

BMJ Open Annual versus biannual azithromycin mass drug administration for the elimination of infectious trachoma in Africa: protocol for a systematic review and meta-analysis using data from individual communities

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ABSTRACT

Introduction Trachoma is an infectious eye disease caused by *Chlamydia trachomatis* and the leading infectious cause of blindness worldwide. WHO recommends community-wide oral azithromycin treatment as part of its trachoma elimination strategy. WHO initially recommended mass drug administration (MDA) with azithromycin once per year for several years, followed by reassessment. However, some districts have failed to eliminate trachoma even after a decade of annual MDA with azithromycin. As a result, WHO has recently advocated for more frequent antibiotics in districts with persistent trachoma. Although no specific frequency of antibiotic distributions has been recommended, several randomised trials have compared annual with biannual mass azithromycin distributions. This review aims to synthesise the available data to assess the effectiveness of biannual azithromycin MDA relative to annual MDA.

Methods and analysis PubMed, Embase, Web of Science, Scopus and Google Scholar will be searched for studies comparing annual and biannual mass azithromycin distributions for trachoma. Community-level data will be extracted using a standardised data extraction form. Authors will be asked to contribute community-level data not available in the manuscript. The main outcome will be *C. trachomatis* infection among 1–9-year-old children, expressed as a community-level prevalence. A secondary outcome will be the presence of trachomatous inflammation-follicular. The analysis will follow principles of a one-stage individual participant data meta-analysis using complete case mixed-effects regression models with a random effect for study to model community-level prevalence data. Statistical heterogeneity will be assessed with the I^2 statistic.

Ethics and dissemination The research will use community-aggregated data and is thus exempt from ethical approval. The results will be submitted for publication in a peer-reviewed journal.

PROSPERO registration number CRD42024526120.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This meta-analysis will use community-level data from numerous cluster-randomised trials.
- ⇒ The study will follow the *Cochrane Handbook* methodology and report finding according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
- ⇒ Biannual mass azithromycin distribution studies are often conducted in hyperendemic trachoma areas and may limit generalisable to other settings.

INTRODUCTION

Trachoma, caused by the bacterium *Chlamydia trachomatis*, remains the leading infectious cause of blindness worldwide, particularly in low- and middle-income countries.¹ The disease is characterised by chronic conjunctival inflammation, leading to scarring, entropion, trichiasis, corneal superinfections and ultimately blindness.² The primary mode of transmission is through direct contact with ocular or nasal discharge from infected individuals, and *C. trachomatis* infection often recurs due to poor immunity and frequent reinfections.^{3 4} WHO has set elimination targets for trachoma, including a prevalence of trachomatous inflammation follicular (TF) in children 1–9 years of age of less than 5%, and a prevalence of trachomatous trichiasis (TT) of less than 0.2% in adults aged ≥15 years in formerly endemic districts.⁵

The global trachoma elimination effort is centered on the SAFE strategy: Surgery for correcting trichiasis, Antibiotics to clear the infection, Facial cleanliness and Environmental improvement to reduce the transmission.⁵ Mass drug administration (MDA) with azithromycin is a cornerstone of the SAFE

strategy, aimed at reducing the bacterial load of *C. trachomatis* and preventing transmission.^{5 6} The effectiveness of annual azithromycin MDA in reducing trachoma burden has been demonstrated in multiple studies.^{7–9}

Despite significant progress towards trachoma elimination, the prevalence of trachoma remains high in some regions of the world. For example, in December 2021, it was estimated that 145 of 176 (82%) districts with persistent TF (ie, prevalence of TF among 1–9-year-olds 5% or greater at two separate trachoma impact surveys without ever having a TF prevalence less than 5%) were located in Ethiopia despite a decade of the SAFE strategy.¹⁰ For such districts, mathematical models have suggested that biannual MDA, particularly for children, may be more effective in clearing ocular chlamydia and reducing the transmission of infection.^{11–13} Randomised trials have not universally come to the same conclusion, though the trials performed to date may not have been adequately powered to detect a small but meaningful difference.¹⁴ In 2021, global expert meetings convened by WHO reached a consensus that MDAs more frequent than once per year should be considered in regions where annual MDA was not leading to trachoma elimination.¹⁰ The present study expands on prior systematic reviews and meta-analysis using data from individual communities' approach to specifically compare trachoma outcomes in communities treated with biannual versus annual mass azithromycin distributions.¹⁴

METHODS AND ANALYSIS

Study design

An individual participant data (IPD)-meta-analysis will be performed, paying attention to the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-IPD guidelines.^{15 16} The protocol has been registered in PROSPERO (registration number: CRD42024526120).

Study population

The target population is children under 10 years of age, based on WHO guidelines that recommend assessing clinical trachoma in children aged 1–9 years.

