PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	WASH Upgrades for Health in Amhara (WUHA): study protocol for a cluster-randomized trial in Ethiopia
AUTHORS	Wittberg, Dionna; Aragie, Solomon; Tadesse, Wondyifraw; Melo, Jason; Aiemjoy, Kristen; Chanyalew, Melsew; Emerson, Paul; Freeman, Matthew; Nash, Scott; Callahan, E.; Tadesse, Zerihun; Porco, Travis; Lietman, Thomas; Keenan, Jeremy

VERSION 1 – REVIEW

REVIEWER	Nana Kwadwo Biritwum BMGF
REVIEW RETURNED	28-Jun-2020

GENERAL COMMENTS	The topic of the study is very relevant and critical to our understanding and the role of WASh interventions in the prevention of trachoma. Its potential impact on policy should not be underestimated. The trial design and statistical analysis looks robust but for such a big trail a specialist statistician will contribute to a more rigorous statistical analysis. I particularly appreciated the summary statistical analysis section with reference to the the supplementary file 5 for further details. In paper further clarity on the ethical issue of not providing antibiotic treatment in a known hyperendemic area for the first 3 years of the study with the potential implications requires addressing. Additionally there is not possible intervention related side reactions in the paper as WASH interventions are not likely to have any side reactions asides the antibiotic and anthelmintic treatments. Clarity on the potential side reactions will be well appreciated as this bluntly refers to side reactions of all interventions. I recommend this paper for publication without any reservations.

REVIEWER	Ben Cooper University of Oxford, United Kingdom
REVIEW RETURNED	12-Oct-2020

GENERAL COMMENTS	Generally the protocol is clear and comprehensive, but there are a few points where some clarification is needed and some where it would be helpful: 1. In the text “A random sample of 30 individuals from each age strata are monitored in each community each year …” Does “each community” correspond to one of the 40 clusters? This could be clearer.

	2. ". In this trial, primary school catchment areas are randomized but only a single cluster is monitored,.." (l147-148). This is unclear. Taken at face value it suggests only one of the 40 randomised clusters is monitored, but that, surely, cannot be the case. 3. line 381: in the primary analysis how will time be specified? 4. l121 "A random sample of 30 individuals from each age strata are monitored in each community each year, with a new random sample drawn after each annual census. In addition, the group of 0-5 year-old children monitored at baseline comprises a cohort that is monitored throughout the study for trachoma and anthropometric outcomes." The primary outcome is " the prevalence of ocular chlamydia by polymerase chain reaction in 0-5 year-old children". I am a little unclear about precisely which 0-5 children this primary outcome will be assessed in. Is it just the new random sample drawn after each annual census, or are the baseline cohort also included whenever still within the 0-5 years age range? 5. What happens of any of the 30 monitored individuals in each strata/community cannot be reached for the PCR test? What happens if they move to another cluster? 6. Will the success of masking to treatment arm be assessed?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Nana Kwadwo Biritwum

Institution and Country

BMGF

Please state any competing interests or state 'None declared':
None declared

The topic of the study is very relevant and critical to our understanding and the role of WASh interventions in the prevention of trachoma. Its potential impact on policy should not be underestimated. The trial design and statistical analysis looks robust but for such a big trail a specialist statistician will contribute to a more rigorous statistical analysis. Travis Porco is the trial's biostatistician. Professor Porco is more than qualified for this study, being a specialist in the analysis of cluster-randomized trials. He is the biostatistician on many of our previous NIH- and Gates-funded cluster-randomized trials (e.g., *PLoS Med* 2020; 17:e1003285; *Am J Ophthalmol* 2020; 214:143; *Lancet Glob Health* 2020; 8:e288; etc.). Dr. Porco was responsible for the trial's statistical analysis plan and his role is included in the Manual of Procedures. We have made no changes to the manuscript.

I particularly appreciated the summary statistical analysis section with reference to the the supplementary file 5 for further details. Thank you.

In paper further clarity on the ethical issue of not providing antibiotic treatment in a known hyperendemic area for the first 3 years of the study with the potential implications requires addressing. Thanks for this suggestion. All study communities had received at least annual mass azithromycin treatments for the past 7 years. Note that chlamydial infection was expected to be quite low because of these treatments. In addition, repeated antibiotic treatments are not necessarily without harm, since they increase the risk of antibiotic resistance. In this context, the IRBs approved the WUHA I intervention in the absence of antibiotics. Moreover, the trial's DSMC reviewed the trachoma and chlamydia data each year and made a recommendation for whether antibiotics should be resumed in the study area. We noted this in the *Ethics and Dissemination* section:

> "Study communities received annual mass azithromycin distributions for the 7 years prior to the study; in this context the ethical review boards approved the WUHA I intervention in the absence of antibiotic therapy."

