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A systematic review and individual participant data meta-analysis of randomized controlled trials on the effectiveness of annual versus bi-annual azithromycin mass drug administration for elimination of infectious Trachoma in Africa: Protocol

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A systematic review and individual participant data meta-analysis of randomized controlled trials on the effectiveness of annual versus bi-annual azithromycin mass drug administration for elimination of infectious Trachoma in Africa: Protocol

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Abstract

Background: Trachoma is an infectious eye disease that is the leading cause of preventable blindness worldwide and caused by *Chlamydia trachomatis*. WHO recommends a four-part strategy for the elimination of trachoma, known as the SAFE strategy: **S**urgery for correcting trachomatous Trichiasis, **A**ntibiotics to clear *C.trachomatis* infection, and **F**acial cleanliness and **E**nvironmental improvement to reduce transmission of Chlamydial trachomatis.Some areas in Ethiopia are experiencing persistent trachoma, where the prevalence of trachomatous inflammation among children ages 1-9 years has remained high (≥30 % TF) despite many years of SAFE strategy. WHO currently recommends annual mass azithromycin distributions as part of the SAFE strategy, but some trachoma experts have suggested that distributing mass azithromycin twice per year could be more effective in areas with recalcitrant trachoma. This review aims to assess the efficacy of biannual azithromycin mass drug administration relative to the current recommendation of annual mass drug administration.

Methods: use an electronic database of PubMed, Scopus, grey literature, and reference searching. All published and unpublished randomized control trial research and government reports related to the effectiveness will be reviewed. Four co-authors will independently assess the identified studies by using the eligibility assessment checklist of JBI. JBI standardized data extraction form will be also used for data extraction and finally entered into Review Manager for data synthesis. A random-effect model will be used to calculate the risk ratio and generate the forest plot and funnel plot in review manager 5.4.1. Stata version 14 (Stata-Corp, College Station, TX) will be used to execute meta-analysis regression to test the effects of covariates in the estimates, and the findings will be reported with a 95% confidence interval. The main outcome will be whether the prevalence of ocular *chlamydia trachomatous* (Ct) is less than 1 %. A secondary outcome will be whether the prevalence of *Trachomatous inflammation follicular* (TF) is less than 5.0% (i.e., a WHO criterion for elimination). The estimated effect measures will be a risk ratio, estimated using principles of an individual patient data meta-analysis. A meta-analysis for dichotomous outcomes will be used. Review manager 5.4.1 will be used to execute the random-effect model of Mantel-Haenszel inverse-variance statistical methods. To measure the primary outcome, a summary statistics effect risk ratio (RR) will be calculated.

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Ethics and dissemination: A trial investigator agreement will be signed to get the original data collected. The results will be disseminated through peer-reviewed publications and conference presentations. Furthermore, this individual participant data meta-analysis will inform the recommendations of the azithromycin mass drug administration distribution frequency for global trachoma experts.

PROSPERO registration number CRD42024526120

Keywords: Effect, Azithromycin, Facial cleanness, Environmental Improvement, Trachoma

Strength and limitation

- Our study seeks to conduct a comprehensive individual participant data systematic review comparing the efficacy of bi-annual versus annual azithromycin distribution in eliminating trachoma in hyper-endemic regions of Africa, focusing on children aged 1 to 9 years who receive mass drug administration interventions.
- We will adhere to the stringent methodology outlined in the Cochrane Handbook and report our findings by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
- A specialized search algorithm, developed by a qualified expert, will be utilized to search two prominent databases for relevant English-language published and unpublished randomized controlled trials.
- It is important to acknowledge that the certainty of evidence from our systematic review may be constrained by the limited number of studies available for inclusion.

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Background

Trachoma is the leading infectious cause of blindness worldwide and is found primarily in low- and middle-income countries(1). It is caused by *Chlamydia trachomatis* (Ct), a contagious intracellular bacterium classified into biovars based on pathobiological characteristics and serovars based on serological reactivity for the major outer membrane protein (MOMP) encoded by (outer membrane protein A) ompA. Serovars largely differentiate biological groups associated with trachoma (A–C), sexually transmitted disease (D–K), and lymphogranuloma venereum (LGV) (L1–L3)(2, 3).

