WHO GUIDELINE ON MASS DRUG ADMINISTRATION OF AZITHROMYCIN TO CHILDREN UNDER FIVE YEARS OF AGE TO PROMOTE CHILD SURVIVAL

World Health Organization

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WHO guideline on mass drug administration of azithromycin to children under five years of age to promote child survival

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ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AMR	Antimicrobial resistance
ARI	Acute respiratory infection
AZM	Azithromycin
CI	Confidence interval
DECIDE	Developing and Evaluating Communication Strategies to support Informed Decisions and Practice based on Evidence
ECG	Electrocardiogram
EML	Essential Medicines List (WHO)
FDR	Food and Drug Administration (US)
GDG	Guideline Development Group (independent of WHO)
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRC	Guidelines Review Committee (WHO)
GSG	Guideline Steering Group (WHO)
IHPS	Infantile hypertrophic pyloric stenosis
IMR	Infant mortality rate
IRR	Incidence rate ratio
LMIC	Low- and middle-income country
MCA	Maternal, Child and Adolescent health
MDA-azithromycin	Mass drug administration of azithromycin
MORDOR	Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance
OR	Odds ratio
PRG	Peer Review Group
SMC	Seasonal malaria chemoprophylaxis
RCT	Randomized controlled trial
U5MR	Under-five mortality rate
UN	United Nations
WHO	World Health Organization

EXECUTIVE SUMMARY

About 5.3 million children under the age of five died in 2018[1]. Most of these deaths occurred in low-income countries, with the highest risk of death in sub-Saharan Africa (69 deaths per 1000 live births). Sustainable Development Goal (SDG) 3 aims to end all preventable deaths of newborns and children under the age of five by 2030, with all countries aiming to reduce under-five mortality to at least as low as 25 deaths per 1000 live births. In contrast, 2018 estimates of child mortality for sub-Saharan Africa stand at 78 per 1000 live births. There is a need to identify simple, feasible and cost-effective interventions to reduce child mortality in low- and middle-income countries (LMICs).

Mass drug administration of azithromycin (MDA-azithromycin) has been effective in containing trachoma[2]. Recent studies have suggested that MDA-azithromycin can reduce child mortality rates[3,4]. Azithromycin is an effective antibiotic for the treatment of acute lower respiratory tract and enteric infections. Although the exact mechanism(s) through which MDA-azithromycin reduces child mortality has not been clearly elucidated, it has been postulated that one route may be through a reduction in the incidence of these infections[5,6,7]. In addition, azithromycin offers short-term protection against *P. falciparum* infection[8]. By decreasing the incidence of these three major causes of mortality, MDA-azithromycin may have an impact on overall child mortality, especially in countries with high under-five mortality and a heavy burden of morbidity due to diarrhoea, pneumonia and malaria.

GUIDELINE PURPOSE AND SCOPE: The purpose of the guideline was to provide an evidence-informed recommendation on whether mass drug administration of azithromycin, as a public health intervention for the reduction of under-five mortality, should (a) be rolled out universally in low-and middle-income countries, (b) be applied only in some situational contexts in low- and middle-income countries or (c) not be used at all.

GUIDELINE DEVELOPMENT PROCESS: In March 2018, the World Health Organization's department of Maternal, Newborn, Child and Adolescent Health (MCA) convened a meeting of technical experts to review newly available evidence on the effect of MDA-azithromycin on child mortality. Details of this meeting are provided in Annex 5. The MORDOR Trial reported a large and statistically significant reduction (13.5%) in overall under-five mortality across its three trial sites (in Niger, Malawi and Tanzania)[4]. This scientific consultation weighed all the available evidence on the effects of MDA-azithromycin on child survival and concluded that the weight of evidence was such that guidance should be provided by WHO for this intervention. WHO/MCA therefore decided to initiate a formal guideline development process towards making a recommendation for or against MDA-azithromycin.

This evidence-informed process was developed using the procedures outlined in the WHO handbook for guideline development. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was followed to prepare evidence profiles related to preselected topics which were based on up-to-date systematic reviews[9]. Developing and Evaluating Communication Strategies to support

1 United Nations Inter-Agency Group on Child Mortality Estimation (UN IGME). Levels and trends in child mortality: report 2019. New York: UNICEF. (https://childmortality.org/wp-content/uploads/2019/10/UN-IGME-Child-Mortality-Report-2019.pdf, accessed 6 May 2020).

2 Taylor HR, Burton MJ, Haddad D, et al. Trachoma. Lancet. 2014; 384:2142–2152.

3 Porco TC, Gebre T, Ayele B et al. Effect of Mass Distribution of Azithromycin for Trachoma Control on Overall Mortality in Ethiopian Children: A Randomized Trial. JAMA. 2009; 302:962-8.

4 Keenan JD, Bailey RL, West SK et al. Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa. N Engl J Med. 2018; 378:1583–1592.

5 Whitty CJ, Glasgow KW, Sadiq ST, et al. Impact of community-based mass treatment for trachoma with oral azithromycin on general morbidity in Gambian children. Pediatr Infect Dis J. 1999; 18:955–958.

6 Coles CL, Levens J, Seidman JC et al. Mass Distribution of Azithromycin for Trachoma Control Is Associated with Short-term Reduction in Risk of Acute Lower Respiratory Infection in Young Children. Pediatr Infect Dis J. 2012; 31:341–346.

7 Mkocha H, Munoz B, Seidman JC et al. Association of Mass Treatment with Azithromycin in Trachoma-Endemic Communities with Short-Term Reduced Risk of Diarrhea in Young Children. Am J Trop Med Hyg. 2011; 85:691–696.

8 Schachterle SE, Mtove G, Levens JP et al. Short-Term Malaria Reduction by Single-Dose Azithromycin during Mass Drug Administration for Trachoma, Tanzania. Emerg Infect Dis. 2014; 20(6):941-949.

9 Schünemann H, Brozek J, Guyatt G, Oxman A, editors. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) handbook 2013 [e-book].

Informed Decisions and Practice based on Evidence (DECIDE), an evidence-to-decision tool that includes intervention effects, values, resources, equity, acceptability and feasibility criteria, was used to guide how the recommendations were formulated by the Guideline Development Group.

Guideline scoping and outcome prioritization were carried out by the Guideline Development Group (members are listed in Annex 4). Evidence-informed recommendations were developed and finalized at a meeting of the guideline development group in Geneva (30 January–1 February 2019). Sixteen external experts served as technical peer reviewers for the preliminary version of this guideline.

Details on the guideline development process are provided in a subsequent section.

AVAILABLE EVIDENCE: The WHO Steering Committee commissioned three systematic reviews to synthesize the evidence relating to *(1)* overall efficacy and in terms of factors which might modify the effect of the intervention; *(2)* antimicrobial resistance (AMR); and *(3)* adverse effects, dose strength and regimen, and potential mechanisms of action whereby MDA-azithromycin is likely to reduce mortality.

After careful consideration of the evidence presented to it at this meeting, the GDG concluded:

- The three randomized controlled trials (RCTs) to evaluate the effect of MDA-azithromycin on mortality substantially differed in design: this precluded simple pooling of their results[3, 4, 10]. In the first two trials there was a statistically significant reduction in all-cause mortality among those randomized to MDA-azithromycin. In the third trial MDA-azithromycin when given with seasonal malaria chemoprophylaxis (SMC) did not reduce the composite outcome of hospitalization or mortality compared to SMC alone.
- All the studies reporting that MDA-azithromycin had an impact on mortality were conducted in sub-Saharan African countries with high under-five child mortality rates in malaria-endemic areas.
- The studies did not find any reduction in the incidence of acute respiratory tract infections, malaria or hospitalizations; two RCTs showed a significant reduction in the incidence of diarrhoea in children who received MDA-azithromycin.
- A few studies have demonstrated considerable resistance of faecal and nasopharyngeal flora to macrolide antibiotics in children receiving MDA-azithromycin. It is not clear whether the administration of MDA-azithromycin for longer time periods to improve childhood mortality would result in an increased circulation of resistant strains in the population. Little is known of the clinical implications of these observed changes.
- The adverse effects of azithromycin are mostly related to gastrointestinal symptoms: diarrhoea, vomiting, abdominal pain and nausea. Infants may possibly be at an increased risk of developing pyloric stenosis, particularly in the first month of life.

RECOMMENDATIONS: After carefully considering the balance of benefits and potential harms of the intervention, along with the values and preferences of the target population, and the ethical, acceptability and feasibility issues of using MDA-azithromycin in children with no clinical indication for treatment, the GDG made two recommendations on implementing MDA-azithromycin. The first recommendation addresses the question of whether the general use of MDA-azithromycin as a child survival intervention in LMICs is appropriate in view of the currently available evidence. The second recommendation offers guidance on a highly selective set of conditions in which MDA-azithromycin might be considered.

[10] Chandramohan D, Dicko A, Zongo I et al. Effect of Adding Azithromycin to Seasonal Malaria Chemoprevention. N Engl J Med. 2019; 380:2197-2206.

RECOMMENDATION 1:

WHO recommends against universal implementation of mass drug administration of azithromycin for prevention of childhood mortality.

(Strong recommendation, low quality evidence)

RECOMMENDATION 2:

WHO recommends that consideration be given to mass drug administration of azithromycin to children 1 to 11 months of age for prevention of childhood mortality in sub-Saharan African settings in which:

- **infant mortality is > 60 per 1000 live births or under-five mortality is > 80 per 1000 live births respectively, and**
- **infant and under-five mortality rates, adverse effects and antibiotic resistance (AMR) are continuously monitored, and**
- **implementation of existing child survival interventions, including seasonal malaria chemoprophylaxis where recommended, is concurrently strengthened.**

(Conditional recommendation, low quality evidence)

REMARKS BY GDG RELEVANT TO IMPLEMENTATION OF THE RECOMMENDATIONS:

- The suggested MDA-azithromycin regimen is presently 20 mg/kg oral azithromycin as a single dose every 6 months: additional work to confirm the optimal dose, frequency and number of intervention cycles is needed. If yearly MDA-azithromycin is provided as part of trachoma prevention programme to infants in target populations, they need only one additional dose in the year.
- Monitoring of AMR at the community level for all antibiotics in WHO's Essential Medicines List for the implementing country should include sentinel surveillance relating to the resistance of nasopharyngeal flora (*Streptococcus pneumoniae* and *Streptococcus pyogenes*), gut flora (*Salmonella spp., Shigella spp. and Enterobacteriaceae*) and common bacteria causing invasive infections.
- The US FDA, UK Medicines Regulatory Agency, Health Canada and Therapeutic Goods Administration (Australia), which approve the use of azithromycin in children for several conditions, all refer to a lack of information on safety and efficacy in children under 6 months. Pharmacovigilance is therefore essential in this age group.
- In settings in which seasonal malaria prophylaxis coverage (SMC) is low, SMC scale-up should take precedence over MDA-azithromycin implementation.
- Local consultation to confirm acceptability, optional participation and preferences, is an important element to consider when planning implementation
- This recommendation is applicable for 2-3 years from the publication of this guideline, at which point the guidelines are expected to be updated with new emerging evidence.