Study area

Communities with endemic trachoma.

Intervention

Biannual mass azithromycin distributions (two MDAs per year, regardless of precisely when these two treatments occur).

Comparator

Annual mass azithromycin distributions (one MDA per year).

Outcomes

The primary outcome will be a positive nucleic acid amplification test for *C. trachomatis*, summarised at the

community level as a proportion. The secondary outcome is the presence of TF on clinical examination, summarised at the community level as a proportion. TF is defined as the presence of five or more follicles at least 0.5 mm in diameter in the central upper tarsal conjunctiva.¹⁷

Inclusion criteria

Cluster-randomised trials in which azithromycin was administered to entire communities or to all children in the community annually or biannually, with conjunctival assessment for TF or a test for *C. trachomatis* performed after treatment in a representative sample of children from each community.

Exclusion criteria

Articles with incomplete data, inaccessible full articles or unclear information on methodology, participants, intervention and outcome; studies that report only mathematical models and articles written in languages other than English.

Search methods for the identification of studies

Electronic databases

PubMed, Embase, Web of Science, Scopus and grey literature via Google Scholar will be searched from inception until 31 December 2024.

Search strategy

An initial search of PubMed databases will be undertaken to identify keywords contained in the title or abstract, and index terms used to describe relevant articles. The core search terms and phrases will consist of the following subject headings from the Medical Subject Headings thesaurus: "Randomized Controlled Trial", "Controlled Clinical Trial", "Azithromycin", "Mass Drug Administration", "*Chlamydia trachomatis*", and "Trachoma"; as well as the following free word terms: "Cluster-randomized", "Control Trial", "Antibiotics", "annual", "yearly", "bi-annual", "twice yearly", "frequency", "Zithromax", "AZT", "Mass treatment", "Mass distribution", "Preventive chemotherapy", "MDA", "Active trachoma", "Trachomatous Inflammation Intense", "Trachomatous Inflammation Follicular", "Ocular chlamydia trachomatis". The Population-Intervention-Comparator-Outcome (PICO) approach will be used to create the final search strategy. A second extensive search will be undertaken using all identified keywords and index terms of identified articles. Finally, the reference lists and bibliographies of all relevant articles will be searched.

Data collection and analysis

Selection of studies

During the review process, databases will be searched and eligible articles will be imported into EndNote. The selection of studies and the assessment of data quality will be guided by the PICO elements outlined above. At least two independent investigators will examine titles and abstracts to remove irrelevant reports, then retrieve the full text of the potentially relevant reports and conduct

a review of the full text. Multiple reports of the same study will be linked. Disagreements on the selection and inclusion of studies between the reviewers will be resolved through discussion and consensus.

Data collection and harmonisation

The community-level data will be collected from the full text or supplemental files. If any community-level data are not available, the corresponding authors will be contacted by email to ask if they would contribute community-level data for the study, including metadata such as data collection methods, population characteristics and contextual factors. To harmonise data, a standardised codebook will be developed. Data will be cleaned via categorising or recoding variables and transforming (eg, converting units or adjusting date formats) to ensure alignment. Persistent differences in the structure or distribution of variables will be addressed through multiple imputation or mixed-effects models.

Data extraction and management

Community-level data extracted from articles will be double-data-entered into a spreadsheet, with discrepancies adjudicated by a third person. Data requested from other investigators will be sent in spreadsheet form. Data will be managed, cleaned and analysed in R V.4.

Quality assessment

Assessment of risk of bias in included studies

The risk of bias will be assessed as low, unclear or high risk for each domain independently by each reviewer using the Cochrane Collaboration's tool for assessing the risk of bias.¹⁸ Discrepancies will be settled through discussion and consensus between the authors. The risk of bias due to the non-availability of community-specific data will be explored with forest plots and funnel plots.

Measure of treatment effect

Risk ratio of a positive trachoma outcome (ie, chlamydia-positive or TF-positive), comparing communities treated with biannual versus annual mass azithromycin distributions. Results will be presented with 95% CIs.

Unit of analysis

The unit of analysis will be the unit of randomisation for each study (ie, the 'cluster' of each cluster-randomised trial, usually a community). Data will be expressed as cluster-level summaries (eg, proportions).

Missing data

The primary analysis will be a complete case analysis. Sensitivity analyses with various assumptions for the missing data (eg, 0% prevalence, 100% prevalence) will be performed if data are missing for more than 15% of clusters.

