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Dose and formulation of azithromycin in mass drug administration studies: a systematic review protocol

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ABSTRACT

Introduction Azithromycin has been given for tropical infectious diseases such as trachoma and yaws by mass drug administration (MDA). As well as controlling the infectious disease in question, MDA may have a beneficial effect in reducing mortality in young children. However, the dose, formulation, frequency and duration of azithromycin used in certain infectious diseases may vary in different studies, and these differences may have impacts on the effectiveness of azithromycin MDA. Furthermore, whether the dose, formulation, frequency and duration are associated with the effectiveness of azithromycin for reducing child mortality—if indeed this effect can be confirmed—remain unknown. In this study, we will investigate whether different strategies such as different dose, formulation, frequency and duration affect the effectiveness of azithromycin MDA on the prevalence of certain infectious diseases or child mortality.

Methods and analysis A narrative systematic review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform will be searched. No language restrictions will be applied. All randomised/quasi-controlled trials, observational studies (cross-sectional studies, cohort studies and case–control studies), case series and registered protocols will be considered. Dose, duration, frequency, rounds and formulations of azithromycin used in MDA will be collected and reviewed. The outcomes will be disease prevalence/control in children and child mortality. Data from the individual studies will not be pooled.

Ethics and dissemination Formal ethical approval is not required since data will be collected from published studies. This systematic review will be published in a peer-reviewed journal and presented at conference meetings.

PROSPERO registration number CRD42018114902

What is already known on this topic?

- Mass drug administration (MDA) is a key strategy for controlling a few infectious diseases.
- WHO recommends azithromycin as an effective agent used in MDA for controlling several infectious diseases.
- MDA may reduce child mortality in young children.

What this study hopes to add?

- The most effective dose, formulation, frequency and duration of azithromycin to facilitate the effects of MDA.
- Whether dose, formulation, frequency and duration of azithromycin make a difference to the possible effect of azithromycin MDA on child mortality.
- Whether age affects the effectiveness of azithromycin MDA.

INTRODUCTION

Mass drug administration (MDA), a key strategy for controlling infectious diseases, aims to give whole populations a pharmaceutical agent to reduce or interrupt pathogen transmission.[1] In low-income and middle-income countries, MDA has been widely used in several diseases, including: trachoma, yaws, onchocerciasis, lymphatic filariasis, schistosomiasis and infection with soil-transmitted helminths.[2] Azithromycin, one of the MDA drugs, is a macrolide antibiotic with a long half-life and low toxicity. It has a wide-spectrum bacteriostatic property against both gram-positive, gram-negative bacteria, atypical bacteria and some protozoa. Azithromycin is well tolerated and appears to be safe for use in children and pregnant women.[3 4] Thus, azithromycin is generally accepted in MDA practice, including the control of trachoma and yaws especially in children[5 6](summarised in table 1).

MDA with azithromycin was first used for trachoma control.[5] WHO recommendations for trachoma are for MDA when the prevalence of trachomatous inflammation-follicular in children aged 1–9 years is ≥5% (with differing number of rounds depending on prevalence categories 5%–9.9%, 10%–19.9%, 20%–29.95% and ≥30%)[7] (table 1). It has also been shown to be beneficial for the control of yaws.[6] WHO's strategy for eradication of yaws

Table 1 WHO strategies for azithromycin mass drug administration (MDA) in children

Diseases	Purpose of MDA	Location	WHO recommended dose	WHO recommended frequency	WHO recommended duration	Combination intervention
Trachoma	Control	Districts with TF_{1-9}*≥5%	20 mg/kg up to 1 g	Annually	At least three doses (years) where TF_{1-9}*≥10%	SAFE†
Yaws	Eradication	Yaws-endemic areas	30 mg/kg up to 2 g	Annually	One single dose	None

*TF in children aged 1–9 years.
†Surgery for trichiasis, antibiotic treatment, facial cleanliness and environmental improvement.
TF, trachomatous inflammation-follicular.

recommends a single round of 30 mg/kg azithromycin MDA with coverage of >90% followed by targeted treatment programmes[8] (table 1). Furthermore, it may have potential beneficial effects for malaria control, because of reduced prevalence after MDA administration.[9] In addition, a few studies also found that azithromycin MDA may play a role in deceasing childhood mortality by reducing the rate of respiratory infections, diarrhoea and malaria.[10–12]

Azithromycin MDA has been exerting benefits on decreasing the prevalence of some infectious diseases like trachoma and yaws. The goal of elimination of trachoma as a public health problem or eradication of yaws has been achieved in some places. However, these diseases still persist in some districts.[13 14] The dose, formulation, frequency and duration of azithromycin used in certain infectious diseases may vary in different studies. For example, a 30 mg/kg dose was used in studies of azithromycin's efficacy against yaws,[6 15] while other studies investigated the effectiveness of 20 mg/kg.[16–18] For trachoma control, two types of formulation including suspension and tables were reported. The frequency of azithromycin MDA has also varied: annually, biannually as well as quarterly administration were adopted among different studies.[19 20] Furthermore, the duration of administration has ranged from 1 to 7 years based on different baseline prevalence.[21 22] In this systematic review, we aim to summarise the variations in dose, formulations, frequency and duration of azithromycin, and explore whether the effectiveness of azithromycin in reducing the prevalence of certain infectious diseases in children and child mortality is influenced by any of these factors. Additionally, we will explore the possible difference of azithromycin MDA in different age groups.