RATIONALE FOR THE RECOMMENDATIONS: the Guideline Development Group made its recommendations based on the following considerations:

Benefits

- MDA-azithromycin led to reduced child mortality (two of three RCTs, low quality evidence).
- All three RCTs were conducted in sub-Saharan African countries with high under-five child mortality rates.
- On subgroup analysis, the largest RCT showed a greater beneficial effect in infants aged less than 1 year than in children aged 1–5 years4.
- The overall risk of death was substantially higher in infants compared to older children in all studies.
- The intervention had no effect on acute respiratory tract infections, malaria or hospitalizations, but led to a lower incidence of diarrhoea in children aged 1–18 months.

Harms

- In treated children, although data are sparse, it has been suggested that the macrolide resistance of gut bacteria may increase after MDA-azithromycin.
- Repeated rounds of MDA may lead to a sustained increase in resistance and require a prolonged drug-free period before resistance declines.
- It is not clear whether mass drug administration of azithromycin over longer time periods to improve childhood mortality would result in the circulation of resistant strains in the community. Available data are insufficient to allow determination of the clinical and public health impact of such circulating resistant strains.
- The adverse effects of azithromycin are mostly gastrointestinal: diarrhoea, vomiting, abdominal pain and nausea. The risk of cardiac toxicity is unknown. There is probably an increased risk of pyloric stenosis developing in the youngest infants.

Values and preferences

- Based on the experience of GDG members, target populations are much more likely to give greater value to a reduction in child mortality than to antimicrobial resistance.
- While determining values and preferences, the GDG focused on mortality as the major benefit and AMR as the major harm of the intervention. One of the systematic reviews commissioned did relate to the safety of Azithromycin. The GDG considered that the azithromycin was generally a safe antibiotic, with mostly mild adverse effects. The two more serious effects, pyloric stenosis and prolonged QT interval, are very rare in the population of interest. The GDG, however, acknowledged the need for pharmacovigilance and therefore included this in their recommendations.

Acceptability

- Based on the extensive experience gained with MDA-azithromycin for trachoma, the GDG concluded that the intervention would be acceptable to local populations and deliverable by national health systems in settings for which the guidelines were applicable.

Feasibility (including resource use considerations)

- The cost of MDA-azithromycin is reasonable and not prohibitive for most low- and middle-income country settings. The intervention could be implemented using the existing human resources found in primary health care settings in these countries. Studies have shown that the cost per dose of MDA varies from $0.37 to $0.74, and the cost per DALY averted varies from $9.98 to $14.26[11,12,13].
- Were the intervention to go ahead, it would be necessary to ensure regular supplies of oral azithromycin and to train health care workers to monitor adverse drug effects and antibiotic resistance at the community level.
- The requirements as stipulated by the GDG in terms of pharmacovigilance and monitoring of antimicrobial resistance.

Equity

- The aim of the conditional recommendation to administer MDA-azithromycin to improve child survival in populations with very high infant and child mortality is to improve equity.
- As a strategy, mass drug administration is likely to achieve equitable population coverage. It is important however not to neglect marginalized populations (e.g. geographically remote or minority ethnic groups) when implementing MDA.

Ethical considerations

- Health inequalities exist because of poor access to potentially life-saving antibiotics in many low-resource settings. It is unethical that populations in low-resource, high-mortality settings should forego the use of antibiotics, particularly when they are potentially life-saving.
- It is difficult to resolve the conflict between current interests (potentially life-saving antibiotic used today) and future interests (effective antibiotics in the future provided antibiotic use today and emerging resistance can be reduced). Since the actual risk and onset of emerging resistance are unknown factors, and subsequent mortality and morbidity are hypothetical, the use of MDA-azithromycin is warranted in populations (with appropriate monitoring of mortality, AMR and pharmacovigilance) in which it is likely to lead to a substantial reduction in child mortality.

[11] Management Sciences for Health. International Medical Products Price Guide, 2015. Geneva: World Health Organization; 2016; :443. (http://msh-priceguide.org/wpcontent/uploads/2017/04/MSH-2015-International-Medical-Products-Price-Guide.pdf).

[12] Cost-effectiveness of mass treatment with azithromycin for reducing child mortality in Malawi: Secondary analysis from the MORDOR trial. Am J Trop Med Hyg. 27 Apr 2020. doi: 10.4269/ajtmh.19-0622 [Epub ahead of print].

[13] Brander RL, Weaver MR, Pavlinac PB et al. Projected impact and cost-effectiveness of community-based versus targeted azithromycin administration strategies for reducing child mortality in sub-Saharan Africa. Clin Infect Dis. 6 Jan 2020; pii: ciz1220. doi: 10.1093/cid/ciz1220 [Epub ahead of print].

- Given the possible adverse effects of azithromycin, locally appropriate consent should be sought and opt-outs made available to parents if mass drug administration is implemented.

Regulatory considerations

- The FDA (US), UK Medicines Regulatory Agency, Health Canada and Therapeutic Goods Administration (Australia) all approve the use of azithromycin in children for several conditions.
- All these regulatory agencies refer however to a lack of information on safety and efficacy in children aged under six months. Pharmacovigilance is therefore important in this age group.

After a substantial discussion of the above considerations, the GDG decided against a universal recommendation of MDA-azithromycin for LMICs.

The GDG took the view, however, that benefits outweigh harms in settings similar to those in which benefits were originally observed, i.e. settings in sub-Saharan Africa with very high infant and child mortality and a heavy disease burden owing to malaria, pneumonia and diarrhoea. The GDG therefore issued a conditional recommendation for use of MDA-azithromycin in infants aged 1–11 months in these settings. Their rationale for this narrow age range was that the intervention should be targeted at the subgroup in which the greatest benefit was observed, and its application limited to a smaller number of individuals in the community.

The GDG recommended that infant and child mortality and antimicrobial resistance should be monitored on a continuous basis, and that other ongoing child survival interventions should be strengthened concurrently.

Plans for updating the guideline: the GDG recommends updating or revising these guidelines within 2–3 years based on review of additional MDA-azithromycin data accruing from large ongoing studies and planned research investments.

INTRODUCTION

BACKGROUND

About 5.3 million children under the age of five died in 2018 *(1)*. Most of these deaths occurred in low-income countries, with the highest risk of death in sub-Saharan Africa (69 deaths per 1000 live births). Given that Sustainable Development Goal (SDG) 3 aims to end all preventable deaths of newborns and children under the age of five by 2030, there is a need to identify simple, feasible and cost-effective interventions to reduce the magnitude of deaths due to pneumonia, diarrhoea and malaria in LMICs.

Mass drug administration of azithromycin (MDA-azithromycin) has been an effective strategy for controlling neglected tropical diseases such as filariasis, trachoma, schistosomiasis and onchocerciasis; it has also been successful in containing trachoma *(2)*. Azithromycin itself is an effective antibiotic for treatment of acute lower respiratory tract and enteric infections. Although the exact mechanism(s) through which MDA-azithromycin reduces child mortality has not been clearly elucidated, it has been postulated that one route could be through a reduction in the incidence of these infections *(3–5)*. In addition, azithromycin also offers short-term protection against P. falciparum infection *(6)*. By decreasing the incidence of these three major causes of mortality, MDA-azithromycin may have an impact on overall child mortality, especially in countries with a high baseline of under-five mortality and related morbidity.

Trachoma has a predilection for the poorest, most remote communities with low levels of hygiene *(7)*. In areas where trachoma is endemic, active (inflammatory) trachoma is common among preschool children, with prevalence rates as high as 60–90%. *Chlamydia trachomatis* is spread by direct contact with fluid from an infected person's eyes or nose, or indirect contact with fluid via clothing or flies. Environmental risk factors include inadequate hygiene, crowded households, inadequate access to water and inadequate access to and use of sanitation *(8)*. Trachoma is hyperendemic in many of the poorest and most rural areas of 37 countries situated in Africa, Central and South America, Asia, Australia and the Middle East. It is endemic across Africa from South Sudan and Ethiopia (which have the highest prevalence of trachoma worldwide) across the Sahelian belt to Guinea and Mauritania in West Africa, as well as through eastern Africa and as far south as Malawi, Zambia and Mozambique. WHO estimates that there are 18 million cases of active trachoma in Africa, accounting for 85% of all cases worldwide. This large trachoma-endemic area in Africa encompasses 15 of the 20 countries with the highest reported under-five mortality rates worldwide (79–133 per 1000 live births in 2016) *(9)*. To eliminate trachoma, a four-pronged SAFE strategy has been adopted: surgery, mass antimicrobial distribution, facial cleanliness interventions and environmental improvement. To date, hundreds of millions of doses of azithromycin have been administered in trachoma control measures. WHO recommends that where the district-level trachoma (follicular) prevalence is ≥ 10%, the "A, F and E" elements should be implemented, including annual district-wide mass drug administration (MDA) of antibiotics (azithromycin 20 mg/kg) for at least three years before re-survey *(10)* .

In 2009, a striking finding was published from a cluster-randomized trial of mass azithromycin distribution in Ethiopia *(11)*. All community residents were randomly assigned to four study arms: annual or biannual azithromycin, quarterly azithromycin for children aged 1–9 years only, or no treatment (treatment delayed for a year). The mortality rate among children in treated communities was half that of untreated communities (OR: 0.51; p=0.02). A subsequent case–control analysis by the same group reported an OR of 0.31 (p=0.06) for the mortality rate among children aged 1–5 years. This effect was unlikely to have arisen from trachoma control given that the disease is non-fatal. More recently, the MORDOR trial *(12)* was conducted in areas of very low trachoma endemicity in Malawi, Niger and Tanzania to test whether biannual mass single-dose azithromycin distribution would reduce all-cause mortality in children. This

study also showed that the intervention had benefits in terms of reduction of child mortality and prompted initiation of this guideline development process.

PURPOSE AND SCOPE

The purpose of the guideline was to provide an evidence-informed recommendation on whether mass drug administration of azithromycin, as a public health intervention for the reduction of under-five mortality, should (a) be rolled out universally in low- and middle-income countries, (b) be applied only in some situational contexts in low-and middle-income countries or (c) not be used at all.

The guideline's target audience consists of public health policymakers at national and regional levels, programme implementation personnel and development partners involved in this potentially population-based intervention. The guideline is intended for any country considering this intervention, especially in a LMIC context.

KEY QUESTIONS (PICO)

In order to identify and evaluate the evidence for mass drug administration of azithromycin (MDA-azithromycin), the Guideline Development Group drew up nine priority questions on the safety and effectiveness of this intervention in children aged 1 to 59 months. These nine questions were bracketed into three categories: clinical efficacy in terms of reduced overall mortality and morbidity (questions 1–3) and potential modifying factors (questions 4–5); impact on antimicrobial resistance (questions 6–7); and issues relating to drug safety, dose and mechanism of action (questions 8–9).

