OPEN LETTER

Azithromycin in labour to reduce maternal and newborn sepsis and associated deaths: the need for a harmonized approach [version 1; peer review: 1 approved]

Elizabeth M. McClure[1], Anna Roca[2], Karen Kotloff[3], Waldemar A. Carlo[4], Umberto D'Alessandro[2], Halidou Tinto[5], Bully Camara[2], Elwyn Chomba[6], Samba O. Sow[7], Amanda Driscoll[2], Jennifer Hemingway-Foday[1], Alan Tita[4]

[1]RTI International, Durham, NC, 27709, USA
[2]Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, Fajara, The Gambia
[3]Department of Pediatrics, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
[4]University of Alabama at Birmingham, Birmingham, AL, USA
[5]Institut de Recherche en Sciences de la Santé, Nanoro, Burkina Faso
[6]University Teaching Hospital, Lusaka, Zambia
[7]Centre pour le Développement des Vaccins, Bamako, Mali

v1 **First published:** 16 May 2023, **7**:72
https://doi.org/10.12688/gatesopenres.14214.1
Latest published: 16 May 2023, **7**:72
https://doi.org/10.12688/gatesopenres.14214.1

Abstract

Maternal and newborn infections are a major contributor to mortality and morbidity globally. Lost-cost, effective and safe interventions are needed to address these. Based on promising findings, azithromycin has been identified as potentially effective antibiotic to reduce maternal and newborn infections in low- and middle-income countries (LMICs). However, robust randomized clinical trials in a range of settings are needed to confirm these findings as well as to understand the implications for antimicrobial resistance. To better understand the impact of azithromycin on maternal and newborn health, at least three clinical trials are being conducted to evaluate azithromycin in LMICs. We describe these trials, the importance of harmonizing study measures and the potential public health impact of azithromycin in LMICs.

Keywords

stillbirth, MITS, azithromycin, pathology

Open Peer Review

Approval Status ✓

	1
version 1 16 May 2023	✓ view

1. **Patrick Duff**, University of Florida College of Medicine, Gainesville, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Elizabeth M. McClure (mcclure@rti.org)

Author roles: McClure EM: Conceptualization, Funding Acquisition, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Roca A**: Conceptualization, Methodology, Writing – Review & Editing; **Kotloff K**: Conceptualization, Methodology, Writing – Review & Editing; **Carlo WA**: Conceptualization, Methodology, Writing – Review & Editing; **D'Alessandro U**: Writing – Review & Editing; **Tinto H**: Writing – Review & Editing; **Camara B**: Writing – Review & Editing; **Chomba E**: Writing – Review & Editing; **Sow SO**: Writing – Review & Editing; **Driscoll A**: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Hemingway-Foday J**: Conceptualization, Writing – Review & Editing; **Tita A**: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by the Bill and Melinda Gates Foundation (INV-008973). The trials mentioned received the following grants: PregnAnZI-2 (ClinicalTrials.gov: NCT03199547): The trial was jointly funded by a grant from the UKRI under the Joint Global Health Trials (JGHT) Scheme, reference number (MC_EX_MR/ P006949) and Bill & Melinda Gates Foundation (OPP1196513). SANTE (ClinicalTrials.gov: NCT03909737): The trial was funded by the Bill & Melinda Gates Foundation (OPP1196125). A-PLUS (ClinicalTrials.gov: NCT03871491): This trial was jointly funded by the National Institute of Child Health and Human Development and the Bill & Melinda Gates Foundation (OPP1196654).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: McClure EM, Roca A, Kotloff K *et al.* **Azithromycin in labour to reduce maternal and newborn sepsis and associated deaths: the need for a harmonized approach [version 1; peer review: 1 approved]** Gates Open Research 2023, **7**:72 https://doi.org/10.12688/gatesopenres.14214.1

First published: 16 May 2023, **7**:72 https://doi.org/10.12688/gatesopenres.14214.1

Background and rationale

While under-5 childhood mortality has decreased over the last two decades, the proportion of neonatal deaths has increased during this period[1]. Infection during pregnancy and the puerperium account for approximately 15% of newborn deaths[3,4]. Maternal sepsis and infections represent about 10% of the global burden of maternal deaths[2]. In such context, there is a need for innovative, context specific interventions to reduce intrapartum sepsis in countries with the highest burden. However, to be sustainable, these interventions should be amenable to scale up in these settings to reduce the burden of both maternal and neonatal mortality.

