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Stronger SAFE: a community-based cluster-randomized trial to strengthen strategies to eliminate trachoma

Submission date
26/01/2021

Recruitment status
No longer recruiting

Registration date
02/02/2021

Overall study status
Completed

Last Edited
31/03/2026

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Trachoma is an eye disease caused by a germ called Chlamydia that many people catch in Ethiopia. It can cause people to become blind. Trachoma is transmitted from eye to eye in different ways. The researchers believe that they can help prevent trachoma by giving everyone in the community azithromycin (an antibiotic) to treat infection, combined with measures designed to stop trachoma from spreading between people. These include personal hygiene and fly control measures. This study will evaluate this novel intervention package to prevent trachoma in the community by comparing these measures to standard trachoma control measures in a community-based clinical trial.

Who can participate?
All individuals who are resident in the study community (clusters) will be invited to participate.

What does the study involve?
A household census will be conducted at baseline which will be updated throughout the trial and will be completed for each enrolled household. A household survey using a questionnaire will be conducted in each household. A trained ophthalmic nurse will examine both eyes in selected children aged 1-9 years in the household. Digital photographs will be taken of the conjunctivae (eyelids). A swab sample of the eyelid will be taken using a cotton swab to test for the presence of the trachoma germ (Chlamydia). These swabs will be tested in laboratories in Ethiopia and the UK. The examination takes a few minutes to complete and will be done using a topical anaesthetic to avoid unnecessary discomfort. The faces of selected children aged 1-9 years will be assessed by the research team using a forehead cloth wipe to examine for cleanliness. This is not uncomfortable and will not cause any pain.
Each household will be given either one or two doses of treatment with the antibiotic tablet (or syrup), azithromycin, every year. This is the same antibiotic that is usually given in this community for trachoma. The decision of whether the household will receive one or two doses will be determined at random (as if picked out of a hat). For households selected to receive two doses, the second dose will be given about 2 weeks after the first. The antibiotic tablets can occasionally cause some mild stomach ache a few hours after taking them. The researchers do

not expect any serious side effects from azithromycin but there is a system in place to monitor any adverse events, and participants will receive instructions from the team about who to contact if there are any concerns or questions after taking the treatment.
Some households will be selected randomly to receive support to improve personal hygiene and to reduce contact with flies. The decision of whether the household will receive this support will be random (as if picked out of a hat). Selected households might receive:
1. A fly trap
2. A scarf or hat: this headwear contains a chemical that flies do not like, called “permethrin”. It may stop flies going to children’s eyes. The scarf is for children aged between 2-9 years old, as these children are the most bothered by flies and the most at risk of trachoma. Children in this age group should be encouraged to wear the headgear when they are outside, and they are being bothered by flies. The amount of permethrin in the scarf is low and safe for children to use. However, children should be discouraged from putting the scarf into their mouth, eyes, or nose.
3. Visits to the household or community from a health volunteer or a member of our research team who will share information, messages and materials related to hygiene.

What are the possible benefits and risks of participating?
This study is designed to benefit communities by contributing new knowledge which will help shape future trachoma control programmes. There may be no individual benefit to participants in the study. If as part of the assessment any significant eye problems are identified in participants the researchers will arrange referral and treatment as appropriate. Azithromycin has been shown to be effective at reducing the amount of eye infection, and it has been shown to reduce illness and deaths in young children. If a household receives personal hygiene and fly control measures, it is possible that there will be fewer flies in and around the house, and it is possible that whilst children are using the headwear they may experience less irritation from fly contact to their face. Improved personal hygiene may lead to participants experiencing fewer illnesses in general.
The collection of the eye swabs is associated with minimal discomfort. Azithromycin is a safe and well-tolerated antibiotic that has been used in Ethiopia (several hundred million doses) and many other countries in the world for this purpose. There should be no risks associated with changing personal hygiene habits. There is a very small risk of skin irritation with wearing permethrin-treated headwear. In a previous trial conducted by the research group, they did not find any problems like this, but it remains a very small risk. Flies caught in the fly traps may present a small risk to people, as flies are unhygienic. Therefore, only those who have been trained in using the trap should touch it. The lure inside the trap does not contain bad chemicals, it is composed of food-based substances including yeast. For these hygiene reasons, it is important that children are discouraged from touching the trap and specifically the lure (bait) or the flies trapped inside.

Where is the study run from?
The study is run from the London School of Hygiene and Tropical Medicine in collaboration with partners in Ethiopia (Oromia Regional Health Bureau, Federal Ministry of Health and Fred Hollows Foundation Ethiopia) and the UK (Fred Hollows Foundation and Wellcome Trust Sanger Institute). LSHTM holds insurance policies which apply to this study.