Each question was described in terms of the following elements: population, intervention, control and outcomes (PICO).

1. Among children aged 1–59 months (P), does periodic MDA-azithromycin at intervals of up to 6 months (I), rather than placebo, co-interventions or no treatment (C), reduce the recipients' relative or absolute overall mortality risk (O)?
2. Among children aged 1–59 months (P), does periodic MDA-azithromycin (I), rather than placebo, co-interventions or no treatment (C), reduce the recipients' relative or absolute cause-specific mortality risk for malaria, diarrhoea, acute lower respiratory infections or other infectious diseases of public health importance (O)?
3. Among children aged 1–59 months (P), does periodic MDA-azithromycin (I), rather than placebo, co-interventions or no treatment (C), reduce the recipients' relative or absolute overall morbidity risk, outpatient clinic visits or hospitalizations, overall and especially for malaria, diarrhoea, acute lower respiratory infections or other infectious diseases of public health importance (O)?
4. Among children aged 1–59 months (P) exposed to periodic MDA-azithromycin (I), rather than placebo, co-interventions or no treatment (C), is the effect on mortality and concomitant side-effects or other risks (AMR) modified by treatment dose or duration (O)?
5. Among children aged 1–59 months (P), is the observed MDA-azithromycin effect on mortality modified by individual, population, regimen, co-intervention or other potential factors? Potential effect modifiers to be considered include but are not limited to geographical site, age structure of the population exposed, baseline mortality rate of the population, immunization status, malarial endemicity, concomitant seasonal malaria chemoprophylaxis, intermittent preventive treatment or bed-net usage,

administration of measles, rotavirus, pneumococcal, *Haemophilus* or other vaccines, water and sanitation, concomitant existence of a humanitarian crisis or any other identifiable and potentially important contextual variable.

6. Among children aged 1–59 months (P), does periodic MDA-azithromycin at intervals of up to 12 months (I), rather than placebo or no treatment (C), increase the recipients' relative or absolute risk of illness related to carriage of intestinal E. coli, Shigella spp., Salmonella spp., or nasopharyngeal S. pneumoniae bacteria with antimicrobial resistance (O) to azithromycin, other macrolides or other antibiotics. If yes, by how much and for how long?

7. Among older children, adolescents or adults in contact with the treated child(P), does periodic MDA-azithromycin at intervals of up to 6 months (I), rather than placebo or no treatment (C), increase the relative or absolute risk of carriage or illness related to intestinal E. coli, nasopharyngeal S. pneumoniae or other bacteria of public health importance (possibly Neisseria gonorrhoeae) with antimicrobial resistance to azithromycin, other macrolides or other antibiotics (O). If yes, by how much and for how long?

8. Among children aged 1–59 months (P), does periodic MDA-azithromycin at intervals of up to 6 months (I), rather than placebo or no treatment (C), increase the recipients' relative or absolute risk of side-effects of public health importance, e.g. cardiac arrhythmia or prolonged QT-time, or pyloric stenosis in younger age groups (O)?

9. 9. If MDA-azithromycin were to be recommended, what is the presumed mode of action and appropriate dose and formulation of azithromycin?

SUMMARIES OF EVIDENCE

OVERVIEW OF EVIDENCE RETRIEVAL, ASSESSMENT AND SYNTHESIS

Three separate evidence reviews were commissioned:

(i) on clinical efficacy and potential effect modifiers;

(ii) on antimicrobial resistance,

(iii) on drug safety (side-effect profile), dose, duration and potential mechanisms of action (for mortality reduction and AMR).

A protocol was developed for each systematic review which included the search terms and strategy, and the associated PICOs used to define inclusion and exclusion criteria. A detailed search strategy for each priority question was decided after a series of discussions between the Guideline Steering Group (GSG) and the lead investigators for each systematic review.

Evidence synthesis for each review is summarized below. In broad terms, each review began with a comprehensive search strategy, identifying and retrieving relevant evidence including evidence for all key outcomes as defined in the key PICO questions. Although there were slight variations in the specific search strategy adopted for each systematic review, in general they included standard electronic databases such as the Cochrane Library, PubMed, Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL), as well as manual research for available evidence and systematic reviews published in relevant conference proceedings and handbooks issued by other health agencies.

Papers identified by the search strategy were screened for inclusion based on their title and abstract. Full texts were reviewed either if an abstract was unavailable and if the abstract indicated a potentially eligible study.

The PRISMA reporting standards flowchart was used to illustrate the search and data extraction process. Inclusion and exclusion criteria were defined for each systematic review. PRISMA reporting standards were also used to draft the systematic review reports based on either randomized controlled trials or observational evidence.

The section below highlights key evidence and findings relevant to each review.

REVIEW 1: EFFECT OF MASS DRUG ADMINISTRATION OF AZITHROMYCIN ON MORTALITY AND MORBIDITY

Evidence sources: Studies selected included both randomized controlled trials and observational studies evaluating the effect of periodic MDA-azithromycin on mortality and morbidity in children aged 1–59 months in any healthcare or community setting.

The types of interventions included were mass drug administration (MDA) of azithromycin as a single dose or in multiple doses at periodic intervals during the study period; *control*: placebo or no treatment.

The authors searched the following electronic databases - MEDLINE via PubMed (up to October 2018), Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, up to Issue 10, 2018), WHOLIS (1986–October 2018) and Web of Science (1990–October 2018) using the search terms ('macrolide' OR 'azithromycin') AND ('child'). They also contacted eminent researchers in this field for information on unpublished and ongoing trials. A search was also made through the reference list of all the trials identified by the above methods.

Overall, a total of 7355 citations were identified, of which 19 were found to be eligible for inclusion in the review. A list of articles excluded after assessing the abstract and/or full text is provided in the appendix. One additional study was identified by the WHO team. A total of 20 articles was therefore included in the review (Annex 1 – PRISMA flowchart).

SYNTHESIS OF RESULTS

All-cause mortality

A total of five studies reported results on the risk of all-cause mortality following MDA-azithromycin in enrolled children *(11–15)*. Of the five, only three were considered by the GDG for assessing the intervention effect *(11–13)*. The remaining two studies were not taken into account: an observational study from Ethiopia with a high risk of selection bias *(14)* and a randomized trial from Niger which primarily compared two different MDA-azithromycin regimens (biannual vs. annual treatment) but without a placebo control *(15)*.

The three studies considered by the GDG were RCTs: the first was conducted in Ethiopia *(11)*, the second was a multi-country cluster RCT in three sub-Saharan countries (Malawi, Niger and Tanzania) *(12)* and the third was a cluster randomized trial in two other sub-Saharan countries (Mali and Burkina Faso) *(13)*. Altogether, the three studies enrolled about 230 000 children (Annex 1). All six countries in which these studies were conducted have high under-five mortality rates (U5MR) ranging from 55 per 1000 live births in Malawi to 111 per 1000 live births in Mali *(16)*.

The first study combined three arms of annual, biannual and quarterly MDA-azithromycin into a single intervention group and then compared it with the placebo control group *(11)*, the second study compared four biannual doses of azithromycin with placebo *(12)* while the third study used three consecutive daily doses on a monthly basis for four months during the peak malaria seasons over three years *(13)*. Two studies adopted a uniform dose of azithromycin (20 mg/kg) at each administration *(11, 12)* while the third used doses of 100 mg and 200 mg for infants aged 3–11 months and children aged 1–5 years, respectively *(13)*. One trial included a co-intervention – seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine and amodiaquine – in both study arms *(13)*.

The first trial reported mortality one year after the intervention *(11)* while the second reported mortality 26 months after initiation of the intervention *(12)*. The third study had reported mortality in children aged under five only during the four months of the peak malaria season each year, but for the purpose of the guideline the GDG considered the mortality risk in children aged under five during the entire three-year study period, using additional data obtained from the study authors *(13)*.

Table 1: MDA-azithromycin studies reporting all-cause mortality

Study, year, country	Study design	Study population and sample size	Intervention	Results	Comments
Porco 2009 *(11)*; Ethiopia	Cluster RCT	Children (aged 1–9 years): N=18215	*Intervention:* Annual, biannual or quarterly administration of azithromycin *Control:* Not receiving MDA-azithromycin	*Mortality one year after MDA-azithromycin initiation:* 5.7 vs 12.1 deaths per 1000 person-years; **Adjusted IRR: 0.53 (95% CI: 0.26–0.84)**	Mortality risk in study children aged 1–5 years considered for this guideline
Keenan 2018 *(12)*; Malawi, Niger, Tanzania	Cluster RCT	Infants aged 1–59 months; N=97047+ 93191	*Intervention:* 4 biannual doses of azithromycin *Control:* Placebo	*Mortality 26 months after MDA-azithromycin initiation:* 14.6 vs 16.5 deaths per 1000 person-years; **Adjusted IRR: 0.86 (95% CI: 0.80–0.93)**	Significant reduction found only in one country (Niger) but not in the other two countries
Chandramohan 2019 *(13)*; Mali, Burkina Faso	Cluster RCT	Infants aged 3–59 months; N=9735+9843	*Intervention:* 4 times annual administration of antimalarial prophylaxis plus azithromycin on days 1,2 and 3, for 3 years *Control:* Antimalarial prophylaxis *plus placebo*	*Mortality by three years after MDA-azithromycin initiation:* 6.0 vs 5.4 deaths per 1000 person-years at risk; **Adjusted IRR: 1.11 (95% CI: 0.87–1.42)**	A co-intervention (seasonal antimalarial chemoprevention; SMC) was used in both intervention groups. SMC is the standard of care in these two countries. Deaths in children up to 5 years of age during the three malaria-transmission seasons were reported in the published paper. All under-five deaths during the entire study period were considered for this guideline (additional data obtained from the authors)

(RCT: randomized controlled trial; IRR: incidence rate ratio)

The GDG was strongly of the opinion that data from the three studies should not be pooled because of the heterogeneity between them regarding the type of intervention (dose, duration and co-intervention), outcome (time of measurement and composite outcome of hospitalization or death in the third study) and geographical context. The first study in Ethiopia *(11)* was an evaluation trial for trachoma elimination that incidentally showed a reduction in childhood mortality in the intervention communities, while the second study in Malawi, Niger and Tanzania was a large-scale, rigorously conducted cluster RCT to evaluate the effect of the intervention on mortality *(12)*. The third trial provided for both intervention and control groups to receive an additional intervention, i.e. seasonal malaria chemoprevention (SMC) in malaria-endemic areas *(13)*.