Based on several studies, treatment with azithromycin, a low-cost antibiotic with immunomodulatory properties, has been identified as a novel approach to reduce maternal, neonatal and child mortality associated with infections[5–7]. Azithromycin can target organisms that may be very frequent pathogens but that historically have not been the target of antimicrobial preventive treatment[8]. Whether there are additional benefits beyond the antimicrobial effects remains to be determined.

During recent years, azithromycin has been delivered at pre-specified intervals through mass drug administration to African children under 5 years of age with the aim to reduce child mortality[9–11]. While these trials showed heterogenic results, the most apparent benefit has been observed among young infants[9–11]. Azithromycin has also been used in randomized clinical trials during pregnancy to reduce preterm birth[11,12]. One meta-analysis of 14 trials of azithromycin in pregnancy, primarily used in conjunction with other treatments, showed reduced risk of preterm birth and low-birth weight, but not significant reductions in other adverse perinatal outcomes[13].

More recently, there has been a growing interest in using azithromycin prophylaxis during labour. One multicenter randomized clinical trial (RCT) of 500 mg azithromycin orally added to the standard prophylactic regimen for women who underwent cesarean delivery following labour or membrane rupture in the US showed that maternal infection was reduced by about 50%[7]. Use of this intervention was reported to be highly cost-saving[14]. A single center test-of-concept RCT in The Gambia including all women in labour found in a *post hoc* analysis that treatment with 2 g of intra-partum azithromycin reduced maternal infections by more than 50% and neonatal infections by more than 25%[16].

These promising results have been tempered by several concerns of risks. One recurrent concern regarding the prophylactic use of azithromycin is the potential for developing macrolide resistance[17–20]. This is a particular consideration for widespread use of azithromycin in populations. In the MORDOR study from sub-Saharan Africa, antimicrobial resistance was associated with mass distribution of azithromycin to preschool children twice yearly for two years[21], though levels returned to baseline in later studies. The individual-randomized trial from The Gambia found that macrolide resistance increases appeared to be transient, at least in populations with low baseline resistance[21]. These studies evaluated resistance through surveillance activities, and it is unclear this translates to resistant infections[22].

A second important concern is the risk of adverse events, that may be rare, but with scale-up to large populations, could result in significant deaths. Azithromycin was associated with cardiac deaths in an observational study of an elderly population with medical comorbidities but not in a younger, healthy population similar to women of reproductive age[23]. Macrolides administered to neonates have been associated with infantile hypertrophic pyloric stenosis in some observational studies[24], while were not reported in infants following a single dose of azithromycin to women in labour in randomized trials in The Gambia where daily active case detection was conducted by study nurses followed by weekly home visits for eight weeks[22]. A recent study administering azithromycin during the neonatal period to more than 10,000 neonates did not show an association between the use of azithromycin and infantile hypertrophic pyloric stenosis[23].

Given the potential public health benefit, balanced with potential risks of population-based interventions in vulnerable populations, a thorough evaluation of the impact of intrapartum azithromycin prophylaxis is needed. Evidence for a new strategy is strengthened when the direction of the findings can be replicated in multiple studies conducted independently in different settings and population. However, when trials of the same intervention result in contradicting findings, policy makers, clinicians and others have a dilemma about how to translate the research findings into policy, delaying the implementation of potentially promising, life-saving interventions.

To explore optimal delivery strategies, dosing frequency, and target population for azithromycin administration to benefit pregnant women and their infants, a variety of approaches have been undertaken. Thus, while evaluating interventions in diverse settings is critical for generalizability, in order to facilitate the interpretation of results, prospective harmonization of data collection and methods is important[24–26].

In the case of intrapartum azithromycin, to date there have been positive results but no definitive RCT from LMICs, where the intervention is most urgently needed. To address this concern, at least three independent groups have launched trials with harmonization of the critical metrics to evaluate the impact of azithromycin given during pregnancy and/or labour on maternal and newborn outcomes in different LMIC settings[27–29]. The BMGF-funded *Sauver avec l'Azithromycine en Traitant les Femmes Enceintes et les Enfants* (SANTE) trial uses a factorial design to randomize pregnant women in Mali to receive antenatal and intrapartum azithromycin or placebo, with their infants randomized to receive azithromycin or placebo at routine 6- and 14-week immunization visits[29]. ThePregnAnZI-2, SANTE and the Azithromycin in Labor Study (A-PLUS) include ancillary studies to address the effect of the intervention on macrolide resistance and the newborn's microbiome. These trials also include secondary objectives to determine additional

potential benefits of the intervention in non-severe infection and infant's growth. The protocols for these trials are published, as part of an intention to harmonize methods, where possible, and to define the trial differences so that the findings ultimately can be better interpreted.

