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BMJ Open WASH Upgrades for Health in Amhara (WUHA): study protocol for a cluster-randomised trial in Ethiopia

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ABSTRACT

Introduction Facial hygiene promotion and environmental improvements are central components of the global trachoma elimination strategy despite a lack of experimental evidence supporting the effectiveness of water, sanitation and hygiene (WASH) measures for reducing trachoma transmission. The objective of the WUHA (WASH Upgrades for Health in Amhara) trial is to evaluate if a comprehensive water improvement and hygiene education programme reduces the prevalence of ocular chlamydia infection in rural Africa.

Methods and analysis Forty study clusters, each of which had received at least annual mass azithromycin distributions for the 7 years prior to the start of the study, are randomised in a 1:1 ratio to the WASH intervention arm or a delayed WASH arm. The WASH package includes a community water point, community-based hygiene promotion workers, household wash stations, household WASH education books, household soap distribution and a primary school hygiene curriculum. Educational activities emphasise face-washing and latrine use. Mass antibiotic distributions are not provided during the first 3 years but are provided annually over the final 4 years of the trial. Annual monitoring visits are conducted in each community. The primary outcome is PCR evidence of ocular chlamydia infection among children aged 0–5 years, measured in a separate random sample of children annually over 7 years. A secondary outcome is improvement of the clinical signs of trachoma between the baseline and final study visits as assessed by conjunctival photography. Laboratory workers and photo-graders are masked to treatment allocation.

Ethics and dissemination Study protocols have been approved by human subjects review boards at the University of California, San Francisco, Emory University, the Ethiopian Food and Drug Authority, and the Ethiopian Ministry of Innovation and Technology. A data safety and monitoring committee oversees the trial. Results will be disseminated through peer-reviewed publications and presentations.

Trial registration number (<http://www.clinicaltrials.gov>): NCT02754583; Pre-results.

Strengths and limitations of this study

- As one of the most comprehensive non-antibiotic interventions implemented for trachoma, this study emphasises all three WASH components (ie, water, sanitation and hygiene) and employs hygiene promotion workers who live and work in the study clusters.
- Designed as an efficacy study of an intensive intervention, the trial has major public policy implications.
- The primary outcome is a microbiological test, which is less subjective than a clinical trachoma assessment and is a more valid indicator of whether transmission of infection has been interrupted.
- Study participants and field staff are not masked to treatment allocation due to the nature of the intervention, but outcome assessors (ie, laboratory personnel and photo-graders) are masked.
- The trial has an initial phase without mass antibiotics (WASH Upgrades for Health in Amhara (WUHA) I; months 0–36) and a subsequent phase with annual mass azithromycin distributions (WUHA II; endpoint at month 84), allowing assessment of the impact of WASH both in the absence and presence of concurrent mass antibiotic distributions for trachoma.
- The trial is being conducted in a region of Ethiopia with hyperendemic trachoma and may not be generalisable to areas with a lower prevalence of infection.

INTRODUCTION

Background

Trachoma, caused by ocular chlamydial infection, is the leading infectious cause of blindness worldwide and a focus of elimination efforts.¹ WHO recommends the four-component SAFE strategy for the elimination of trachoma: Surgery, Antibiotics, Facial cleanliness and Environmental improvements (eg, water and sanitation).² While numerous randomised clinical trials have demonstrated the efficacy of mass azithromycin distributions, antibiotics alone do not appear to be

sufficient for elimination in areas with hyperendemic trachoma.^{3–10}

Facial hygiene promotion and environmental improvements (ie, the ‘F’ and ‘E’ components of SAFE) are thought to be important for trachoma elimination.^{11 12} However, evidence supporting the efficacy of non-antibiotic measures for preventing transmission of ocular chlamydia comes primarily from observational studies, with no confirmatory randomised trials to date.^{13–16} Moreover, very few studies have implemented a comprehensive water, sanitation and hygiene (WASH) package with a trachoma endpoint, even though many believe that only the full SAFE strategy will be effective to prevent transmission of trachoma.^{17 18}

WASH Upgrades for Health in Amhara (WUHA) is an ongoing cluster-randomised trial sponsored by the National Eye Institute to test the efficacy of a comprehensive WASH intervention for trachoma. The trial’s ultimate goal is to support evidence-based decision-making for trachoma programme managers.