The GDG therefore considered the results of the three studies separately. The study in Ethiopia showed a significantly reduced risk of mortality one year after the intervention (adjusted IRR: 0.53; 95% CI: 0.26–0.84) in children aged 1–5 years *(11)*. The cluster RCT in Malawi, Niger and Tanzania also showed a significant reduction in mortality 26 months after the intervention in children aged 1–5 years (incidence rate ratio: 0.86; 95% CI: 0.80–0.93). Subgroup analysis of the study revealed that there was a significant reduction in mortality in one country only (Niger) but not in the other two countries *(12)*. The third trial involving SMC did not show any reduction in a combined outcome of hospitalization or mortality risk in children aged 3 to 59 months over its three year duration (incidence rate ratio: 1.11; 95% CI: 0.87–1.42) *(13)*.

In view of these serious inconsistencies (the first study showing a remarkedly large mortality reduction *(11)*, the second, multi-country study reporting a significant reduction overall but inconsistent results for different ages and settings *(12)* and the third study *(13)* failing to find any significant difference in the risk of hospitalization or mortality) and heterogeneity (lack of uniformity of studies which precluded pooling of their data), the quality of evidence was graded as ***low***.

Subgroup analysis: Two studies included infants aged less than a year *(12, 13)*: subgroup analysis of intervention effects on age-linked mortality (aged < 1 year vs 1–5 years) was conducted for these studies. In one of them, beneficial effects were similar for infants aged less than a year (RR: 0.81; 95% CI: 0.72–0.91) and children aged 1–5 years (RR: 0.88; 95% CI: 0.82–0.96) *(12)*. The other study failed to detect a significant impact for either age subgroup, although the trend was beneficial for infants aged less than a year (RR: 0.77; 95% CI: 0.42–1.41) but not in children aged 1–5 years (RR: 1.17; 95% CI: 0.90–1.53). Confidence intervals in these groups however overlapped *(13)*.

One study compared the risk of mortality with different azithromycin regimens. It found no evidence of any difference in the risk of mortality between groups of children receiving biannual treatment, and those receiving annual treatment for three years (IRR: 0.81; 95% CI: 0.66–1.0) *(15)*.

Infection-related mortality

Only a single study – the multi-country RCT in Mali and Burkina Faso – reported on the risk of infection-related mortality, i.e. deaths secondary to ARI, acute febrile illness, malaria and other infectious causes *(13)*. There was no reduction in this risk with MDA-azithromycin (RR: 1.26; 95% CI: 0.79–2.0). Two other studies reported that infection-related deaths accounted for 40–71% of total deaths but did not provide separate details on the incidence of infection-related mortality in the two groups *(11, 12)*.

Morbidity

Acute respiratory infection (ARI)

Two cohort studies *(4, 17)* and two cluster RCTs *(3, 13)* examined the effects of MDA-azithromycin on the incidence of ARI. While one study was conducted in Nepal *(17)*, the other three were conducted in Tanzania *(4)*, Gambia *(3)* and Mali and Burkina Faso *(13)*. None of the studies showed any reduction in the risk of ARI with MDA-azithromycin. The quality of evidence was graded as ***low***.

Diarrhoea

The four studies that investigated the incidence of ARI also reported on the incidence of diarrhoea *(3, 5, 13, 17)*. The two cohort studies did not find any difference between MDA-azithromycin versus no azithromycin,

but the two cluster RCTs showed a significantly reduced risk of diarrhoea (RR: 0.52, 95% CI: 0.41–0.66 (3) and RR: 0.85, 95% CI: 0.79–0.91 (9)). The quality of evidence was graded as ***low***.

Malaria

Two studies – one observational study in Tanzania *(6)* and one RCT in Mali and Burkina Faso *(13)* – reported on the incidence of malaria. While the former reported a significantly reduced risk of P. falciparum parasitemia in children aged 1–10 years (RR: 0.32; 95% CI: 0.12–0.87), the latter reported no difference in the incidence of laboratory-confirmed malaria in children aged 0–5 years (RR: 0.97; 95% CI: 0.94–1.01). The quality of evidence was graded as ***very low***.

Hospitalizations

Only one study – the multi-country RCT in Mali and Burkina Faso *(13)* – reported on the incidence of hospital admissions for four months every year following MDA-azithromycin versus placebo. It found no reduction in the incidence of hospitalizations (RR: 0.98; 95% CI: 0.79–1.2). Malaria was the most common cause of hospitalization (72%). The quality of evidence was graded as ***very low***.

(GRADE tables for all the above outcomes are displayed in Annex 1.)

REVIEW 2: EFFECT OF MASS DRUG ADMINISTRATION OF AZITHROMYCIN ON ANTIMICROBIAL RESISTANCE

A systematic literature search was undertaken to identify published clinical evidence relevant to the review question. The authors searched MEDLINE and Embase using relevant medical subject headings, free-text terms and study-type filters; search terms included variations of "macrolides" or "azithromycin", "mass drug administration", "antimicrobial resistance" and "child", and the Cochrane filter was applied for "randomized controlled trials". Most of the studies included were from the African continent but a few studies carried out in a non-African setting, e.g. in Nepal or Australia, were included owing to their similar study design. The search covered manuscripts published from 1997 to the most recent studies in 2019.

Potentially relevant studies were identified from the search results by reviewing titles and abstracts. Full papers were then obtained and reviewed against pre-specified inclusion and exclusion criteria in order to identify those studies that addressed the review question. If there was any uncertainty as to whether articles met the inclusion criteria they were discussed with the other co-authors. Articles selected for full-text review were obtained using MEDLINE or Embase via Ovid. The names of article authors appearing in the search results were not blinded for abstract or full-text review.

Studies included had been carried out in children aged 1–59 months or their household contacts, mostly in the African region. Interventions included MDA with azithromycin, clarithromycin or erythromycin at intervals of up to 12 months. Selected studies reported on AMR testing on intestinal, nasopharyngeal or conjunctival samples and cleared the Cochrane filter for randomized controlled trials.

In total, 26 articles were identified. Eighteen of these studies met the inclusion criteria and were included in the final analysis (see the PRISMA figure in Annex 2). Most studies took place in either eastern (6/18, 33%) or western Africa (5/18, 28%): five (28%) were randomized controlled trials.

SYNTHESIS OF RESULTS

Impact on carriage of resistant gut bacteria: treated children

Macrolide resistance

Susceptibility data on gut bacteria after MDA-azithromycin were sparse. Results from one randomized controlled trial in Tanzania show that single MDA-azithromycin treatments seem to substantially increase the rate of macrolide-resistant E. coli *(18)*. Younger age and previous diarrhoea were associated with increased odds of resistance carriage, probably because these children are more exposed to circulating environmental strains via faecal-oral transmission routes. Resistance carriage tapered over time, but macrolide resistance remained elevated over baseline levels six months after dosing and underlying resistance genes may persist *(18)*.

The trial by Doan et al. *(19)* is nested in the MORDOR study *(12)*: it reports an increase in macrolide genetic determinants in the gut of preschool children after four biannual azithromycin treatments compared to placebo. No difference had been observed at baseline. This finding indicates that selective pressure from the distributed treatments increased macrolide resistance.

Resistance to other antibiotics

Co-resistance to other classes of antibiotics would present a major public health concern. Doan et al. *(19)* were unable to demonstrate a significant difference between the MDA versus placebo group for any non-macrolide resistance determinants using phenotypic assays or unbiased sequencing.

Impact on carriage of resistant nasopharyngeal bacteria: treated children

Macrolide resistance

Absence of macrolide resistance in nasopharyngeal *S. pneumoniae* after one round of MDA-azithromycin emerged in several studies in Nepal and Tanzania, all of which showed that substantial AZM resistance did not develop between 6–12 months after a single treatment dose *(20)*, especially in areas where baseline carriage prevalence of resistant strains was low *(21)*. Even on repeated annual mass treatments with AZM, pneumococcal macrolide resistance has not been shown to exceed 5% six months after a second treatment *(17)*. It is therefore likely that less frequent antibiotic distributions select for lower pneumococcal resistance *(17, 20, 21)*.

Additional exposure to multiple rounds of MDA-azithromycin seems to increase drug-resistant pathogens independently of baseline resistance rates. Studies demonstrating a baseline macrolide resistance rate for *S. pneumoniae* of ≤ 5% *(22-24)* report sharp rises in AZM-resistant pneumococcal isolates, peaking at up to 80% shortly after multiple mass azithromycin treatments. Although resistance rates dropped again after cessation of MDAs, they did not return to baseline levels again. The recent placebo-controlled trial by Doan et al. reports macrolide resistance rates in nasopharyngeal pneumococcus after multiple MDAs that are about four times higher than in placebo controls. Systematic reviews of the literature in fact show that resistance increases with multiple rounds of azithromycin for trachoma, at least in studies that were able to isolate pneumococci successfully in most children. An important limitation in some of these studies is the lack of pre-treatment baseline measurements of *S. pneumoniae* antibiotic resistance in the treated or untreated teams, making it difficult to determine whether resistance selection was due primarily to the

trachoma control programmes. These results are challenged by the Gambian trial by Burr et al., which did not find evidence of a pronounced rise of pneumococcal macrolide resistance after one or multiple MDA rounds *(25)*.

There is some evidence to suggest that pneumococcal resistance may decline over time in the absence of any further treatment. In the non-controlled study of a single community in Australia described above, respectively 55% and 35% of treated children exhibited macrolide resistance 2–3 weeks and two months after a single dose of azithromycin, whereas only 6% did so six months later *(19)*. Although this community did not receive mass azithromycin—approximately half of the children received azithromycin—the study nonetheless suggests that resistance reduces in an individual child after the antibiotic selection pressure is lifted. This has been confirmed by studies carried out in Ethiopia in which the prevalence of pneumococcal macrolide resistance decreased substantially after cessation of mass azithromycin treatments: from about 80% to 20% 12–24 months after the final treatment.

Resistance to other antibiotics

Three MDA-azithromycin rounds in Gambia were associated with a short-term increase in the prevalence of nasopharyngeal azithromycin-resistant or macrolide-inducible clindamycin-resistant *S. aureus (26*). Resistance rates dropped again after MDA-azithromycin cessation, but not to baseline levels.

Studies after single or multiple MDA provision of a macrolide have not demonstrated persistent resistance development in nasopharyngeal S. pneumoniae to penicillin. However, there is evidence that increased cotrimoxazole resistance is common *(20, 21)*. Coles et al. *(27)* found increasing cotrimoxazole resistance in the non-MDA-treatment arm compared to similar same baseline levels of resistance in both treatment and non-MDA-treatment arms. Doan et al. reported high levels of cotrimoxazole resistance, but no difference in resistance between treatment groups (multiple MDA versus placebo). Cotrimoxazole is still indicated in various infections, although it is no longer the WHO-recommended antibiotic for community-acquired pneumonia. Cross-resistance with sulfadoxine/pyrimethamine has been described: treatment of malaria with this medication has resulted in increased colonization with cotrimoxazole-non-susceptible S. pneumoniae. However, limited data are available to indicate whether cotrimoxazole resistance is persistent.