Ocular chlamydial infection causes conjunctival inflammation. Chronic conjunctival inflammation eventually results in scarring, entropion, and trichiasis, with the latter predisposing to corneal superinfections and blindness(4). Trichiasis is painful and leads to corneal abrasions, superinfections, corneal opacity, and blindness. Immunity to chlamydia is poor which results in months-long infections in young children, and frequent re-infections (5-7). WHO's targets for elimination are a prevalence rate of trachomatous inflammation follicular (TF) less than 5% in 1–9-year-olds, and of trachomatous trichiasis (TT) unknown to the health system <0.2% in adults aged ≥15 years. The number of people at risk of trachoma in 2016 was around 200 million and 50% of the endemicity found in Niger, Mali, and Ethiopia. living more than 75 million people are living more than 75 million people are living in trachoma-endemic areas in Ethiopia, the largest number in any country in the world. The backlog of people who urgently need eyelid surgery to prevent blindness stands at over 693,000 in Ethiopia – again, the largest number of any country in the world(8).

World Health Organization (WHO) has endorsed a comprehensive intervention package known as **SAFE** (Surgery to correct Trachomatous Trichiasis, Antibiotics to reduce the bacterial infection, Facial Cleanliness, and Environmental Improvement to reduce transmission) to eliminate trachoma as a public health problem (9). Hence based on this intervention, elimination as a public health problem is defined as a prevalence of TT "unknown to the health system" of <0.2% in adults aged ≥15 years in each formerly endemic district, a prevalence of TF in children aged 1-9 years of <5%, sustained for at least two years in the absence of ongoing antibiotic mass

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treatment, in each formerly endemic evaluation unit, and the existence of a system able to identify and manage incident TT cases, using defined strategies, with evidence of appropriate financial resources to implement those strategies(1).

Trachoma control in Ethiopia, where all districts were once endemic, began in 2001 and attained full scale-up of SAFE strategy by 2010. Annual mass distributions of azithromycin and Facial cleanness and Environmental improvement strategy of SAFE have been administered for over 10 years in much of Ethiopia. Despite these interventions, as of 2019, 30 (18.8%) districts remained with TF >30%, with some having a prevalence of TF as high as 55%. Numerous cluster-randomized trials have shown that annual mass drug administration (MDA) of azithromycin is effective at reducing the community burden of ocular chlamydia [10-13). Furthermore, more mathematical models have estimated that treating children twice per year could eliminate infection [11]. However, areas with the most hyper-endemic diseases have been unable to eliminate ocular chlamydial infections even after more than a decade of repeated SAFE strategy implementation. One strategy for areas with recalcitrant trachoma is to distribute additional rounds of mass azithromycin, and several trials have been done comparing biannual (i.e., twice yearly) to annual mass drug administration. This review aims to assess the effect of annual versus bi-annual azithromycin mass drug administration, to eliminate trachoma in Africa.

Methods

Study inclusion and exclusion criteria

In this review, we will include only cluster-randomized controlled trials published in the English language that consist of either annual or bi-annual antibiotics distribution of the SAFE strategy (i.e., Antibiotics, Facial cleanness, or Environmental improvements) among children aged 1 to 9 years.

Study exclusion criteria

Articles with incomplete data, inaccessible full articles, and those with unclear information on methodology, participants, intervention, and outcome will be excluded from the review. Citations without abstracts and/or full text, commentaries, anonymous reports, letters,

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duplicate studies, and editorials, and published or unpublished studies written in languages other than English will be excluded from the review. Additionally, Studies that report only mathematical models, case reports, and reviews will be excluded.

Study population**:** Children aged 1-9 years.

Study area**:** We will include only studies conducted in Africa.

Types of interventions

The "Annual versus bi-annual antibiotics" intervention is one of the program components known by the acronym "SAFE". The "SAFE" strategy is a community-based health intervention that eliminates and reduces the prevalence of active trachoma among children and adults in Ethiopia.

Comparator**:** "Communities and individuals who received the annual or bi-annual antibiotics intervention" versus "No "Antibiotics" strategy intervention for trachoma elimination".