Objectives

This study aims to determine the efficacy of a comprehensive WASH package for reducing ocular chlamydia infection and trachoma.

METHODS AND ANALYSIS

Trial design

WUHA is a parallel-group, cluster-randomised trial in which 20 clusters receive a comprehensive WASH package and 20 control clusters do not receive a WASH intervention until the conclusion of the trial. Mass antibiotics are not given during the first 3 years of the trial (WUHA I), but annual mass azithromycin distributions are administered over the subsequent 4 years (WUHA II). Communities have annual follow-up during the 7-year study period.

Participants

Study area

The study area is composed of rural communities in the Sekota Zuria, Sekota Ketema and Gazgibella Woredas (ie, districts) of the WagHemra Zone of Amhara Region, Ethiopia, an arid region of the Ethiopian highlands with hyperendemic trachoma. Mass azithromycin distributions were distributed annually from May 2009 to June 2015, and a supplemental mass treatment was administered in October 2014.

Randomisation unit

The unit of randomisation is the primary school catchment area, chosen because schools are likely an important place for transmission of ocular chlamydia and because they are a logical place to perform hygiene education activities.

Study population

All primary schools outside of the largest town in the woreda and within a 4-hour drive and/or walk from the

main road are eligible. A location in the school catchment area thought to have the most potential to be developed into a water point (ie, a hand-dug well or protected spring) based on a geohydrological survey is classified as the randomisation unit’s potential water point, and all households within a 1.5 km radius are censused and monitored annually.

Census

A baseline door-to-door population census enumerates all individuals from all households within a 1.5-km radius of the potential water point. The census is updated each year approximately 1 month prior to the scheduled monitoring visit. The census is conducted by trained Ethiopian enumerators masked to study arm. At each census, the name, age, sex, vital status (ie, alive, died, unknown) and residence status (ie, living in household, moved within community or moved outside community) are collected for each household member, and the geo-coordinates are collected for each household. In addition, all primary schools, health facilities and water points used by the household are recorded. Individuals documented as alive and living in the community are eligible for interventions and monitoring.

Monitoring population

A stratified random sample of community members selected from the most recent study census is monitored each year of the trial, with strata defined as children 0–5 years (ie, up to but not including the sixth birthday), children 6–9 years (ie, up to but not including the tenth birthday), and individuals 10 years or older. 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 (ie, repeated cross-sectional random sampling). 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. In addition to these repeated cross-sectional samples, the group of children 0–5 years old monitored at baseline comprises a cohort that is monitored throughout the study for trachoma and anthropometric outcomes.

Assignment of interventions

Randomisation

Clusters are randomised in a 1:1 ratio to intervention or delayed intervention after the baseline census by the trial biostatistician. The randomisation sequence is generated in R (R Foundation for Statistical Computing, Austria, Vienna) as a simple random sample without stratification or blocking. Concealment of allocation is ensured at the cluster level by performing randomisation after the baseline census and at the individual level by offering the intervention to all community members. The study coordinator is responsible for implementation of the randomisation sequence.

Masking

It is not possible to mask the study participants to treatment allocation given the nature of the intervention. Although individuals in the non-intervention communities could potentially improve their hygiene due to knowledge of their allocated treatment group, this is not likely—especially given the difficulty in causing behaviour change even under optimal programmatic conditions.¹⁹ Field personnel (ie, for the census, examinations and treatments) are not informed of the treatment allocation or study objectives, although it is possible they could determine this information from other means. All laboratory personnel (ie, chlamydia PCR, chlamydia serology and soil-transmitted helminth outcomes) and photographers (ie, clinical trachoma outcomes) are masked to treatment arm. There are no plans to assess success of masking.