Children have been observed to carry high rates (13–15%) of tetracycline-resistant *S. pneumoniae* strains at baseline before MDA treatment *(22, 23)*. Although Keenan et al. did not report an increase in the proportion of tetracycline-resistant isolates after mass antibiotic treatments, Skalet et al. showed increasing numbers after a year, both in treated children and time-matched untreated controls. Another study by Keenan reported high rates of tetracycline resistance a few months after repeated rounds of MDA. Pre-treatment data were not collected, so it remains uncertain whether the effect is fully linked to previous azithromycin treatment.

Skalet et al. *(22)* and Haug et al. *(28)* have described a non-significant trend of rising clindamycin resistance after several courses of MDA-azithromycin, while Doan et al. reported a significant difference in pneumococcal clindamycin resistance between the MDA and placebo groups. Another study *(17)* found no clindamycin-resistant S. pneumoniae strains after a single MDA treatment.

Information on pneumococcal resistance to sulfamethoxazole or chloramphenicol is sparse and does not show a consistent pattern.

No meropenem- or levofloxacin-resistant pneumococcus strains were identified in either of the treatment groups in the recent placebo-controlled trial by Doan et al.

Impact on carriage of resistant gut bacteria: household contacts

Macrolide resistance

A study carried out in Tanzania suggests moderate rates of azithromycin resistance in E. coli isolates among children born after the last of four MDA-azithromycin treatments *(29)*.

Impact on gut microbiome and co-resistance

The gut is known to be a reservoir for antibiotic resistance genes. Antibiotics save lives, but can cause dysbiosis of the gut microbiota, i.e. a disturbance in its composition and function, and select for antibiotic-resistant microbes. Several studies have evaluated the effects of antibiotic exposure on paediatric gut microbiome diversity, with conflicting results. One recent study evaluated the effects of azithromycin on gut microbiome diversity in children from an antibiotic-naive community in Niger using 16S rRNA gene sequencing. In this double- blind, randomized, controlled trial, healthy children treated with one dose of AZM showed a reduction in the intestinal microbial y-diversity five days after treatment. Furthermore, AZM caused community-level alterations, as demonstrated by reduced total microbiome richness (y-diversity) in the treatment group compared with the placebo group.

Selection for resistant bacteria may limit our future ability to control previously treatable and emerging infections. Once antibiotic treatment is stopped, the microbiota may present a certain degree of resilience, being capable of returning to a composition similar to its initial state, although it often does not completely recover. Accordingly, antibiotic-induced microbiota alterations including resistant strains may persist, even when treatment was discontinued a long time beforehand. This concern is compounded by the possible development of co-resistance, in which complex multidrug resistance phenotypes affect different antimicrobial classes.

Impact on carriage of resistant nasopharyngeal bacteria: household contacts

Macrolide resistance

Most studies have focused on the impact of resistance at the level of the individual child. Information on the impact of MDA-azithromycin on antibiotic resistance in populations is therefore limited, in spite of the fact that exposed children eventually return to the non-exposed population and, moreover, that they are likely to transmit colonizing pathogens to other household members. One Tanzanian study reported high AZM resistance rates in nasopharyngeal *S. pneumoniae* and *S. aureus* isolates from children living in a district where multiple MDA rounds had ceased four years beforehand, suggesting transmission of resistant isolates between household contacts *(29)*. However, without any pre-treatment resistance data this conclusion remains speculative.

Resistance to other antibiotics

No studies were identified which investigated antibiotic resistance (other than macrolide-related) in the respiratory bacteria of household contacts of MDA-treated children.

SUMMARY

The beneficial effects of mass azithromycin treatments for endemic diseases are clear. MDA-azithromycin for trachoma has been very successful in reducing the prevalence of ocular strains of chlamydia, and may result in the elimination of infection in some areas. The adverse effects of mass treatments are much less certain. Although some studies show considerable faecal and nasopharyngeal macrolide resistance following regular MDA-azithromycin, these studies are often predicated on the assumption that MDA will be discontinued in a relatively short timeframe. In such cases, macrolide resistance, especially in *S. pneumonia*, may revert to baseline levels. It is uncertain whether MDA programmes implemented for longer time periods to improve childhood mortality outcomes might breach a specific threshold resistance and thereby become prevalent enough to sustain the circulation of resistant strains: their impact on enteric pathogens in particular and the clinical impact of circulating resistant strains cannot be determined based on currently available data.

Implications for the future

For future studies, an improved standardized approach to monitoring emerging resistance is needed to detect unintended consequences. Given that azithromycin is administered at the community level, resistance surveillance should aim to obtain repeated cross-sectional data for colonizing bacteria across exposed communities (children and adults) rather than focusing solely on exposed children. Relevant target bacteria include *S. pneumoniae, S. aureus* and *S. pyogenes* (nasopharyngeal) and gram-negative species, including *Salmonella* spp., *Shigella* spp. and the *Enterobacteriaceae* (e.g. *E. coli* and *Klebsiella* spp.) as these are also key human pathogens, and resistance mechanisms may affect the efficacy of "Access" category antibiotics in WHO's essential medicines list (EML) for the treatment of severe bacterial infections. In addition to community-based surveillance, tracking changes in the resistance of pathological organisms in children with severe illness who present to health facilities in the exposed areas is important in order to register any adverse clinical effects.

REVIEW 3: SERIOUS ADVERSE EFFECTS AND DOSE FOR MASS DRUG ADMINISTRATION OF AZITHROMYCIN

Overall safety of azithromycin

A literature search was made of the MEDLINE, PubMed, the Cochrane Central Register of Controlled Trials, Embase, CINAHL and International Pharmaceutical Abstracts databases. All searches extended from the origins of the database until October 2018 and included all languages. The authors scanned adverse drug reaction (ADR) spontaneous reporting systems and safety communication announcements. The search strategy included a combination of the medical subject headings and the free-text terms "azithromycin" and "children". Various inclusion criteria were applied. *(1)* Patients: infants, toddlers, children and adolescents aged from 1 month to 18 years with any disease condition, or healthy. *(2)* Intervention/Exposure: azithromycin. *(3)* Comparison: other medicines, placebo or no comparison. *(4)* Study design: randomized controlled trials, cohort studies, case-control studies, case series, case reports and pharmacokinetics studies. Studies enrolling newborns only (0–28 days) were excluded.

Patients were divided into three age groups: infants and toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 18 years) based on the guidelines of the International Council for

Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The daily dosage of azithromycin for children was divided into four groups following the guidelines of the World Health Organization (WHO) and British National Formulary (BNF): 1) < 10mg/kg, 2) 10–20mg/kg, 3) 20–30mg/kg and 4) ≥ 30mg/kg. Adverse events (AEs) and ADRs were categorized using the terminology supplied by the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1) *(30)*.

The authors calculated the pooled incidence of AEs/ADRs based on number of events in a defined number of participants in randomized controlled trials (RCTs) and prospective cohort studies. These trials and studies then underwent meta-analysis. Pre-planned subgroup analyses of age and daily dosage in RCTs and prospective cohort studies were done for common AEs/ADRs detected by pooled incidence.

A total of 118 articles reporting on azithromycin safety were identified after the literature search: these included 78 RCTs, 20 prospective and seven retrospective cohort studies, 11 case reports and two pharmacokinetic studies (see the PRISMA figure in Annex 3) and pooled a total of 146 102 patients aged from 1 month to 18 years.

Of the 78 RCTs, 72 evaluated the effectiveness and safety of azithromycin in the treatment of infectious diseases and/or symptoms, two in persons with asthma-like symptoms and one in obsessive–compulsive disorder, while three specifically evaluated the effectiveness and safety of MDA-azithromycin. For this last group, two RCTs compared annual treatment (a single oral dose of azithromycin, height-based dosing equivalent to 20 mg/kg) with biannual treatment (a single oral dose every six months, two rounds, height-based dosing equivalent to 20 mg/kg). The other RCT compared biannual mass oral azithromycin (a single oral dose every six months, four rounds, approximately 20 mg/kg) with placebo. Eleven RCTs compared azithromycin with placebo, while others assessed the comparative safety of azithromycin in relation to other antibiotics. Seven RCTs compared azithromycin in different dosages and for different durations.

Overall risk of adverse events

The overall risk of AEs in the non-MDA-azithromycin randomized controlled trials and prospective cohort studies showed that gastrointestinal AEs were the most common. Diarrhoea was the most common AE, accounting for 18.7% of all AEs with a risk of 3.61 per 100 children. Other common AEs included vomiting (risk: 2.51 per 100 patients), abdominal pain (risk: 1.33 per 100 patients) and nausea (risk: 0.74 per 100 patients).

Adverse events in MDA-azithromycin studies

Adverse events (AEs) were inadequately reported in the three RCTs that evaluated MDA-azithromycin. Two studies *(11, 15)* described no serious AEs but gave no details of safety monitoring. The MORDOR study *(12)* reported 11 cases of serious AEs (4 malaria, 1 respiratory infection, 1 ileus, 1 coma and 4 deaths) among 97 047 children based on a system of spontaneous reporting by village informants and health facilities. Toxicity in MDA-azithromycin studies was poorly reported, with only 11 AEs reported in 103 488 patients. By contrast, the 74 RCTs that did not involve MDA-azithromycin detected 2203 AEs in 9558 children.

Cardiac toxicity

Most studies in children did not evaluate the risk of cardiac toxicity. Three randomized controlled trials reported on cardiac adverse events, with two studies recording the QT interval on the electrocardiogram (ECG). One study in Egypt described a prolonged QT in 50 out of 61 children (82%) receiving azithromycin (250mg for children ≤ 25 kg, 500 mg for children > 25 kg, weekly for 6 months) *(31)*. The other 11 children showed a shortened QT. In this study however, the authors failed to report criteria for diagnosing QT interval prolongation and shortening. Moreover, no details were supplied on how the QT interval was measured

or calculated. The control group did not have ECGs, making a robust interpretation of the reported data extremely difficult. These results should therefore be interpreted with caution.

One study in 31 children aged 4 to 14 years with acute-onset neuropsychiatric syndrome reported two cases of borderline QTc (440–460 ms) and four cases of raised heart rate *(32)*. The borderline ECGs were considered abnormal by cardiologists who reviewed them. The children had received azithromycin (10 mg/kg up to 500 mg per day) or placebo for 4 weeks. One child in the placebo group had a raised heart rate.

One study reported an irregular heart rate in 10 out of 140 (7.1%) wheezy preschool children aged 12–60 months receiving 5 days' azithromycin (10 mg/kg on day one, and 5 mg/kg for next four days). Four out of 139 children in the control group exhibited an irregular heart rate *(33)*.

Pyloric stenosis

A retrospective cohort study *(34)* compared the rate of idiopathic hypertrophic pyloric stenosis (IHPS) in infants who received azithromycin (n=4875) with that of infants who did not receive a macrolide during the first 90 days of life (n=1 067 459). Results showed that exposure to azithromycin did not increase the risk of IHPS (RR: 0.71, 95% CI: 0.36–1.43). However, when stratified by age at the time of exposure, the risk of IHPS increased if azithromycin exposure occurred in the first two weeks of life (adjusted OR: 8.26; 95% CI: 2.62–26.0). This risk persisted, although to a lesser degree, in infants who had been exposed to azithromycin between 2 and 6 weeks of age (adjusted OR: 2.98; 95% CI: 1.24–7.20).

