatal Pneumonia or ARI by InterVA5	All children 7 days to 59 months old reported in the endline survey or prospective cohort follow-up visits (Figure 1) by any member of the compound	Cox proportional hazards model	Non pneumonia deaths will be excluded from the denominator and numerator.
Pneumonia point prevalence	Children who meet the 2014 WHO IMCI definition for pneumonia or severe pneumonia, including hypoxemia	All children present in the compound on the day of the survey and who had a complete clinical assessment completed	Mixed-effects logistic regression	If there are sufficient numbers, we will conduct a multinomial model, with categorical pneumonia
Women's wellbeing	A sum of the scores from the 7 SWEMBAS questions to give a total score	Women aged 16-49 who completed the endline survey	Mixed-effects linear regression	
Knowledge of pneumonia	Women who name both fast and difficulty breathing as signs of pneumonia	Women aged 16-49 who completed the endline survey	Mixed-effects logistic regression	Repeat analysis just on women with children currently under-five
Care-seeking for childhood illnesses	Women who self-reported visiting a formal healthcare provider (including primary, secondary, private or government facilities) within 48 h of illness recognition	Women aged 16-49 years who self-reported that their child has signs and symptoms of illness in the 2-weeks prior to the survey	Mixed-effects logistic regression	If there are sufficient numbers, we will explore different illnesses (e.g. pneumonia vs malaria).
Exclusive breastfeeding	Caregiver self-report current exclusive breastfeeding	Children of eligible women aged 0-6 months	Mixed-effects logistic regression	
Vitamin A	Caregiver reported or vaccine card confirmed receipt of 2 doses of vitamin A	Children of eligible women aged 18-59 months	Mixed-effects logistic regression	
Vaccine coverage	Caregiver reported or vaccine card confirmed receipt of: BCG, polio x 4, dpt/penta x 3, pcv x 3, measles x 3	Children of eligible women aged 18-59 months	Mixed-effects logistic regression	Each vaccine as separate analysis, and analysis of all vaccines complete
Handwashing with soap	Any self-reported access to soap and water in their home for handwashing	Compounds which take part in the endline survey	Mixed-effects logistic regression	
Household air pollution	Any self-reported cooking indoors with wood/charcoal or dried grass by women in the compound	Compounds which take part in the endline survey	Mixed-effects logistic regression	

General analysis principles:

Multiple testing: We will not adjust for multiple hypothesis testing, given all the primary and secondary outcomes were pre-specified.

Levels of confidence and p-values: All confidence intervals and statistical tests will be 2-sided, in line with the superiority design of the trial. A statistical significance threshold of 5% will be used, and 95% confidence intervals presented for all inferential statistics.

Blinding: The primary analysis of the primary and secondary outcomes will be done on a blinded dataset, where the trial cluster allocation has been masked. These main results will be shared with the TSC and co-Investigators for review, and following approval from the independent statistician on the TSC, the dataset will be unblinded. Sensitivity and secondary analyses will be conducted on unblinded data.

Missing data: Primary analyses of the primary and secondary outcomes will use complete case analysis. For analyses where >10% of the records are excluded due to missing data (and <25% are missing – above this level of missingness multiple imputation is less valid) we will explore the pattern of missing data and if appropriate (i.e. missing at random) conduct a sensitivity analysis with multiple imputation. For the primary outcome, we will also check whether the proportion of cases missing data is balanced between intervention and control arms.

References

1. Colbourn T, Nambiar B, Bondo A, Makwenda C, Tsetekani E, Makonda-Ridley A, et al. Effects of quality improvement in health facilities and community mobilisation through women's groups on maternal, neonatal and perinatal mortality in three districts of Malawi: MaiKhanda, a cluster randomised controlled effectiveness trial. International Health. 2013;5(3):180-95.
2. King C, Burgess RA, Bakare AA, Shittu F, Salako J, Bakare D, et al. Integrated Sustainable childhood Pneumonia and Infectious disease Reduction in Nigeria (INSPIRING) through whole system strengthening in Jigawa, Nigeria: study protocol for a cluster randomised controlled trial. Trials. 2022;23(1):95. doi: 10.1186/s13063-021-05859-5.
3. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med. 2018;6(7):121. Epub 2018/06/30. doi: 10.21037/atm.2018.02.12. PubMed PMID: 29955581; PubMed Central PMCID: PMCPMC6015946.