Primary outcomes

(1) The prevalence rate of ocular chlamydial infection < 1%

2. The prevalence rate of trachomatous inflammation follicular <5 %

Search methods for identification of studies

Electronic searches

This review will be conducted to compile the current evidence base, using published articles as well as grey literature documenting the effectiveness of the implementation of annual or bi-annual azithromycin mass drug administration programs in children living in Africa. The electronic databases searched will be PubMed, Google Scholar, and Scopus, till 2024. The search strategy included using both separation and combination of the Boolean operators like "OR" or "AND". In addition, wild card characters are also used.

Search Strategy

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The search database will include PubMed, Scopus, and Google Scholar. 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 be “Cluster randomi?ed”, “control trial” , “Randomi?ed controlled trial”,” controlled clinical trial”,“Assessing “, “Evaluation, “ “investigating “changing “ , “efficacy” , “efficacious” , “Impact” ,”Effect”, “Effective” ,“Antibiotics" , “annual” , “yearly” ,”bi-annual”, “twice yearly “frequency “Azithromycin” , “Zithromax” , “AZT”, “Mass Drug Administration“, “Mass treatment, “, “Mass distribution”, Preventive chemotherapy” , “MDA”, OR “Active trachoma”, “Trachomatous Inflammation Intense”, “Trachomatous Inflammation Follicular”, “Ocular chlamydia trachomatous”, “Africa ”. To fit searching databases and undergoing comprehensive search strategy will be developed using different Boolean operators. A second extensive search will be undertaken using all identified keywords and index terms. The third step will be a search of the reference lists and bibliographies of all relevant articles.

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 protocol of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(7). More than two authors will examine titles and abstracts to remove irrelevant reports. Then we will retrieve the full text of the potentially relevant reports and a full review of the text will be conducted to select and fulfill the eligibility criteria for inclusion in the study. We will link multiple reports of the same study. If there is disagreement on the selection and inclusion of studies between the two authors then we will resolve it through discussion.

Data extraction and management

Author, year of publication, the regions where the study was conducted, study design, type(s) of intervention, number of events, and total events at the cluster level in both the intervention and control groups. If data is not reported, the authors of the articles or trail investigators will be contacted to ask them to share data. Two researchers (TZ and SA) will independently conduct the selection process and assess the trials for eligibility. Both researchers will conduct data extraction and will check for discrepancies. Discrepancies will be

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discussed with other researchers (JK and GD). The extracted data will cleaned and coded. A Review Manager 5.4.1 calculator will be used to convert the different measures of effect reported, to risk ratio, and the sort data will be entered directly into Review Manager 5.4.1 for analysis. A random-effect model will be used to calculate the risk ratio and generate the forest plot and funnel plot in review manager 5.4.1. STATA version 14 (Stata-Corp, College Station, TX) will be used to execute meta-analysis regression to test the effects of covariates in the estimates, and the findings will be reported with a 95% confidence interval.

Quality assessment

Assessment of risk of bias in included studies

For the assessment of the risk of bias-included studies. The risk of bias will be assessed as low, unclear, high risk for each domain. The risk of bias graph for Cochrane Collaboration's tool for assessing the risk of bias will be used (14). Secondly, any discrepancies in the studies included in the review will be settled through discussion and consensus between the authors.

Measure of treatment effect

The study's dependent variables will be dichotomous types of data and will be categorized as ***Effective*** *if the chlamydia trachomatous infection prevalence (Ct) <1% or if the prevalence of trachomatous Inflammation follicular (TF) < 5%/* ***Not*** *Effective if the Ct prevalence >1 % or TF>5%,* the 'Antibiotics' strategy eliminates and reduced the prevalence of active trachoma and ocular *C. trachomatis* among children in Africa. To estimate the effect measure, the risk ratio (RR) will be calculated.

Unit of analysis and measure of treatment effect

In this review, we will use the risk ratio (RR) to estimate the dichotomous data, "Yes for effectiveness, and No for ineffectiveness" of the "A" strategy for trachoma elimination and reducing the prevalence of trachoma and ocular chlamydia infection in Africa, and all the findings will be reported with 95% confidence intervals. The unit of analysis will be the unit of randomization for each study (i.e., the "cluster" of each cluster-randomized trial, usually a community).