Conclusions

Azithromycin toxicity is mainly related to gastrointestinal symptoms: diarrhoea, vomiting, abdominal pain and nausea. The risk of cardiac toxicity is unknown. There is probably an increased risk of pyloric stenosis developing in the youngest infants. Evidence on potential harm is almost entirely derived from studies in which the macrolide was not administered as MDA-azithromycin. The evidence of risks following MDA-azithromycin for infants in resource-poor countries are based on a limited number of studies.

Azithromycin dose and formulation

Dose

The MDA-azithromycin dose applied was similar in trachoma and malaria studies (20 mg/kg, up to a maximum dose of 1 g). In yaws, a dose of 30 mg/kg azithromycin was used in most studies (n=5) whereas a dose of 20 mg/kg was used in two studies. A dose of 20 mg/kg was used in four studies *(11, 12, 14, 15)* that investigated the effect of MDA-azithromycin on mortality.

Formulation

The formulation was poorly documented in the studies: most failed to report the formulation used. A suspension was usually used for younger children (usually children aged 1–7 years or unable to swallow). One study applied a weight of <15 kg as a cut-off point for distribution of suspension. Tablets were used for older children.

Treatment frequency and duration

A single dose of azithromycin was administered at varying intervals and for different durations. In the four studies that investigated mortality, the frequency ranged from one dose to six-monthly for three years. One

study also evaluated annual, six-monthly and quarterly administration. The largest study evaluated MDA-azithromycin at six-monthly intervals over a period of two years.

Mode of action

The mode of action of azithromycin in relation to its possible beneficial effect on mortality in young children is unclear. No study evaluating this effect and its impact on individual infectious diseases has investigated its mode of action.

Conclusion

A dose of 20 mg/kg azithromycin administered as a suspension at six-monthly intervals for a maximum of two years was delivered in the largest study evaluating its effect on mortality. This study found evidence of reduced child mortality. It would therefore be reasonable to use this dose, formulation and regimen in any further studies to determine whether MDA-azithromycin reduces child mortality.

RECOMMENDATIONS

THE GDG MADE TWO RECOMMENDATIONS:

RECOMMENDATION 1:

WHO recommends against universal implementation of mass drug administration of azithromycin for prevention of childhood mortality.

(Strong recommendation, low quality evidence)

RECOMMENDATION 2:

WHO recommends that consideration be given to mass drug administration of azithromycin to children 1 to 11 months of age for prevention of childhood mortality in sub-Saharan African settings in which:

- **infant mortality is > 60 per 1000 live births or under-five mortality is > 80 per 1000 live births respectively, and**
- **infant and under-five mortality rates, adverse effects and antibiotic resistance (AMR) are continuously monitored, and**
- **implementation of existing child survival interventions, including seasonal malaria chemoprophylaxis (SMC) where recommended, is concurrently strengthened.**

(Conditional recommendation, low quality evidence)

REMARKS BY GDG RELEVANT TO IMPLEMENTATION OF THE RECOMMENDATIONS:

- The suggested MDA-azithromycin regimen is presently 20 mg/kg oral azithromycin as a single dose every 6 months: additional work to determine the optimal dose, frequency and number of intervention cycles is needed. If yearly MDA-azithromycin is provided as part of trachoma prevention programme to infants in target populations, they need only one additional dose in the year.
- Monitoring of AMR at the community level for all antibiotics in WHO's "Access" category in the EML list for the implementing country should include sentinel surveillance relating to the resistance of nasopharyngeal flora (Streptococcus pneumoniae and Streptococcus pyogenes), gut flora (Salmonella spp., Shigella spp. and Enterobacteriaceae) and common bacteria causing invasive infections.
- The US FDA , the UK Medicines Regulatory Agency, Health Canada and Therapeutic Goods Administration (Australia), which approve the use of azithromycin in children for several conditions, all refer to a lack of information on safety and efficacy in children under 6 months. Pharmacovigilance is therefore essential in this age group.
- In settings in which seasonal malaria prophylaxis (SMC) coverage is low, SMC scale-up should take precedence over MDA-azithromycin implementation.

- Local consultation to confirm acceptability, optional participation and preferences, is an important element to consider when planning implementation
- This recommendation is applicable for 2-3 years from the publication of this guideline, at which point the guidelines are expected to be updated with new emerging evidence

RATIONALE FOR THE RECOMMENDATIONS

The Guideline Development Group made its recommendations based on the following considerations:

Benefits

- MDA-azithromycin led to reduced child mortality (two of three RCTs, low quality evidence).
- All three RCTs were conducted in sub-Saharan African countries with high under-five child mortality rates.
- On subgroup analysis, the largest RCT showed a greater beneficial effect in infants aged less than 1 year than in children aged 1–5 years.
- The overall risk of death was substantially higher in infants compared to older children in all studies.
- The intervention had no effect on acute respiratory tract infections, malaria or hospitalizations, but led to a lower incidence of diarrhoea in children aged 1–18 months.

Harms

- In treated children, although data are sparse, it has been suggested that the macrolide resistance of gut bacteria may increase after MDA-azithromycin.
- Repeated rounds of MDA may lead to a prolonged increase in resistance and require a prolonged drug-free period before resistance declines.
- It is not clear whether MDA-azithromycin over longer time periods to improve childhood mortality would result in the circulation of resistant strains in the community. Available data are insufficient to allow determination of the clinical and public health impact of such circulating resistant strains.
- The adverse effects of azithromycin (from studies where it has not been used as MDA) are mostly gastrointestinal: diarrhoea, vomiting, abdominal pain and nausea. The risk of cardiac toxicity is unknown. There is probably an increased risk of pyloric stenosis developing in the youngest infants.

Values and preferences

- Based on the experience of GDG members, target populations are much more likely to give greater value to a reduction in child mortality than to antimicrobial resistance.
- While determining values and preferences, the GDG focused on mortality as the major benefit and AMR as the major harm of the intervention. One of the systematic reviews commissioned did relate to the safety of Azithromycin. The GDG considered that the azithromycin was generally a safe antibiotic, with mostly mild adverse effects. The two more serious effects, pyloric stenosis and prolonged QT interval, are very rare in the population of interest. The GDG, however, acknowledged the need for pharmacovigilance and therefore included this in their recommendations.

Acceptability

- Based on the extensive experience gained with MDA-azithromycin for trachoma *(35)*, the GDG concluded that the intervention would be acceptable to local populations and deliverable by national health systems in settings for which the guidelines were applicable.

Feasibility (including resource use considerations)

- The cost of MDA-azithromycin is reasonable and not prohibitive for most low- and middle-income country settings.
- The intervention could be implemented using the existing human resources found in primary health care settings in these countries. Studies have shown that the cost per dose of MDA varies from $0.37 to $0.74 *(36)*, and the cost per DALY averted from $9.98 to $14.26 *(37, 38)*.
- Were the intervention to go ahead, it would be necessary to ensure regular supplies of oral azithromycin and to train health care workers to monitor adverse drug effects and antibiotic resistance at the community level.
- The requirements as stipulated by the GDG in terms of pharmacovigilance and monitoring of antimicrobial resistance.

Equity

- The aim of the conditional recommendation to administer MDA-azithromycin to improve child survival in populations with very high infant and child mortality is to improve equity.
- As a strategy, mass drug administration is likely to achieve equitable population coverage. It is important however not to neglect marginalized populations (e.g. geographically remote or minority ethnic groups) when implementing MDA.

Ethical considerations

- Health inequalities exist because of poor access to potentially life-saving antibiotics in many low-resource settings. It is unethical that populations in low-resource, high-mortality settings should forego the use of potentially life-saving antibiotics.
- It is difficult to resolve the conflict between current interests (potentially life-saving antibiotic used today) and future interests (effective antibiotics in the future provided antibiotic use today and emerging resistance can be reduced). Since the actual risk and onset of emerging resistance are unknown factors, and subsequent mortality and morbidity purely hypothetical, the use of MDA-azithromycin is warranted in populations (with appropriate monitoring of mortality, AMR and pharmacovigilance) in which it is likely to lead to a substantial reduction in child mortality.
- Given the possible adverse effects of azithromycin, locally appropriate consent should be sought, and opt-outs made available to parents if mass drug administration is implemented.

Regulatory considerations

- The FDA (US), UK Medicines Regulatory Agency, Health Canada and Therapeutic Goods Administration (Australia) all approve the use of azithromycin in children for several conditions.

- All these regulatory agencies refer however to a lack of information on safety and efficacy in children under 6 months. Pharmacovigilance is therefore important in this age group.

After a substantial discussion of the above considerations, the GDG decided against a universal recommendation of MDA-azithromycin for LMICs.

The GDG took the view, however, that child survival benefits outweigh harms in settings similar to those in which benefits were observed in research studies (i.e. settings in sub-Saharan Africa with very high infant and child mortality and a heavy disease burden owing to malaria, pneumonia and diarrhea) even though overall quality of evidence was rated as low. The GDG prioritized the public health urgency and immediate relevance of the goal i.e. reducing child mortality, which stubbornly remains unacceptably high in these settings. The GDG considered that the evidence for reduction of child mortality was particularly compelling in the case of infants under 1 year of age. The GDG therefore decided on a conditional recommendation for use of MDA-azithromycin in infants aged 1–11 months in these settings. Their rationale for this narrow age range was that the intervention should be targeted at the subgroup in which the greatest benefit was observed, and its application limited to a smaller number of individuals in the community, thereby reducing the risk of emergence of antimicrobial resistance.

The GDG also emphasized that implementation of other ongoing child survival interventions should be strengthened concurrently to avoid the possibility of diverting resources from ongoing programmatic activities.

The GDG carefully considered the possible harms, and therefore also made the recommendation conditional upon close monitoring of mortality, antimicrobial resistance and pharmacovigilance.

RESEARCH GAPS

The Guideline Development Group highlighted the limited evidence available in some knowledge areas and indicated that further research on MDA-azithromycin to improve the survival of children aged under five was required in the following areas:

- All trials of MDA-azithromycin and child mortality have been conducted in a few African countries; additional research in non-African and other African settings is needed.
- Research is required on the effects of MDA-azithromycin in relation to potential interactions with routine vaccines, notably the possible reduction of pathogen-specific mortality following administration of pneumococcal and *Haemophilus influenzae* b vaccines.
- Assessments of longer-term MDA-azithromycin use on child mortality and antimicrobial resistance in MORDOR trial are still under way: their results are likely to provide important guidance for programmes.
- The effect of MDA-azithromycin on the circulation of resistant bacteria in the wider community, rather than just treated children, is not known. More antimicrobial resistance surveillance is needed, with repeated cross-sectional data on colonizing bacteria in children and adults in communities where MDA-azithromycin is implemented.
- Tracking changes in the antimicrobial resistance of pathological organisms are required, especially in children with severe illness presenting to health facilities in areas implementing MDA-azithromycin.
- Additional research is needed to confirm the optimal dose, frequency and number of MDA-azithromycin cycles.
- Evidence on the adverse effects of azithromycin is almost entirely derived from studies in which it is not mass-administered. Pharmacovigilance is required for adverse effects in infants when azithromycin is mass-administered, particularly in those aged under six months.