Methods

The trials are being conducted in The Gambia and Burkina Faso (the PregnAnZI-2 Trial), Mali (the SANTE Trial) and within the Global Network for Women's and Children's Health Research, a multi-site research network conducting research in 8 sites in 7 LMICs including Democratic Republic of Congo, Kenya, Zambia, Guatemala, Bangladesh, India and Pakistan (the A-PLUS Trial). Table 1 summarizes the population, intervention, comparator, and outcomes (PICO) features of these trials. In addition, Table 2 summarizes the secondary outcomes.

Discussion

There are several important commonalities of these trials that will facilitate meta-analyses to address gaps in the current

Table 1. Population, intervention, comparator, outcomes (PICO) comparison.

	PregnAnZI-2	A-PLUS	SANTE
Population	**Pregnant women in labour**	**Pregnant women in labour**	**Pregnant women seeking routine antenatal care**
Intervention	2 g of oral intrapartum azithromycin	2 g of oral intrapartum azithromycin	2 g of oral azithromycin, twice during pregnancy and once intrapartum Infants receive 20mg/kg azithromycin or placebo alongside the first and third doses of pentavalent vaccine
Comparator	Placebo	Placebo	Placebo
Primary Outcomes	• Composite of neonatal sepsis or neonatal death, excluding deaths from severe birth asphyxia, very low birth weight or severe congenital malformations.	• Incidence of maternal death or sepsis within 42 days post-delivery in the intervention vs. placebo group. • Incidence of intrapartum/neonatal death or sepsis within 28 days post-delivery	• Composite of stillbirth and infant death through 6–12 months of age (maternal intervention) • Infant death from the time of first dose through 6–12 months of age (infant intervention)
Sample Size	12,000	34,000	33,600
Study Sites	The Gambia; Burkina Faso	India; Bangladesh, Pakistan, DRC, Kenya, Zambia and Guatemala	Mali

Table 2. Trial inclusion and exclusion criteria.

	PregnAnZI-2	A-PLUS	SANTE
Main Inclusion Criteria	Pregnant women in labour ≥16 years who signed consent during Antenatal Care (ANC) and oral consent to continue participation during labour	Pregnant women in labour ≥28 weeks who plan to deliver vaginally at health facility Presence of one or more live fetus confirmed via a fetal heart rate by Doptone Age ≥ 18 years of age (14–17 years per local standards)	Pregnant women estimated to be ≥14 weeks gestation according to the study algorithm and presenting at a study facility for routine antenatal care Intend to reside in the study area for at least 6 months post-delivery
Main Exclusion Criteria	Known HIV infection; any chronic or acute conditions; planned caesarean section or known required referral; known severe congenital malformation, intrauterine death or allergy to macrolides; and drugs known to prolong QT interval taken during the last 2 weeks, such as chloroquine, quinine, piperaquine, and erythromycin.	Evidence of chorioamnionitis or other infection requiring antibiotic therapy Arrhythmia or history of cardiomyopathy Allergy to azithromycin or other macrolides Use of azithromycin, erythromycin, or other macrolide within 3 days of randomization. Planned Cesarean delivery Preterm labour with no plan to proceed to delivery Advanced stage of labour and pushing or too distressed to give informed consent Incapable of consenting Medical conditions considered a contraindication per clinical judgement	In active labour Known allergy to macrolide antibiotics. Current treatment with azithromycin for a medical condition (this can be a temporary exclusion if the drug is later discontinued)

research. First, the intrapartum intervention, including the dosage, was carefully considered. Given the success with a single oral dose of 2 g in The Gambian trial, an oral azithromycin dose of 2 g was selected for the proposed interventions. The PregnAnZI-2 and the A-PLUS trials administered a single 2 g dose of azithromycin during labour, while SANTE administered a single 2 g dose at an antenatal care visit in the second and/or third trimester and during labour or within 24 hours thereafter. The administration of the azithromycin within 24 hours after delivery is justified by the high concentration of azithromycin arriving to the newborns through the breast milk. All three trials utilized a double-blind, placebo-controlled RCT design, selected as the optimal trial methodology.