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Dealing with missing data

Principally, we will design strategies for dealing with missing data from the selected studies. According to the Cochrane Library review, the authors agreed to ignore the missing data. Lastly, we will perform sensitivity analyses to investigate the possible impact of the selected outcome.

Assessment of heterogeneity

Heterogeneity between studies will be checked by assessing the chi-squared statistic and its degree of freedom (df), and the I^2 index at a 95% confidence interval (15, 16). The described I^2 percentage indicates the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). For example, thresholds for the interpretation of I^2 will be categorized as follows: 0-40% might not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity, and 75-100% represent considerable heterogeneity (17). However, the I^2 value can be misleading, since the importance of inconsistency depends on several factors, thus subgroup and sensitivity analysis will be employed.

Assessment of reporting biases

The Egger regression test will be done via the funnel plot to assess the presence of publication bias in the studies included in the review. If the funnel plot indicates symmetric dots of an inverted funnel shape, it shows the absence of publication bias. In the review manager, studies evaluating the effectiveness of the "annual versus bio annual azithromycin distribution " strategy will be categorized into two intervention traits (I) Annual mass administration of azithromycin and (ii) Bi-annual azithromycin distribution subgroup analysis will be done to determine the random heterogeneity between the estimates of primary studies.

Data synthesis

A meta-analysis for dichotomous outcomes will be used, with effects estimated from the cluster-level data using principles of an individual participant data meta-analysis. Review manager 5.4.1 will be used to execute the random-effect model of Mantel-Haenszel inverse-variance statistical methods. In addition, we will estimate the RR from the cluster-level data with a log-binomial regression or a robust Poisson regression if the log-binomial model does not converge, including random intercepts for the cluster (to account for

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correlated values at different time points) and the study (to account for correlated values between communities in the same study). We perform similar analyses using data in which the prevalence of chlamydia one month after each treatment is imputed based on the efficacy of azithromycin observed in previous studies. Finally, we will calculate the total prevalence time for each cluster as the area under the curve of a plot of prevalence over time (using the imputed data) and then compare this estimate of prevalence time between treatment groups in a mixed effects linear regression adjusted for baseline prevalence, with random effects for the study (to account for the correlation of values within a given study).

Subgroup analysis and investigation of heterogeneity

The main subgroup analysis will be done based on the endemicity of trachoma at baseline to determine if the efficacy of biannual vs annual mass azithromycin distributions depends on baseline trachoma prevalence.

We will assess the presence of statistical heterogeneity in the meta-analyses by visual inspection of the forest plot and Chi-squared test for heterogeneity at a threshold P-value of 0.05. In the presence of heterogeneity, subgroup analysis will be maintained. Statistical evidence for the presence of heterogeneity between subgroups will calculated and quantified as high (considerable), moderate, and low with ranges of 75% or more, 50–75%, and 25% or less for I^2, respectively

DISCUSSION

Mass azithromycin distributions have demonstrated high efficacy in treating trachoma; however, regions with the most severe disease burden have struggled to completely eradicate ocular chlamydial infections despite prolonged antibiotic interventions. Administration of a single dose of azithromycin to the entire community significantly reduces the prevalence of ocular chlamydia, with repeated treatments leading to further decreases. Nonetheless, the challenge of eliminating infection persists in hyper-endemic areas. One proposed approach for addressing persistent trachoma is the implementation of additional rounds of mass azithromycin distribution, with some studies comparing biannual to annual administration. This review aims to evaluate the impact of annual versus bi-annual azithromycin mass drug administration in Africa for trachoma elimination. Utilizing robust methodology outlined in the Cochrane

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Handbook and adhering to the PRISMA statement, this individual participant data meta-analysis seeks to provide valuable insights for global trachoma experts. It is important to note that the certainty of evidence from this systematic review may be constrained by the limited number and quality of available studies.

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Ethics and dissemination

A trial investigator agreement will be signed to get the original data collected. The results will be disseminated through peer-reviewed publications and conference presentations. Furthermore, this individual participant data meta-analysis will inform the recommendations of the azithromycin mass drug administration distribution frequency for global trachoma experts.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research

Contributors: TZ designed the protocol. TZ and JK wrote the first draft of the protocol. SA, JK, 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.