When is the study starting and how long is it expected to run for?
March 2019 to August 2024

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
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Additional identifiers

Protocol serial number
LSHTM Ethics Ref 17494

Study information

Scientific Title
Stronger SAFE: a cluster-randomized trial of double-dose oral azithromycin combined with facial cleanliness & environmental improvement strategies for trachoma elimination

Acronym
Stronger SAFE

Study objectives
Multiple rounds of SAFE implementation has proven insufficient to eliminate trachoma in some hyperendemic regions in Ethiopia. Strengthened, more effective antibiotic treatment schedules and transmission suppressing approaches (F&E) are needed. The researchers propose to test, in a four-arm cluster-randomized trial, the hypothesis that Stronger SAFE, comprising of enhanced azithromycin treatment (two single doses of azithromycin (A) 2 weeks apart) combined with targeted transmission-interrupting hygiene and fly-control strategies (F&E), can more effectively control trachoma, determined by measuring the presence of ocular Chlamydia trachomatis (Ct) by PCR, than current standard approaches (SAFE), in a trachoma-hyperendemic region in Ethiopia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 04/06/2019, London School of Hygiene and Tropical Medicine Research Ethics Committee (Keppel Street, London, WC1E 7HT, UK; +44 (0)207 636 8638; ethics@lshtm.ac.uk), ref 17494
2. Approved 11/12/2020, Oromia Regional Health Bureau (PO Box 24341, Addis Ababa, Ethiopia; +251 (0)113 717 277; ohbhead@telecom.net.et), ref: FHFE/DCD/484/2020
3. Approved 15/12/2020, National Research Ethics Review Committee (PO Box 23976, Addis Ababa, Ethiopia; +251 (0)118 721 747; nrerc2019@gmail.com), ref: FHFE/DCD/0183/2020
4. Approved 03/12/2020, Ethiopian Food, Medicines and Health Care Administration (PO Box 5681, Addis Ababa, Ethiopia; +251 (0)552 414 123; regulatory@fmhaca.gov.et), ref: 02/25/33/44

Primary study design
Interventional

Study design
Single-region community-based single-masked parallel-group four-arm cluster-randomized interventional trial

Study type(s)
Other

Health condition(s) or problem(s) studied
Prevention of (via transmission interruption) and treatment of ocular infection with Chlamydia trachomatis in trachoma-endemic communities

Interventions
The 68 clusters will be randomly allocated into four arms using a computer-generated sequence, with an equal number of clusters in each arm (1:1:1:1). Restricted randomization may be considered in order to ensure balance between arms for any important cluster-level variables at baseline. Once the clusters are allocated to the four arms, a statistician independent to the study will run a program to randomly allocate each of the four potential interventions summarised below:
1. Standard antibiotic / standard F&E (control)
2. Standard antibiotic / enhanced F&E
3. Enhanced antibiotic / standard F&E
4. Enhanced antibiotic / enhanced F&E (Stronger SAFE)

Antibiotic Interventions:
Oral azithromycin (Pfizer) will be provided by the International Trachoma Initiative. The height-based dosage will follow the standard schedule, 20 mg/kg up to a maximum dose of 1g.
1. In Standard Antibiotic Arms: a single dose of oral azithromycin will be given to all individuals above 6 months of age as mass drug administration (MDA) given for three annual rounds. This is in accordance with the national policy for trachoma control and will be conducted by the regional trachoma control programme.
2. In Enhanced Antibiotic Arms: an additional single dose of oral azithromycin (20 mg/kg up to a maximum dose of 1 g) will be given 2 weeks after the programmatic MDA to all individuals above the age of 2 years for three annual rounds.

F&E Interventions:
1. Standard F&E: Programmatic promotion of latrine construction and facial hygiene through health-promotion messaging and collaboration with the WASH (Water, Sanitation, Hygiene) sector to advocate improved water supply.
2. Enhanced F&E Intervention Package: The additional WASH interventions comprise an entomological control component and a hygiene behaviour change component. The Entomological Control will consist of a 'push-pull' strategy. The "Push" is an insect repellent product permethrin-treated scarf, worn around the neck by children aged 2-9 years of age, which will provide personal protection from eye-seeking flies. The "Pull" involves odour-baited fly traps deployed at the household level, during the hot season only, to reduce local fly population density. The Hygiene Behaviour Change Package will seek to change facial hygiene practices. The intervention package is designed to be a series of low-cost, sustainable enhancements to the standard F&E package. i) Increasing the perceived value of face washing by adding to or amplifying the motivational drivers associated with face washing. ii) Providing cues in the environment to remind/trigger face washing. iii) Lowering the transaction costs associated with face washing by encouraging the provision of convenient soap and/or water and/or utensils for face washing.

Intervention Type
Mixed

Primary outcome(s)
Cluster-adjusted prevalence of ocular Chlamydia trachomatis (Ct) infection measured by quantitative real-time PCR (polymerase chain reaction) detected on conjunctival swabs in children aged 1-9 years at 36 months post-intervention. The cluster level estimate of the prevalence of Ct will be based on a random sample of 60 children per cluster.