Second, the important outcomes were prospectively harmonized. Each trial is examining core outcomes, including mortality. The PregnAnZI-2 and the A-PLUS trials are also assessing maternal and newborn infections, and hospitalization rates. Therefore, an individual participant meta-analysis will be possible as the protocols including outcomes were harmonized as much as possible.

The primary neonatal outcome is intrapartum/neonatal death or sepsis within 28 days after birth. For the A-PLUS trial, the primary maternal outcome is maternal death or sepsis within 28 to 42 days after delivery and PregnAnZI-2 maternal sepsis. The primary aim of the antenatal and intrapartum dosing in SANTE is a composite outcome of stillbirths and infant mortality through 6–12 months. SANTE's co-primary aim will assess the efficacy of azithromycin for the prevention of infant deaths from the time of the first infant dose, administered alongside the first dose of pentavalent vaccine, through 6 to 12 months of age.

In addition, the sample size for each of the trials is substantial, allowing cumulatively, full evaluation of potentially rare adverse events. For example, concerns have been raised about potential adverse effects of intra and antepartum azithromycin on the pulmonary and gastrointestinal systems. Altogether, these trials will provide a comprehensive picture of the potential of short-term adverse events associated with azithromycin given during in labour.

Furthermore, several factors mitigate concerns about antibiotic resistance. The design of each of the trials use a single prophylactic intrapartum dose of antibiotic/placebo rather than multiple prophylactic dose administration. Both have also included women at both high- and low-risk for infection. The prophylactic use of azithromycin, if effective, will reduce the risk of infection and in turn reduce the overall use of antibiotics to treat infection as already shown in other trials[6,14]. To better assess this, all 3 trials are monitoring for resistant infection. In addition, the trials are conducting in-depth investigations that will inform on the impact of azithromycin use on potential changes to the microbiome.

Besides the similarities, there are several important differences in the trials, including secondary outcomes (Table 3) as well as among prospectively planned ancillary studies to assess important research questions. PregnAnZi-2 is assessing the impact of the intervention on growth. One of the main areas is the concern about AMR. To address this, the A-PLUS and SANTE trials have a sub-study to assess AMR of those randomized to azithromycin vs. placebo while the PregnAnZI-2 trial has several secondary endpoints to determine the extent of the impact on macrolide resistance in both mothers and babies.

There have been concerns about the impact of azithromycin on the microbiome. The PregnAnZI-2, A-PLUS and SANTE trials will conduct detailed microbiome assessments for a subset of participants (mothers and newborns). Future studies might correlate differences in microbiome due to antibiotics with longer-term outcomes of the child and mother.

As with other interventions administered during pregnancy, assessing the potential for long-term neurological effects on children is another public health concern. To help address this issue, the PregnAnZI-2 study will be following infants until 36 months after birth to assess neurodevelopmental outcomes. The A-PLUS trial will also evaluate neurodevelopmental outcomes among a subset of children at 24 months of age.

Conclusions

Azithromycin is an inexpensive macrolide that shows promise for improving health in LMICs. To date, numerous clinical trials have assessed the effect of azithromycin on maternal, newborn, and child survival as well as health for a range of conditions and using a range of outcomes. Since the puerperal period is the time with the highest risk of sepsis for women and their newborns, assessing the potential effect of this intervention during the time of highest risk is a necessity. With the public health concerns of increasing antimicrobial resistance globally, it is of special importance that these trials definitively address potential of antimicrobial resistance associated with azithromycin, and various approaches will be studied across the trials.

RCTs provide the strongest evidence needed to weigh the benefits and safety of interventions to improve health outcomes. Given the time and costs involved, prospective harmonization of trial outcomes is important whenever possible to allow for meaningful comparisons across trials and meta-analyses to evaluate outcomes among sub-groups. The three trials on azithromycin described here represent an opportunity to

Table 3. Trial secondary maternal, neonatal and child outcomes.