GUIDELINE DEVELOPMENT PROCESS

Following publication of the MORDOR trial, WHO organized an informal meeting of technical experts to review the available evidence on MDA-azithromycin in March 2018. The purpose of this consultation was to assess whether available evidence merited development of a WHO guideline for MDA-azithromycin. Its conclusion was that a formal guideline development process was required.

The MCA department formed a Guideline Steering Group (GSG) made up of technical officers from six departments across WHO whose expertise was relevant to the MDA-azithromycin guideline development issue. These departments were MCA, Immunization, Vaccines and Biologicals (IVB), Essential Medicines and Health Products (EMP), Antimicrobial Resistance (AMR), Neglected Tropical Diseases (NTD) and the Global Malaria Programme (GMP).

GUIDELINE DEVELOPMENT GROUP (GDG)

The GDG convened by WHO consisted of internationally recognized experts in different fields relevant to this guideline. A full list of GDG members is provided in Annex 4. GDG finalized the questions relating to evidence synthesis at an electronic scoping meeting devoted to this guideline. At a subsequent face-to-face meeting, GDG reviewed the evidence on possible benefits and harms, and developed guideline recommendations using GRADE methodology.

QUALITY OF EVIDENCE GRADING

GRADE methodology was used by the reviewers, GDG methodologist and GDG members to evaluate the quality of evidence. This methodology is widely used in evaluating quality of evidence and strength of recommendations *(39)*: the Cochrane Collaboration and WHO have adopted GRADE methods for developing systematic reviews and recommendations. GRADE tables summarize details about the studies reviewed, including study outcomes, limitations, possible inconsistency, indirectness, imprecision and other factors that might affect judgements relating to quality of evidence. GDG members then apply this grid to assess the overall quality of evidence as high, moderate, low or very low as defined in Table 1.

Table 1. Definition of quality of evidence using the GRADE methodology

Quality	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

GRADE: Grading of Recommendations, Assessment, Development and Evaluation.

The evidence retrieval process for the three groups of priority questions is based on the methods outlined in the WHO Handbook for Guideline Development *(40)*.

MANAGING CONFLICTS OF INTEREST

All members of the GDG were required to sign and submit a Declaration of Interests (DoI) prior to taking part at the meetings. The WHO Guideline Steering Group (GSG) reviewed these documents prior to the GDG meeting to determine whether any factor was present that would preclude or limit the participation of group members. No conflicts of interest were declared which required GSG action. One invited GDG member chose to withdraw from participation before completing the DoI. Biographies of potential members were posted on a public website. No comments were received in response to this public posting of GDG member biographies.

DECISION-MAKING PROCESS

The GDG meeting to develop recommendations was convened from 30 January to 1 February 2019. The meeting was designed to allow participants to discuss each evidence review in detail. Each commissioned review was presented by the lead scientist who had prepared the review and GRADE tables, and the scientist was further available during the meeting to provide clarifications or additional information as required by the GDG.

This was followed by discussions on acceptability, feasibility, equity, ethics and regulatory considerations. Decision-making tables, prepared by the GDG methodologist, included interventional benefits and risks from a public health perspective, values and preferences, and the acceptability and feasibility of implementing any recommendations (including resources needed, with a focus on national programmes in resource-limited or other settings). Decision-making tables were finalized with GDG input. Using these tables as a matrix, initial recommendations were drafted by the GDG co-chairs and methodologist. These draft recommendations were debated and revised in group discussions. Each recommendation was finally adopted by consensus.

GDG members determined the strength of each recommendation based on the criteria set out in Table 2.

Table 2. Assessment criteria for strength of recommendations

Strength of recommendation	Rationale
Strong	The GDG is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional	The GDG concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects. However, the recommendation applies only to a specific group, population or setting OR new evidence may result in changing the assessment of balance of risk to benefit OR the benefits may not warrant the cost or resource requirements in all settings.
No recommendation	Further research is required before any recommendation can be made.

The draft guideline document was finalized by GSG and sent to all GDG members for comment. Written responses were received from fifteen of the eighteen members, and their feedback was incorporated in a revised version of the guideline document.

PEER REVIEW GROUP

The draft guideline document was reviewed by an external Peer Review Group (PRG) to ensure that all available evidence had been considered, and that recommendations were clear and unambiguous. Twenty-two experts were requested to review the draft guideline document, seventeen of whom completed their review and forwarded comments and suggestions. The list of peer reviewers from various WHO regions and their different disciplines and affiliations is provided in Annex 4.

DISSEMINATION AND PLANS FOR UPDATING

DISSEMINATION

The current guideline will be posted on the WHO website, including the WHO MCA website *(41)*. In addition, it will be distributed across a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other UN agencies and nongovernmental organizations.

PLANS FOR GUIDELINE UPDATING

WHO GSG will continue to follow research developments in relation to mass drug administration to improve child survival in risk groups, particularly since the quality of evidence in this proposal was found to be low. The GDG has recommended guideline updating in two to three years. The department of Maternal, Newborn, Child and Adolescent health will coordinate this guideline update in line with the formal procedures set out in the *WHO Handbook for Guideline Development (40)*.

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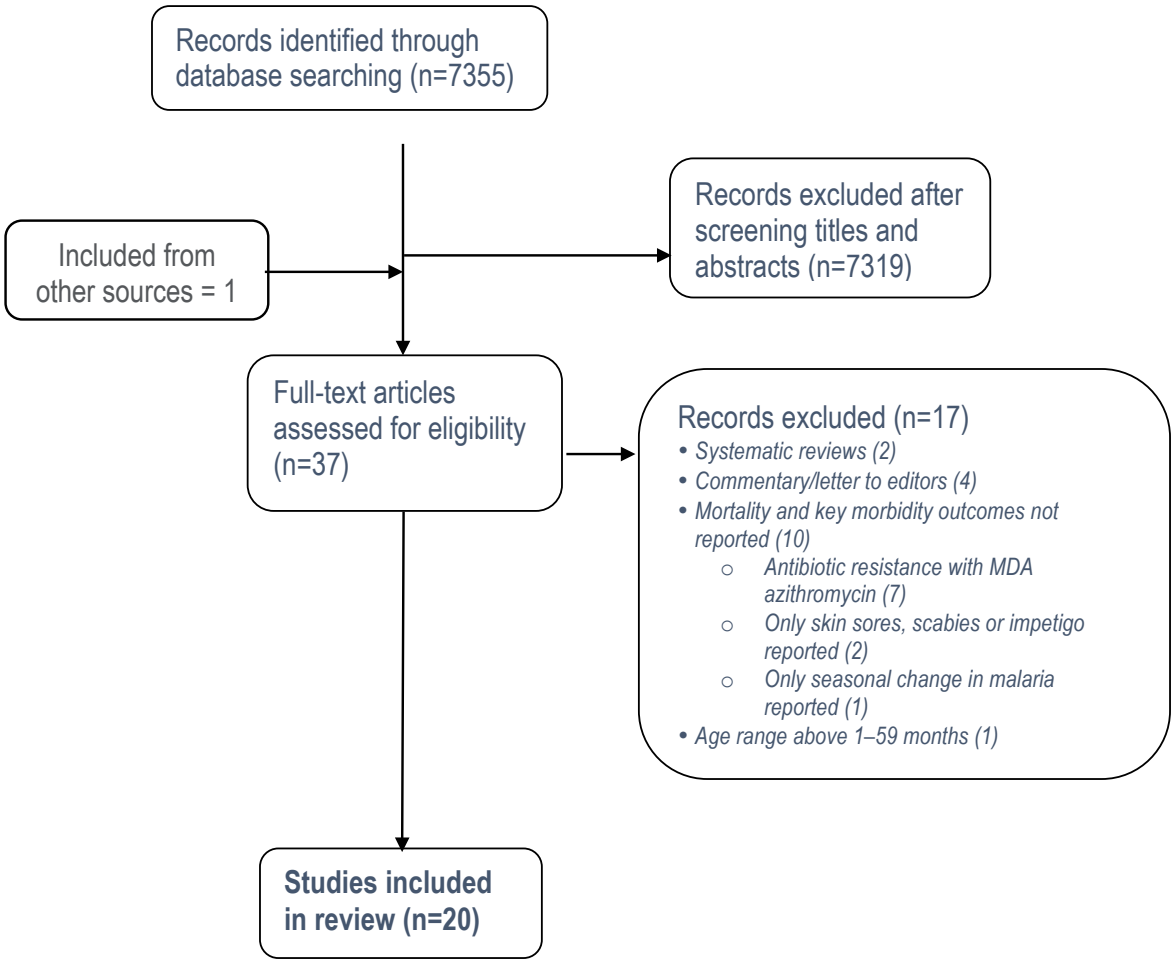
ANNEXES

ANNEX 1: PRISMA FLOWCHART – STUDY SELECTION FOR REVIEW 1



GRADE PROFILE SUMMARY

Table 1: Efficacy in reducing under-five child mortality: azithromycin versus placebo

Outcome	Co-intervention	Studies	Effect estimate	Limitations	Inconsistency	Imprecision	Quality of evidence
Mortality	None	2 RCTs	Porco 2009: 5.7 vs. 12.1 deaths per 1000 person-years; Adjusted IRR: 0.53 (95% CI: 0.26–0.84) Keenan 2018: 14.6 vs. 16.5 deaths per 1000 person-years; Adjusted IRR: 0.86 (95% CI: 0.80–0.93)	No major limitations	Some inconsistency	Large heterogeneity, pooling of effect size not possible	Low
	Seasonal malaria chemo-prophylaxis	1 RCT	Chandramohan 2019: 6.0 vs 5.4 deaths per 1000 person-years at risk; Adjusted IRR: 1.11 (95% CI: 0.87–1.42)				

Table 1 contd… GRADE domains for assessment of mortality effects

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	MDA of azithromycin	placebo or no mass prophylaxis	Relative (95% CI)	Absolute (95% CI)		
3	RCT	not serious	serious [a]	not serious	serious [b]	not suspected	-	-	-	-	LOW	CRITICAL

Two small studies with significant reduction but the third large study with no significant difference in the risk of mortality

a. Large heterogeneity

b. pooling of studies not possible

Table 2: Efficacy in reducing under-five child morbidity: MDA-azithromycin versus placebo (other outcomes)