Contamination

Cluster-randomised trials are subject to contamination if the intervention or its effects spread to neighbouring communities. In this trial, primary school catchment areas are randomised. 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. In addition, hygiene promotion measures that might be especially subject to contamination (eg, radio announcements) are purposefully not included in the intervention. Contamination would reduce statistical power but not invalidate a positive result.

WASH intervention

Formative research

Hygiene education is most effective when confined to a few key messages, repeated in many different settings.²⁰ We focus on two behaviours likely to have the greatest impact on trachoma: (1) using soap and water to wash a child's face twice per day, and (2) consistently using latrines for defecation. Messaging (eg, times of day to wash the face, inclusion of soap, promotion of simple pit latrine) is based on pre-study focus group discussions and local government programmes. A logic model was created to inform and describe the study interventions (online supplemental file 1).

Household-based interventions

All components of the intervention are implemented after the baseline census and randomisation. Household-based interventions are implemented in all households enumerated in the census (ie, within 1.5 km of the potential water point).

Hygiene promotion team

A hygiene coordinator and health promotion workers (HPWs) hired specifically for the study assist the study coordinator with WASH package implementation to help ensure high uptake of the WASH intervention in all study clusters. HPWs, who work and live in the intervention

communities, visit each household at least once per month to promote positive hygiene behaviour change, with an emphasis on face-washing and latrine use. In addition to study-specific trainings, the study coordinator and hygiene coordinators attend Community-Lead Total Sanitation and Hygiene (CLSTH) and Children's Hygiene and Sanitation (CHAST) training workshops administered by Catholic Relief Services in order to provide context about hygiene promotion interventions.

Hygiene education book

An illustrated, 65-page hygiene book was developed through a series of focus group discussions with health and education bureaus at the regional, zonal and woreda levels and refined through field-testing with community members (online supplemental file 2). This hygiene education book contains chapters on face-washing, hands-washing, clothes-washing, water collection, latrine use, latrine construction and wash station construction, and is designed to be understandable for illiterate community members. The book is used by the HPWs as their primary educational tool during household hygiene education visits. All enrolled households receive a copy in the local language of their choice (ie, Amharic or Hintsanga). Books are distributed each year to households newly enrolled in the trial.

Household infrastructure

Each household enumerated in the census receives a wash station consisting of a 25-litre jerry can with an attached faucet and a mirror (figure 1). Wash stations are distributed each year to newly identified households and to households with irreparably broken stations. Each household also receives four bars of soap per household per month.

Albendazole distribution

All children aged 12–72 months on the baseline census receive a single dose of albendazole (200 mg for children aged 12–23 months and 400 mg for children 24 months or older) during a mass campaign approximately 6 months post-randomisation to supplement the school-based albendazole distribution that occurs throughout the Amhara region. Programmatic mass albendazole distributions do not occur after the first year of the study.

Azithromycin distribution

No mass azithromycin distributions are provided during the first 36 months of the trial (ie, WUHA1). Communities received 7 years of annual mass antibiotic treatments just before enrolment into the trial, so chlamydia prevalence was expected to be very low, and antibiotic distributions may have overpowered any effect of WASH. The first part of the trial thus tests whether providing the WASH intervention in the absence of antibiotics prevents re-emergent infection. However, it is possible that WASH measures are effective only when combined with mass antibiotic distributions. Thus, annual mass azithromycin treatments are provided to both the intervention and control clusters



Figure 1 Household wash station distributed as a component of the study, consisting of a jerry can with faucet and mirror.

starting after the month 36 visit (ie, WUHA II), allowing a comparison of antibiotics plus WASH versus antibiotics alone. All individuals enumerated on the 36-, 48-, 60- and 72-month censuses receive a single oral dose of azithromycin (20 mg/kg for children using height-based approximation; 1 g for adults), except children under 6 months, pregnant women and those allergic to macrolides, who are offered a 6-week course of ophthalmic tetracycline two times a day instead.²¹

Community-based interventions

These aspects of the intervention are available for anyone in the community, regardless of whether they are enumerated on the census.