REVIEW QUESTIONS

1. To summarise the existing evidence on dose, formulation, frequency and duration of azithromycin for MDA in children with infectious diseases.
2. To investigate whether the dose, formulation, frequency or duration affects the success of MDA in children—both in terms of prevalence in certain infectious diseases and overall child mortality.
3. To explore the different effectiveness in different age groups receiving MDA.

SEARCHES

PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform will be searched. A searching strategy has been developed (online supplementary appendix 1) and the searching process will be updated before submission. The reference lists of selected articles will be checked for additional studies. No language restrictions will be applied.

To identify studies regarding azithromycin, the keywords 'azithromycin' or 'sumamed' or 'zithromax' will be used. For MDA research, the keywords 'mass drug administration' or 'mass administration' or 'mass treatment' or 'mass distribution' or 'preventative chemotherapy' or 'MDA' will be used to select the studies involving MDA. Then, the above two steps will be combined.

TYPES OF STUDY TO BE INCLUDED

Population

Children aged up to 15 years old.

Intervention

Azithromycin MDA and the dose, formulation, frequency and duration of administration for whole population (data for children subgroup can be obtained) or children.

Comparison

For randomised/quasi-controlled trials: comparisons are placebo, or no treatment, or other medicine, or different dose, formulation, frequency and duration of azithromycin MDA.

For observational studies, case series and published protocols: no comparison.

Outcome

1. Summarise the doses, formulation, frequency and duration of azithromycin MDA used for each infectious disease.

2. Effect on prevalence of infectious disease in children, for which the azithromycin MDA was distributed by dose, duration and frequency, with subgroup analysis by age group.
3. Effect on child mortality by dose, duration and frequency, with subgroup analysis by age group.

Study design

Study inclusion and exclusion criteria

Inclusion criteria: (1) Randomised/quasi-controlled trials, observational studies (cross-sectional studies, cohort studies and case–control studies), case series or published protocols that have investigated azithromycin MDA, (2) Children are included and (3) Disease prevalence/control, child mortality after azithromycin MDA were reported.

Exclusion criteria: (1) Mathematical modelling studies, animal studies, case reports, editorials, conference abstracts and reviews and (2) Independent outcome for children not listed

SELECTION OF STUDIES

After removal of duplications, titles and abstracts will initially be screened for relevance. Full texts of potentially relevant studies that passed the initial screening will be reviewed for eligibility. Two review authors (YY and TX) will assess the trials for eligibility and methodological quality without consideration of the results. Any disagreement will be discussed until we reached consensus. If unresolved, a third reviewer (LZ) will be involved. Reasons for excluding any trial will be documented.

DATA EXTRACTION AND MANAGEMENT

The candidate articles will be imported to EndNote. Standardised forms in Excel will be used. Two review authors (YY and TX) will extract the data and check for discrepancies at each level (title, abstract and full paper) using the inclusion and exclusion criteria. We will extract data regarding:

1. General information: the infectious disease that MDA was given for, author, year(s) the study took place, year of publication, country, sample size, sociodemographics of participants and setting.
2. Study methodology: study design, included/excluded criteria for participants and guideline source.
3. Details of azithromycin MDA: dose, formulation, frequency, duration and combination with other medicines;
4. Comparison: details for placebo or no treatment, or other medicine.
5. Possible social and financial factors contributing to MDA administration: such as gender.
6. Study outcomes and limitations.
7. Discussion re possible factors for effectiveness of azithromycin MDA.

RISK OF BIAS (QUALITY) ASSESSMENT

Two reviewers (YY and TX) will independently assess the risk of bias of included studies. We will rate the quality of the evidence using Oxford Centre for Evidence-based Medicine's Levels of Evidence and Grades of Recommendation. For randomised studies, we will use the criteria outlined in the Cochrane Handbook for Systematic Reviews of interventions.[23] Risk of bias will be assessed according to the following criteria:

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participant and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting and whether the study was free of selective outcome reporting (reporting bias).

For non-randomised studies, the modified the risk of bias in non-randomized studies of interventions (ROBINS-I) tool will be used for the assessment of the quality in terms of seven domains.[24 25]

STRATEGY FOR DATA SYNTHESIS

We will not pool the data from the individual studies. A narrative systematic review will be conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[26] http://www.prisma-statement.org. A flow diagram will summarise the number of articles retained at each screening stage and provide the reasons for exclusion. Extracted data from all studies will be narratively presented through tables.

ANALYSIS OF SUBGROUPS OR SUBSETS

Subgroups will be defined by (1) type of diseases, such as trachoma, yaws, malaria, and doses, formulations, frequencies and durations in each disease will be assessed and (2) paediatric patients in different age groups.

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Contributors YY designed and prepared this protocol; TX is involved in all aspects of the study and will coordinate the review process; LZ contributed to the revision of the protocol and will contribute to data collection and analysis; IC and SQ contributed to the idea of the topic and revised the manuscript. HC and DM contributed to the design of the quality assessment and will contribute to data collection and analysis. All coauthors contributed to the preparation and approval of this manuscript.

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Competing interests IC is editor in chief of BMJ Paediatrics Open.

Patient consent for publication Not required.

Ethics approval Formal ethical approval is not required since data are collected from published studies. The study will hopefully establish whether dose, duration or formulation of azithromycin are important in relation to either control of the underlying infection being treated or overall child mortality. This systematic review will be published in a peer-reviewed journal and presented at conference meetings.

Provenance and peer review Not commissioned; externally peer reviewed.

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