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ABSTRACT

Introduction: Trachoma is an infectious eye disease caused by *Chlamydia trachomatis* and the leading infectious cause of blindness worldwide. The World Health Organization (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 re-assessment. 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 randomized trials have compared annual with biannual mass azithromycin distributions. This review aims to synthesize the available data to assess the effectiveness of biannual azithromycin mass drug administration relative to annual mass drug administration.

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 standardized 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 (TF). The analysis will follow principles of a one-stage individual participant data (IPD) 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.

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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.

Registration: PROSPERO number CRD42024526120

Keywords: Effect, Azithromycin, Facial cleanness, Environmental Improvement, Trachoma

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Strengths and limitations

- This meta-analysis will use community-level data from numerous cluster-randomized trials and account for the short-term efficacy of azithromycin, providing a comprehensive assessment of the potential benefits of biannual azithromycin distributions for trachoma.
- The study will be conducted with attention to the methodology outlined in the Cochrane Handbook and the findings will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
- Studies of biannual mass azithromycin distributions are typically conducted in areas with hyperendemic trachoma, and thus may not be generalizable to all settings with endemic trachoma.

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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 characterized 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 re-infections.[3 4] The World Health Organization (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 around 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 (i.e., 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

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clearing ocular chlamydia and reducing the transmission of infection.[11] Randomized 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.[12] 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 upon prior systematic reviews by employing an individual participant data (IPD) approach to specifically compare trachoma outcomes in communities treated with biannual versus annual mass azithromycin distributions.[12]

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.[13 14] 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*, summarized at the community level as a proportion. The secondary outcome is the presence of TF on clinical examination, summarized at the community level as a proportion. TF is

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defined as the presence of five or more follicles at least 0.5mm in diameter in the central upper tarsal conjunctiva.[15]

Inclusion criteria: Cluster-randomized 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; articles written in languages other than English.

Search methods for identification of studies

Electronic databases. PubMed, Embase, Web of Science, Scopus, and grey literature via Google scholar will be searched from inception until December 31, 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 (MeSH) 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

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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 harmonization. The community-level data will be collected from the full text or supplemental files. If any community-level data is not available the corresponding authors will be contacted by email to ask if they would contribute community-level data for the study, including meta-data such as data collection methods, population characteristics, and contextual factors. To harmonize data a standardized codebook will be developed. Data will be cleaned via categorizing or re-coding variables and transforming (e.g., 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 analyzed in R version 4.

Quality assessment

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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.[16] Discrepancies will be settled through discussion and consensus between the authors. The risk of bias due to nonavailability of community-specific data will be explored with forest plots and funnel plots.

Measure of treatment effect. Risk ratio of a positive trachoma outcome (i.e., chlamydia-positive or TF-positive), comparing communities treated with biannual versus annual mass azithromycin distributions. Results will be presented with 95% confidence intervals.

Unit of analysis. The unit of analysis will be the unit of randomization for each study (i.e., the "cluster" of each cluster-randomized trial, usually a community). Data will be expressed as cluster-level summaries (e.g, proportions).

Missing data. The primary analysis will be a complete case analysis. Sensitivity analyses with various assumptions for the missing data (e.g., 0% prevalence, 100% prevalence) will be performed if data is 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,

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we will impute the prevalence of chlamydia one month after each treatment, based on the efficacy of azithromycin observed in previous studies.[17] 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.[18-20] We will compare this 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% confidence interval.[21 22] Thresholds for the interpretation of I^2 will be categorized as follows: 0-40% (not important), 30-60% (moderate heterogeneity), 50-90% (substantial heterogeneity), and 75-100% (considerable heterogeneity).[23]

Subgroup analysis. It is possible that the effectiveness of biannual MDAs relative to annual MDAs could depend on the endemicity of trachoma (i.e., 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 a lower-prevalence and higher-prevalence group. In the second subgroup analysis we will stratify studies based on the timing of the biannual treatments (i.e., 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

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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 pre-specifies *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 azityromycin.[12] Several limitations should be noted. The datasets will not contain many covariates on other interventions (e.g., other components of the SAFE strategy, seasonal malaria chemoprevention) or risk factors that could impact trachoma, although the randomized 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 generalizable to all districts with endemic trachoma.