Community water point

A geohydrological survey identifies the most promising area to construct a water point in each randomisation unit. The water point (eg, hand-dug well, capped spring or shallow borehole) is constructed during the first year post-randomisation. Each study cluster forms a water committee, and members receive basic training in maintenance after construction of the water point. Water point implementation is conducted by Catholic Relief Services and the local Ethiopian nongovernmental organisation Water Action.

Supplemental messaging

Annual hygiene trainings are performed for government-appointed health extension workers, women's health development army members and local priests to help facilitate hygiene messages. A kick-off event is held at the unveiling of the water point to review the hygiene messages and gain community buy-in.

School-based interventions

Primary schools are targeted for hygiene education because children are the main transmitters of ocular chlamydia.^{22 23} Efforts are made to encourage children to disseminate their hygiene knowledge to other members of their households.

Curriculum

A primary school hygiene curriculum designed by the investigators specifically for the study consists of five to six age-appropriate lesson plans per year for grades 1 through 4. Lesson plans cover a wide array of topics, including face-washing, hand-washing and latrine use (online supplemental file 3). Curriculum development was iterative, with several rounds of feedback from teachers and health officials as well as thorough pilot-testing with teachers and students in the study area. Teachers are trained in the curriculum before each school year.

WASH clubs

Primary schools in this region of Ethiopia offer extra-curricular clubs moderated by teachers, including WASH clubs. We provide training materials for WASH activities (eg, songs, dances, dramas, community engagement activities) to existing WASH club leaders and work with principals of schools to ensure that WASH clubs are formed if they do not already exist.

WASH process indicators: intervention clusters

The RE-AIM framework (Reach, Efficacy, Adoption, Implementation and Maintenance) is used to assess whether the WASH interventions are being implemented as planned.^{24 25} Intervention uptake is summarised for each community, results are reviewed with hygiene coordinators and HPWs, and specific actions taken in communities with deficiencies.

Hygiene coordinator spot-checks

The study's hygiene coordinator conducts biannual spot-checks in each intervention cluster throughout the duration of the intervention. Spot-checks are designed to determine uptake of the school hygiene curriculum, usability of the study water point, presence and functionality of household latrines and wash stations, and practice of the targeted hygiene behaviours. A random sample of eight households with pre-school children per cluster is visited at each spot-check to document the presence of a wash station and its functionality (eg, presence of water in the container and soap), the presence of a latrine and its functionality (eg, whether walls and a roof are present),

and evidence for latrine use (eg, trodden latrine path, fresh faeces in the pit).

HPW spot-checks

The HPWs keep a log of each household in the community and document uptake of study interventions (eg, wash stations, latrines) and behaviours (eg, clean faces, latrine use) at each monthly visit.

Focus group discussions

Focus group discussions are conducted each year of the intervention in a sample of intervention clusters. HPWs purposefully select a representative sample of adopter and non-adopter households, with equal representation from men and women.

Patient and public involvement

The study participants and the health and education bureaus at the regional, zonal and woreda levels contribute to the development of the intervention's hygiene book and school curriculum via focus group discussions. Community members are consulted on the intervention annually in order to guide intervention decision-making. The results of the study will be disseminated to the participants and local health and education bureaus.

Implementation fidelity

Hygiene infrastructure and behaviours are monitored in all communities to provide an assessment of the impact of the intervention relative to no intervention.

Household WASH survey

A random sample of 33% of households is invited for a survey at each annual census. Census workers are not informed of the study purpose or the randomisation allocation. The survey questions capture both self-reported hygiene behaviours as well as objective observations of latrines and wash stations.

Structured observations

A 24-hour structured observation of face-washing and latrine behaviours is conducted in a random sample of five households per community from all communities.

Facial cleanliness

Face photographs are taken during the annual monitoring visits and graded for the presence of ocular and nasal secretions.

Primary and secondary outcomes

The primary outcome is the prevalence of ocular chlamydia by PCR in children 0–5 years old, 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. A key secondary outcome is improvement in clinical trachoma, assessed by conjunctival photography. Other secondary outcomes are listed in [table 1](#).