Certainty assessment							Patient numbers		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Imprecision	Publication bias	MDA- azithro-mycin	placebo or no mass prophylaxis	Relative (95% CI)	Absolute (95% CI)		
Infection related mortality												
1	RCT	serious [a]	serious[b]	not serious	serious [c]	not suspected	94/10 885	89/10 852	OR: 1.26 (0.79–2.00)	2 fewer per 1000 (from 2 fewer to 8 more)	VERY LOW	CRITICAL
Acute respiratory tract infection (assessed by questionnaire)												
4	RCT	serious [d,e]	not serious	not serious [if]	serious [c]	none	-	-	RR: 0.91 (0.81–1.02)	-	LOW	IMPORTANT
Diarrhoea (assessed by questionnaire)												
4	RCT	serious [d,e]	serious [g]	not serious [f]	not serious	none	-	-	RR 0.74 (0.58–0.94)	-	LOW	IMPORTANT
Malaria (follow-up at 1 month: assessed by parasitaemia using real-time PCR)												
2	RCT	serious [h,i]	serious [g]	not serious [f]	serious [c]	none	10 399/ 11 240	10 859/11 171	RR 0.63 (0.22–1.81)	360 fewer per 1000 (from 758 fewer to 787 more)	VERY LOW	IMPORTANT
Hospital admissions (follow-up at 4 months)												
1	RCT	serious[i]	serious [b]	not serious	serious [c]	none	184/ 10 885	188/10 852	RR 0.98 (0.79–1.20)	0 fewer per 1000 (from 4 fewer to 3 more)	VERY LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

a. Bias in analysis - outcome measured only during the intervention period of 4 months in a year and not for the entire study period, i.e. from enrolment until death or exit from the study; also, analysis not adjusted for clustering

b. Single study

c. 95% CI around the pooled estimate includes no effect and 95% CI limits exclude meaningful benefit

d. Analysis not adjusted for cluster in one RCT; analysis in another RCT included the risk during the intervention period of 4 months and not during entire study period

e. Risk of measurement bias in the 2 observational studies but they account for <50% weight in pooled analysis

f. 2 out of the 4 studies had enrolled children of all ages (upper limit of 10 and 14 years, respectively); the median age in 1 study was 5 years while the mean age in the other was 6 years

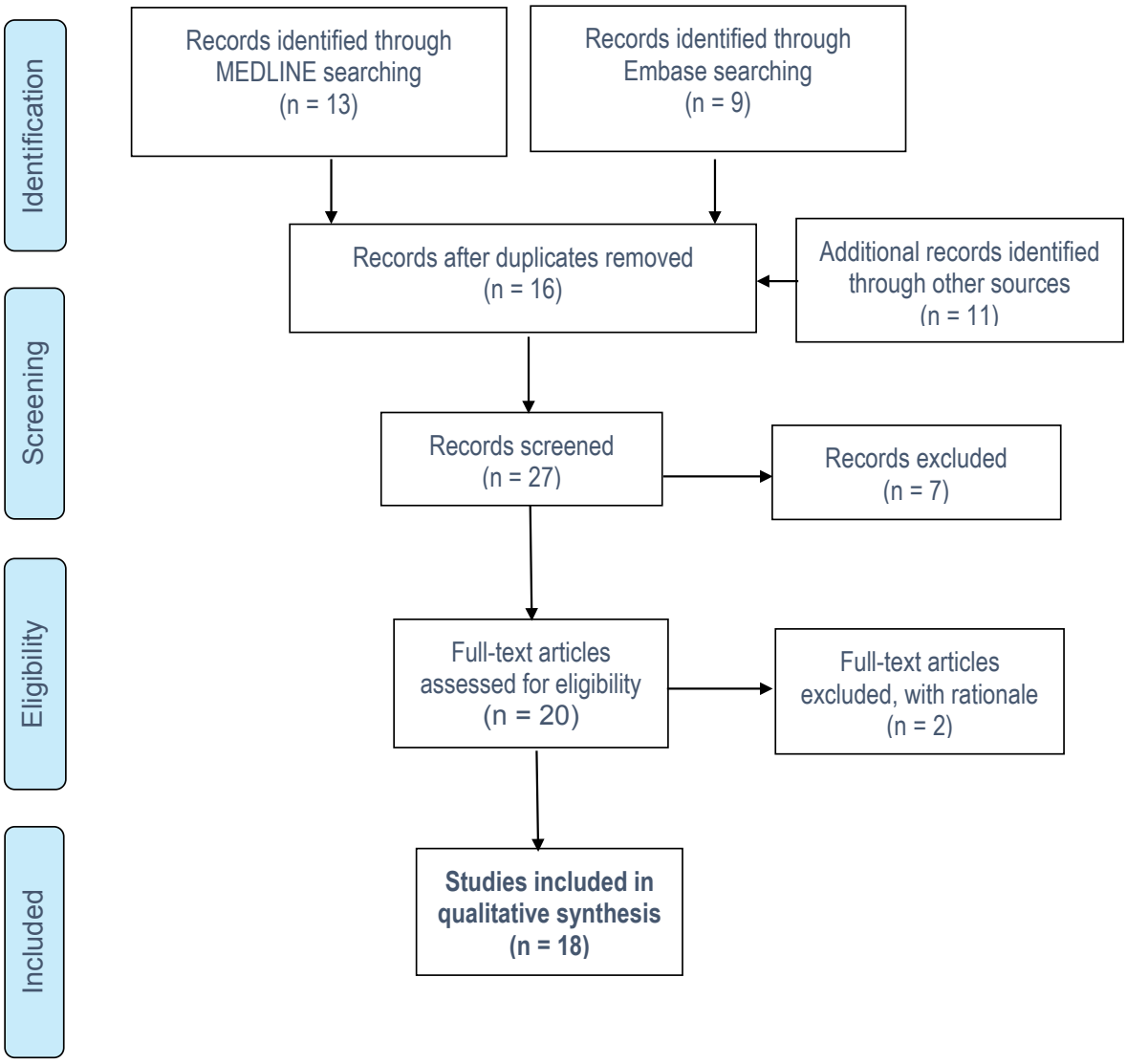
g. I2 >60% and P for heterogeneity <0.1

h. Risk of selection bias in the observational study (villages with high trachoma prevalence received MDA Azithromycin while those with low prevalence didn't receive it) but the study contributed to 40% of weight in pooled analysis

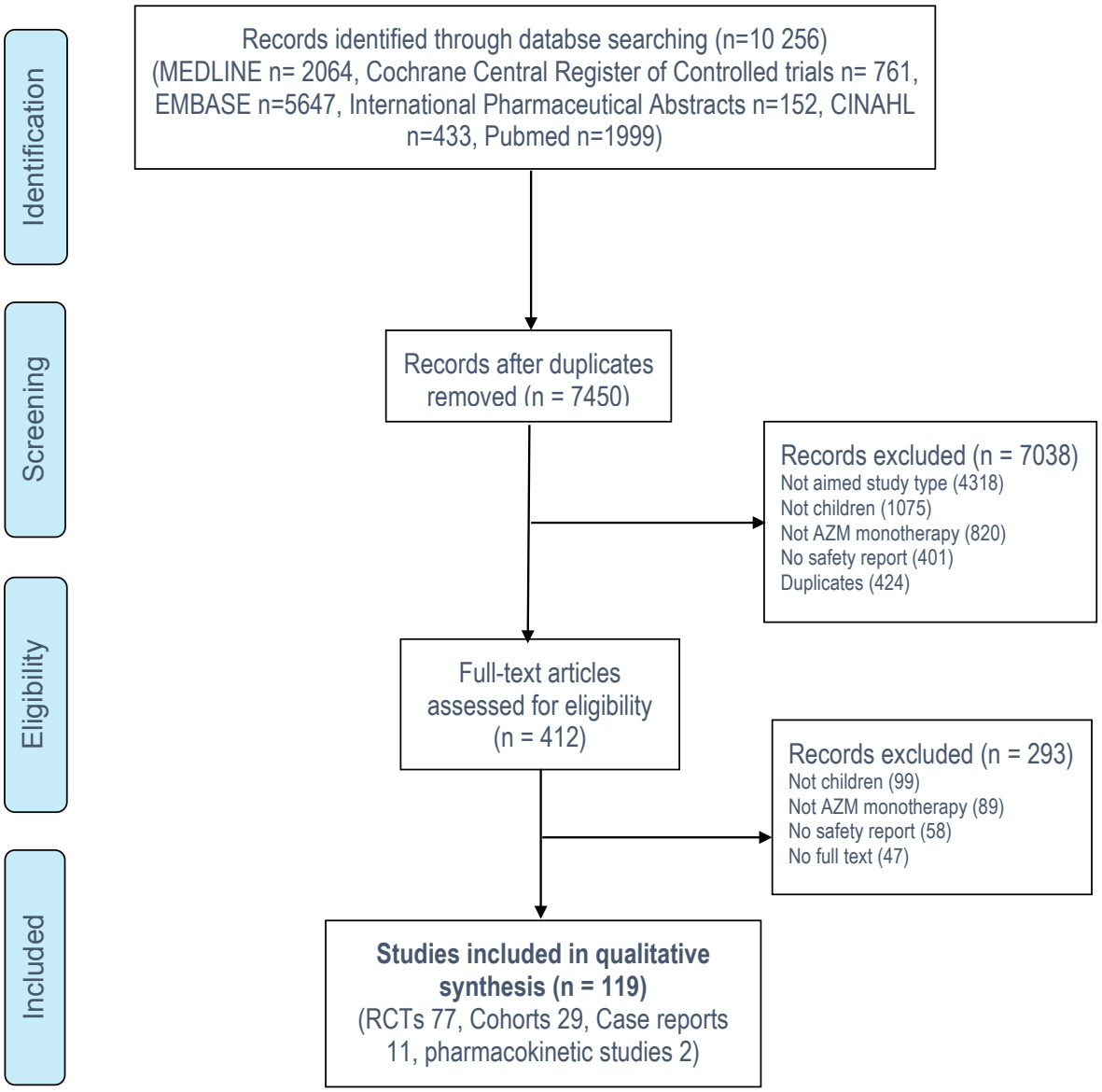
i. Bias in analysis - outcome measured during the intervention period and not the entire study period - that contributed to 60% of weight in pooled analysis

NB: Data on number of patients and absolute effect could not be estimated for acute respiratory tract infection and diarrhea because one study (Coles 2011) provided data as episodes per person-years

ANNEX 2: PRISMA FLOWCHART - ARTICLE SELECTION FOR REVIEW 2



ANNEX 3: PRISMA FLOWCHART - ARTICLE SELECTION FOR REVIEW 3



ANNEX 4: ACKNOWLEDGEMENTS

The WHO department of Maternal, Newborn, Child and Adolescent Health gratefully acknowledges the contributions made by many individuals to the development of this guideline.

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Methodologist: Roger Chou (Oregon Health Sciences University, USA)

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Zulfiqar Bhutta	Professor, The Hospital for Sick Children, Canada	Paediatrics
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ANNEX 5: EXPERT GROUP CONSULTATION

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