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However, such hyperendemic regions are those that are most likely to benefit from biannual treatments, and thus the most relevant study population.

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

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Ethics and dissemination

This analysis will use de-identified 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 Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) Statement.[14] Investigators who contribute data for the study will be offered authorship if they agree to meet other authorship criteria (e.g., review and approve the manuscript, agree to be accountable for all aspects of the work).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Contributors: TZ designed the protocol. TZ and JK wrote the first draft of the protocol. SA, JK, 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 guarantor.

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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. The World Health Organization (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 re-assessment. 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 randomized trials have compared annual with biannual mass azithromycin distributions. This review aims to synthesize the available data to assess the effectiveness of biannual azithromycin mass drug administration relative to annual mass drug administration.

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 standardized 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 (TF). The analysis will follow principles of a one-stage individual participant data (IPD) 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.

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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.

Registration: PROSPERO number CRD42024526120

Keywords: Effect, Azithromycin, Facial cleanness, Environmental Improvement, Trachoma

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Strengths and limitations

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

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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 characterized 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 re-infections.[3 4] The World Health Organization (WHO) has set elimination targets for trachoma, including a prevalence of trachomatous inflammationfollicular (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 around 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 (i.e., 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

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clearing ocular chlamydia and reducing the transmission of infection.[11-13] Randomized 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 upon 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*, summarized at the community level as a proportion. The secondary outcome is the presence of TF on clinical examination, summarized at the community level as a proportion. TF is

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defined as the presence of five or more follicles at least 0.5mm in diameter in the central upper tarsal conjunctiva.[17]

Inclusion criteria: Cluster-randomized 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; articles written in languages other than English.

Search methods for identification of studies

Electronic databases. PubMed, Embase, Web of Science, Scopus, and grey literature via Google scholar will be searched from inception until December 31, 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 (MeSH) 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

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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 harmonization. The community-level data will be collected from the full text or supplemental files. If any community-level data is not available the corresponding authors will be contacted by email to ask if they would contribute community-level data for the study, including meta-data such as data collection methods, population characteristics, and contextual factors. To harmonize data a standardized codebook will be developed. Data will be cleaned via categorizing or re-coding variables and transforming (e.g., 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 analyzed in R version 4.

Quality assessment

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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 nonavailability of community-specific data will be explored with forest plots and funnel plots.

Measure of treatment effect. Risk ratio of a positive trachoma outcome (i.e., chlamydia-positive or TF-positive), comparing communities treated with biannual versus annual mass azithromycin distributions. Results will be presented with 95% confidence intervals.

Unit of analysis. The unit of analysis will be the unit of randomization for each study (i.e., the "cluster" of each cluster-randomized trial, usually a community). Data will be expressed as cluster-level summaries (e.g, proportions).

Missing data. The primary analysis will be a complete case analysis. Sensitivity analyses with various assumptions for the missing data (e.g., 0% prevalence, 100% prevalence) will be performed if data is 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,

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we will impute the prevalence of chlamydia one 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 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% confidence interval.[23 24] Thresholds for the interpretation of I^2 will be categorized 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 (i.e., 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 a lower-prevalence and higher-prevalence group. In the second subgroup analysis we will stratify studies based on the timing of the biannual treatments (i.e., 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

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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 pre-specifies *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 azityromycin.[14] Several limitations should be noted. The datasets will not contain many covariates on other interventions (e.g., other components of the SAFE strategy, seasonal malaria chemoprevention) or risk factors that could impact trachoma, although the randomized 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 generalizable to all districts with endemic trachoma.

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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 synthesize existing cluster-randomized trials that have assessed the effectiveness of biannual versus annual mass azithromycin treatments for trachoma. The study will provide important information for trachoma programs as they consider WHO's guidance to consider more-frequent-than-annual mass azithromycin distributions in districts with persistent trachoma.

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Ethics and dissemination

This analysis will use de-identified 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 Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) Statement.[16] Investigators who contribute data for the study will be offered authorship if they agree to meet other authorship criteria (e.g., review and approve the manuscript, agree to be accountable for all aspects of the work).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Contributors: TZ designed the protocol. TZ and JK wrote the first draft of the protocol. SA, JK, 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 guarantor.

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