Table 1 Pre-specified outcomes assessed in WUHA

Outcome	Method	0–5 years	6–9 years	≥10 years
Presence of ocular chlamydia	PCR	X*	X	X
Ocular chlamydial load	PCR	X	X	X
Worsening of clinically active trachoma	Photography	X	X	X
Clinical signs of trachoma	Photography	X	X	X
Presence of chlamydia antibodies	DBS serology	X	X	X
Presence of soil-transmitted helminths in stool	Microscopy, PCR	X	X	
Height, weight over time	Anthropometry	X		
Presence of nasopharyngeal pneumococcus	Bacterial culture	X		
Presence of pneumococcal antibiotic resistance	Disk diffusion	X		
Presence of health clinic visit	Chart review	X	X	X

*Primary outcome.

DBS, dried blood spot; PCR, polymerase chain reaction.

Summary of examination procedures

Procedural details can be found in the manual of procedures (online supplemental file 4); key features are summarised here. All specimens are labelled with a five-digit random identifier to aid in masking.

Conjunctival swabbing

The right upper eyelid is everted and a Dacron swab (Thermo Fisher Scientific, Waltham, MA) passed over the conjunctival epithelium three times, rotating 120° between each pass. Swabs are stored on ice in the field and at –20°C within 8 hours of collection. Swabs are stored at a local health facility in the study area for several weeks before being transported on ice to the Amhara Public Health institute (Bahir Dar, Ethiopia), where they are stored at –20°C until processed with the RealTime quantitative PCR assay on the m2000 platform (Abbott Molecular, Des Plaines, IL) to detect *Chlamydia trachomatis* DNA. Two randomly selected individuals per cluster receive a second swabbing to assess outcome reproducibility. Negative control swabs are collected in each cluster at the beginning and end of the monitoring visit by waving the swab gently in the air.

Photography

Face photographs and photographs of the everted right superior tarsal conjunctiva are taken in triplicate using

a Samsung Galaxy NX camera equipped with a 60 mm $f/2.8$ macro lens (Seoul, South Korea), with camera settings set automatically by the mobile application (ISO 400, native flash engaged, automatic white balance, aperture priority, $f/11$ for face, $f/32$ for conjunctiva). Photographs are uploaded to a secure server (Salesforce.com, San Francisco, CA) and eventually graded at a grading centre at the University of Gondar (Gondar, Ethiopia). Photo-graders masked to treatment allocation, study visit and participant identifier assign clinical trachoma grades to each eye using a modification of previously described grading systems.^{26 27} Photographs from baseline and the final visit are also presented side-by-side to photo-graders masked to treatment allocation and study visit, and the more severe clinical presentation is noted.

Blood sampling

Blood from a finger stick is applied to five of six ears of a TropBio filter paper disk (Cellabs, Sydney, Australia), allowed to air dry and then placed in plastic bags with desiccant packets. Dried blood spots are stored at -20°C until shipped to the US Centers for Disease Control and Prevention (Atlanta, GA) for serologic testing, including for the chlamydial antibodies pgp3 and CT694.²⁸

Stool sampling

A container with a plastic bag liner is given to participants or their caregiver with instructions to provide a stool sample. Participants unable to produce stool take the materials home and are instructed to collect a stool sample the following morning, which is retrieved by study personnel later that day. Fresh stool samples are divided into two specimen containers in the field, with 1 g transferred to a tube with 10 mL sodium acetate–acetic acid–formalin (SAF) and 500 mg transferred to an empty tube subsequently filled with 500 mL 5% potassium dichromate. Stool samples are stored and transported similarly to conjunctival swabs; the samples stored in SAF are processed at the Amhara Public Health Institute for ova and parasites and the samples stored in potassium dichromate are processed at Smith College (Northampton, MA) with a PCR assay for soil-transmitted helminths.²⁹

Nasopharyngeal swab sampling

A FLOQSwab (COPAN Diagnostics, Murrieta, CA) is inserted approximately 10 mm through the right nostril, then twisted at the posterior aspect of the nasopharynx. The swab is stored in a tube with skim milk–tryptone–glucose–glycerine (STGG) media. Tube storage and transport is similar to conjunctival swabs. Nasopharyngeal swabs are processed at the Amhara Public Health Institute; standard microbiological methods are used to isolate *Streptococcus pneumoniae* and then a disk diffusion assay used to determine antimicrobial resistance to penicillin, azithromycin, tetracycline, and clindamycin.