Data analysis and synthesis

A meta-analysis for dichotomous outcomes will be used, with effects estimated from the cluster-level data using

principles of a one-stage IPD meta-analysis. The risk ratio from the cluster-level data will be estimated with log-binomial regression or a robust Poisson regression if the log-binomial model does not converge, including fixed effects for baseline prevalence and time after the baseline treatment, and random intercepts for the cluster (to account for correlated values at different time points) and the study (to account for correlated values between communities in the same study). We acknowledge that most trials will have relatively infrequent monitoring visits that will not capture the benefit of antibiotics immediately after treatment. To better capture the full effect of antibiotics over the entire time frame of the study, we will impute the prevalence of chlamydia 1 month after each treatment, based on the efficacy of azithromycin observed in previous studies.¹⁹ We will then estimate the total burden of infection over the study period for each cluster as the area under the curve of a plot of the prevalence over time (using the imputed data), adopting methods used to estimate infectious burden for viral infections.^{20–22} We will compare this area under the curve (AUC) estimate between treatment groups in a mixed-effects regression adjusted for baseline prevalence and study duration, with a random effect for the study to account for the correlation of values within a given study. All analyses will be performed with the latest version of R.

Assessment of heterogeneity

Heterogeneity between studies will be checked with the I^2 index and 95% CI.^{23 24} Thresholds for the interpretation of I^2 will be categorised as follows: 0–40% (not important), 30–60% (moderate heterogeneity), 50–90% (substantial heterogeneity) and 75–100% (considerable heterogeneity).²⁵

Subgroup analysis

It is possible that the effectiveness of biannual MDAs relative to annual MDAs could depend on the endemicity of trachoma (ie, less benefit of a second MDA in communities with a lower prevalence of trachoma) or on the timing of the biannual treatments. Thus, we plan to perform two subgroup analyses. In the first subgroup analysis, we will stratify communities by baseline prevalence of TF among children, using the median prevalence to classify communities into lower-prevalence and higher-prevalence groups. In the second subgroup analysis, we will stratify studies based on the timing of the biannual treatments (ie, whether the second MDA was scheduled to be administered within 3 months of the first MDA).

DISCUSSION

Mass azithromycin distributions have demonstrated high efficacy in treating trachoma; however, regions with the most severe disease burden have struggled to eliminate trachoma as a public health problem despite prolonged antibiotic interventions. One proposed approach for addressing persistent trachoma is the implementation

of additional rounds of mass azithromycin distribution, with some advocating for biannual mass treatment. This review aims to aggregate the community-level data from multiple studies that have compared biannual versus annual mass azithromycin distributions, which may provide a more accurate assessment of the role of biannual mass antibiotics.

The proposed study prespecifies *C. trachomatis* and TF among children as the outcomes of interest. Ocular chlamydia was chosen as the primary outcome since the main goal of mass azithromycin distributions is to reduce chlamydia infections in the community. TF was chosen as a secondary outcome because of its importance as a key indicator of elimination for WHO. The outcomes will be assessed in children since children are most likely to have ocular chlamydia and clinical signs of trachoma. Evaluating both clinical and microbiological outcomes will provide a more comprehensive assessment of the impact of annual versus biannual MDA regimens.

The proposed study's chief strengths are its use of community-level data, which will allow adjustment of baseline trachoma prevalence, as well as imputation of the short-term reductions in trachoma following MDA, which will provide a more complete assessment of the effects of antibiotics over the entire study period. The study question is distinct from previous meta-analyses in that it focuses specifically on comparing biannual and annual mass azithromycin.¹⁴ Several limitations should be noted. The data sets will not contain many covariates on other interventions (eg, other components of the SAFE strategy, seasonal malaria chemoprevention) or risk factors that could impact trachoma, although the randomised study design should mitigate the threat of bias. Most studies of biannual treatments will likely have been conducted in areas with hyperendemic trachoma and may not be generalisable to all districts with endemic trachoma. However, such hyperendemic regions are those that are most likely to benefit from biannual treatments, and thus the most relevant study population.

In summary, individual community data meta-analysis will be performed to synthesise existing cluster-randomised trials that have assessed the effectiveness of biannual versus annual mass azithromycin treatments for trachoma. The study will provide important information for trachoma programmes as they consider WHO's guidance to consider more-frequent-than-annual mass azithromycin distributions in districts with persistent trachoma.

ETHICS AND DISSEMINATION

This analysis will use deidentified data and is thus exempt from ethical approval. The results will be disseminated through peer-reviewed publications and presentations at academic conferences following recommendations from the PRISMA-IPD statement.¹⁶ Investigators who contribute data for the study will be offered authorship if they agree to meet other authorship criteria (eg, review

and approve the manuscript, agree to be accountable for all aspects of the work).

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Contributors TZ designed the protocol. TZ and JDK wrote the first draft of the protocol. SA, JDK and GD provided critical appraisal regarding the design of the individual participant data systematic review and revised the manuscript. All the authors approved the final version of the protocol. TZ is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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