We also noted in the *Data Monitoring* section:

> "The DSMC meets annually, providing recommendations about whether the trial should be stopped or continued and whether antibiotics should be provided to study communities, and also recommendations…"

Additionally there is not possible intervention related side reactions in the paper as WASH interventions are not likely to have any side reactions asides the antibiotic and anthelmintic treatments. Clarity on the potential side reactions will be well appreciated as this bluntly refers to side reactions of all interventions. We tried to clarify this in the Adverse events section:

> "Community members are instructed to notify HPWs in the case of any intervention-related adverse events, including those due to antibiotic and antihelminthic distributions as well as any thought to be due to the WASH interventions."

I recommend this paper for publication without any reservations.

Reviewer: 2
Reviewer Name

Ben Cooper

Institution and Country

University of Oxford, United Kingdom

Please state any competing interests or state 'None declared':
None

Generally the protocol is clear and comprehensive, but there are a few points where some clarification is needed and some where it would be helpful:

1. In the text "A random sample of 30 individuals from each age strata are monitored in each community each year …" Does "each community" correspond to one of the 40 clusters? This could be clearer. Thanks for pointing this out; we changed the language in this section from "community" to "cluster" to clarify this point in the *Monitoring Population* section:

> "A random sample of 30 individuals from each age strata are monitored in each of the 40 clusters annually, with a new random sample drawn after each annual census…"

2. ". In this trial, primary school catchment areas are randomized but only a single cluster is monitored,.." (l147-148). This is unclear. Taken at face value it suggests only one of the 40 randomised clusters is monitored, but that, surely, cannot be the case. We clarified that while we randomized based one school district, a single cluster is monitored from within each of the 40 school catchment areas. See the *Contamination* section:

> "Within each school catchment area, only a single cluster of households receives the community-based interventions and monitoring, effectively creating a buffer zone which should prevent contamination."

3. line 381: in the primary analysis how will time be specified? Thank you for pointing out the ambiguity. Our plan is to assess time as a continuous variable as the number of months from baseline. We have clarified this in the *Statistical Analysis Plan (supplemental file 5)*. We also added to the *Statistical Methods* section:

> "Post-baseline cluster-specific prevalences of ocular chlamydia are modeled in a mixed effects linear regression model that includes treatment allocation, time since baseline in months, and baseline chlamydia prevalence as fixed effects, and a random intercept for cluster."

4. l121 "A random sample of 30 individuals from each age strata are monitored in each community each year, with a new random sample drawn after each annual census. In addition, the group of 0-5 year-old children monitored at baseline comprises a cohort that is monitored throughout the study for trachoma and anthropometric outcomes." The primary outcome is " the prevalence of ocular chlamydia by polymerase chain reaction in 0-5 year-old children". I am a little unclear about precisely which 0-5 children this primary outcome will be assessed in. Is it just the new random sample drawn after each annual census, or are the baseline cohort also included whenever still within the 0-5 years age range? Thanks for pointing this out; we did not do a good job differentiating clearly enough the two types of sampling. As the reviewer points out, we monitor (A) repeated cross-sectional samples (i.e., a new random sample in the age group each study visit) and also (B) the longitudinal sample of 0-5 year-old children from baseline. The primary analysis is based on the repeated cross-sectional samples. We tried to clarify this in the *Monitoring Population* section:

> "A random sample of 30 individuals from each age strata are monitored in each of the 40 clusters annually, with a new random sample drawn after each annual census (i.e., repeated cross-sectional random sampling). If 30 individuals from one of the populations cannot be reached, additional children are added via random sampling. In addition to these repeated cross-sectional samples, the group of 0-5 year-old children monitored at baseline comprises a cohort that is monitored throughout the study for trachoma and anthropometric outcomes."

And also in the *Primary and Secondary Outcomes* section:

> "The primary outcome is the prevalence of ocular chlamydia by polymerase chain reaction in 0-5 year-old children, assessed from the repeated cross-sectional random samples at 12, 24, and 36 months for WUHA I and at 48, 60, 72, and 84 months for WUHA II."

5. What happens of any of the 30 monitored individuals in each strata/community cannot be reached for the PCR test? What happens if they move to another cluster? If 30 individuals from one of the

populations cannot be reached, additional children are added via random sampling. If a child moves we make no attempt to track them down in another cluster. Note that for the cross-sectional samples, the sampling is based on the most recent census (ie 1 month prior), and while possible that a child would have moved in the interim, this is not likely in practice. We have added clarifying text in the *Monitoring Population* section:

> "If 30 individuals from one of the populations cannot be reached, additional children are added via random sampling. No attempt is made to track children who move out of a study cluster."

6. Will the success of masking to treatment arm be assessed? We will not specifically assess the success of masking to treatment arm. We clarified in the Masking section:

> "There are no plans to assess success of masking."