Anthropometry

A wooden stadiometer (Schorr Productions, Olney, MD, USA) is used to measure standing height for children who

can stand or recumbent length for those who cannot. A Seca 874 floor scale (Seca, Hamburg, Germany) is used for weight measurements. Both height and weight are taken in triplicate, with the median value used for analyses.

Data collection, management and analysis

Data collection

Census and examination data are collected on mobile devices using a custom-designed software application (Conexus, Los Gatos, CA) and then uploaded to a relational database on Salesforce.com (Salesforce, San Francisco, CA). The data can be monitored in real time via customisable dashboards on the Salesforce website. Data from spot-checks are collected with a Research Electronic Data Capture (REDCap) mobile application and uploaded to a database stored at the University of California, San Francisco. Structured observation data are collected on paper and entered into a REDCap database.

Statistical methods

Sample size

Power calculations are based on a cluster-level two-sample t-test and assume a SD of 10% in the community-specific prevalence of ocular chlamydia based on a prior trial in Ethiopia, a significance level of 5% and no clusters lost to follow-up.¹⁴ Under these assumptions, 22 communities per arm would be required to achieve 80% power to detect an 8% difference in ocular chlamydia between the two arms. However, due to a severe drought in the study area at the beginning of the trial, only 40 potential water points could be identified. The sample size was thus reduced to 20 per arm, providing 79% power (ie, 3% less power than the originally planned sample size) to detect an 8% effect size.

Primary analysis

Post-baseline cluster-specific prevalences of ocular chlamydia are modelled 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. The treatment by time interaction term is included only if it is statistically significant, in which case statistical significance will be determined from the deviance statistic contrasting the model with all terms versus the model without the treatment and treatment-by-time interaction terms. More details are available in the statistical analysis plan (online supplemental file 5).

Secondary analyses

Secondary outcomes will be analysed at the cluster level with a similar approach to the primary outcome. Chlamydial load and helminth density will be analysed as a cluster-specific index. Worsening of clinical trachoma will be assessed in an individual-level analysis of the cohort of children aged 0–5 years at baseline using a mixed-effects logistic regression model with a random intercept for the cluster term. Anthropometric outcomes will also be assessed in the cohort of children 0–5 years old

at baseline, and modelled in an individual-level analysis using a mixed-effects linear regression with a random intercept and slope for children nested in cluster.

Significance testing

Monte Carlo permutation at the cluster level will be implemented, with a two-sided alpha level of 0.05 for each phase of the study (ie, WUHA I and WUHA II).

Cost analysis

The costs of all aspects of the intervention will be tabulated during the study for use in cost-effectiveness analyses.

Monitoring

Data monitoring, harms and auditing

A Data Safety and Monitoring Committee (DSMC) is responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and monitoring the overall conduct of the trial. 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 relating to the selection, recruitment and retention of participants, and data management and quality control.

Adverse events

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. HPWs in turn relay this information to hygiene coordinators.

ETHICS AND DISSEMINATION

Ethical approval

Approval for the study was obtained from the University of California, San Francisco Institutional Review Board (14-14004), the Emory University Institutional Review Board (IRB00077946), the National Research Ethics Review Committee of the Ethiopian Ministry of Science and Technology (310/036/2015), and the Ethiopian Food and Drug Authority (02/25/33/39). Community leaders provide verbal consent before enrolment of the community in the trial. Each participant or a guardian provides verbal consent before any study activity, with separate consent required for census, examinations and intervention at each study visit. 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.

Dissemination policy

The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication. Results will also be shared directly with the participating communities.

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