Key secondary outcome(s)

1. Cluster-adjusted prevalence of Ct infection measured using qPCR in children (1-9 years) at baseline, 2, 12, 24, 26 months
2. Cluster-adjusted prevalence of TF and TI in children (1-9 years) measured by conjunctival examination at baseline, 2, 12, 24, 26, 36 months
3. Cluster-adjusted proportion of children (1-9 years) with clean faces measured using a facial cleanliness score at baseline, 2, 12, 24, 26, 36 months
3. Fly (Musca sorrbens) density and diversity measured using trap counts and morphological identification each month from baseline throughout the trial (until 36 months)
4. Fly-eye contact in children 2-9 years of age measured using videography monthly from baseline throughout the trial (until 36 months)
5. Cluster-adjusted mean daily frequency of good quality face washing among pre-school, school-age children and primary caregivers measured through household observations at baseline, 2, 12, 24, 26, 36 months
6. Process indicators to measure exposure to, adherence and recall of the F&E interventions measured using a mixed-methods approach at baseline, 3, 6, 12 and 24 months
7. Cluster-adjusted prevalence of malnutrition measured using anthropometry (height and weight for age z-scores) in children (1-60 months) at 24 and 36 months
8. Cluster-adjusted prevalence of clinic and hospital visits (specific and all-cause) for children (1-60 months) measured by caregiver recall at 24 and 36 months
9. Cluster-adjusted prevalence of diarrhoeal and respiratory illness in children (1-60 months) measured by caregiver recall at 24 and 36 months

Completion date
31/08/2024

Eligibility

Key inclusion criteria
Cluster residents eligible for interventions:
1. All individuals over the age of 6 months for Standard Azithromycin Arms (one dose delivered by the national trachoma control programme) and over the age of 2 years in the Enhanced Azithromycin Arms (a second dose delivered in the context of the Trial)
2. Informed consent (and assent where applicable) and to be randomly allocated to one of the four study arms
3. Do not fulfill exclusion criteria for administration of azithromycin

Children eligible for assessment for outcomes:
1. All children between the ages of 1-9 years inclusive
2. Informed consent and agreement of parent (or guardian as appropriate) for the child to participate

Participant type(s)
All

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit

6 Months

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Children under the age of 6 months for Standard Azithromycin Arms (one dose delivered by the national trachoma control programme) and under the age of 2 years in the Enhanced Azithromycin Arms (a second dose delivered in the context of the Trial)
2. Severe illness (defined as a condition that carries a high risk of mortality, where patients are acutely unwell or obtunded such that it would not be ethical to include them in the study) or incapacity (where, if the individual is under the age of 18 years of age, it is assumed on the grounds of immaturity that the child will be unable to make certain decisions such as whether to participate in a research study. In the case of children, those with parental responsibility can consent for them on their behalf. Where an adult lacks capacity, as with the case with certain mental illness, cognitive disorders or acutely due to drugs or alcohol toxicity, they would be excluded from the study. An adult lacking in the ability to understand information relevant to the decision, retain information long enough to be able to make the decision, use or weigh up the information or communicate the decision by any means by definition is deemed to lack decision-making capacity and would therefore be excluded from the study)
3. Inability to communicate
4. Known hypersensitivity to azithromycin
5. Known hypersensitivity to permethrin
6. Women who self report to be in the first trimester of pregnancy (for azithromycin). All women of childbearing age will be asked if they are pregnant. If they report pregnancy within the first trimester they will not be given azithromycin. If azithromycin is given inadvertently in the first trimester of pregnancy, because the woman did not know she was pregnant, this would not be a cause for concern because azithromycin is safe in pregnancy.
7. Confirmed to be taking medications that may cause a serious drug interaction if taken with azithromycin. At the point of enrolment to the study each participant will be screened to check that they are not taking any of the medications listed below at the time of azithromycin MDA and if they are, they will be excluded from the study.

Date of first enrolment
10/02/2021

Date of final enrolment
01/08/2024

Locations

Countries of recruitment
Ethiopia

Study participating centre
West Arsi Zone (participating site)
Ethiopia
-

Sponsor information

Organisation
London School of Hygiene & Tropical Medicine

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Anonymised datasets will be made publicly available, to ensure the data are available for other investigators to explore. Specific permission for this is requested in the consent form. The full details of these data-sharing plans will be made available at a later date, upon publication of the study protocol.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	Primary outcome	24/03/2026	31/03/2026	Yes	No
Results article	Secondary outcomes	24/03/2026	31/03/2026	Yes	No
Protocol article		23/12/2024	17/01/2025	Yes	No
Other publications		14/08/2024	15/08/2024	Yes	No
Statistical Analysis Plan	Appendix	24/03/2026	31/03/2026	No	No
Study website		11/11/2025	11/11/2025	No	Yes