	PregnAnZI-2	A-PLUS	SANTE
Maternal Outcomes	• Post-partum sepsis: maternal hospitalizations within 28 days of delivery for endometritis or culture-confirmed infection of sterile site or wound infection; • Endometritis; • Wound infection: perineal or caesarean wound infection • Mastitis: breast pain, redness, tenderness and localised mass with or without fluctuance; • Malaria: clinical suspicion confirmed by either positive blood film test for malaria or a RDT for malaria; • Fever: axillary temperature ≥38.0 C of two readings with 10 min interval; • Antibiotic use during the post-partum follow-up • Hospitalizations: any hospital admission; • Mortality up to 4 wks.	• The primary maternal outcome in a high-risk for infection population • Incidence of maternal infections • Subsequent maternal antibiotic therapy after randomization to 42 days postpartum • Time from drug administration until initial discharge after delivery • Maternal readmissions and admissions to special care units within 42 days postpartum or unscheduled care • Maternal gastrointestinal symptoms or other reported side effects • Maternal death due to sepsis	• A composite outcome of maternal mortality and hospitalization (for events other than planned surgery or trauma) while pregnant or within 42 days of termination of pregnancy • Spontaneous abortions and early stillbirths occurring before 22 weeks gestational age • 14-day period prevalence of malaria, pneumonia, or diarrheal illness reported at follow up visits (ANC follow up, delivery, and 6 weeks postpartum visits)
Neonatal Outcomes	• Neonatal sepsis and neonatal mortality • Culture-confirmed sepsis; • Fever • Clinical bacterial skin infections • Clinical bacterial conjunctivitis • Infection (omphalitis) • Malaria • Use of any prescribed antibiotics • All cause neonatal hospitalization excluding those due to injuries.	• Neonatal deaths due to sepsis and all-cause neonatal death • Other neonatal infections • Neonatal readmissions and admissions to special care units within 42 days postpartum • Neonatal initial hospital length of stay • Neonatal unscheduled visit for care • Neonatal death due to sepsis • Incidence of pyloric stenosis	• Death within 24 hours (all-cause) • Early neonatal death, 0-6 days (all-cause) • Late neonatal death, 7-28 days • Neonatal death, 0-28 days (all-cause) • Gestational age at birth • Birth weight
Infant/child Outcomes	• All-cause hospitalization during follow up • Infant mortality: all-cause mortality • Malnutrition (measured by z-scores): anthropometric measurements at 6 and 12 months of age.	Neurologic (BSID) outcomes at 24-mos postpartum for sub-set of infants	• 7-day period prevalence of malaria, pneumonia, or diarrheal illness reported at follow up visits (at approximately 6 weeks, 14 weeks, 6 months and 12 months of age • Anthropometric parameters (weight-for-age z-score, length-for-age z-score, weight-for-length z-score, head circumference, MUAC
Microbiologic secondary outcomes (and others)	For infants: *S. pneumoniae* and *Klebsiella spp* in the nasopharynx; *E. coli, Pseudomonas spp, Klebsiella spp* from rectal swab and *S. aureus, GBS, GAS* in the oropharynx. For mothers: prevalence of *S. aureus, GBS, GAS, E. coli, Pseudomonas spp, Klebsiella* in BM; *S. pneumoniae, Klebsiella spp* in the nasopharynx and *S. aureus, GBS, GAS* in the oropharynx. Resistance to AZI, oxacillin and amoxicillin. Microbiome analysis in nasopharyngeal samples, rectal swabs (babies) and breast milk (women)	Testing of antimicrobial resistance by culture at 7, 42 days and up to 3 months for all dyads and between 6 and 12 after randomization for culture of maternal and infant samples (nasopharyngeal and rectal) to test for antimicrobial resistance by culture, microbiome and the effects on the resistome	*Streptococcus pneumoniae* in the nasopharynx (pregnant women and infants) *Escherichia coli* in the rectum (pregnant women and infants) Genetic determinants of antimicrobial resistance in the gut and nasopharyngeal microbiomes (pregnant women and infants) Stool and serum biomarkers of environmental enteric dysfunction and/or improved growth hormone axis function (infants) Composition of the vaginal (maternal), gut (maternal and infant) and nasopharyngeal (maternal and infant) microbiome Malaria infection (pregnant women and infants)
Safety endpoints	SAEs in mothers and infants Infantile hypertrophic pyloric stenosis	SAEs in mothers and infants Infantile hypertrophic pyloric stenosis	SAEs in mothers and infants Infantile hypertrophic pyloric stenosis

Gates Open Research 2023, 7:72 Last updated: 22 MAY 2023

gain substantial, high-quality data across diverse populations to inform the use of azithromycin in pregnancy to reduce sepsis and other adverse pregnancy outcomes.

Data availability

No data are associated with this article.

References

1. GBD 2019 Under-5 Mortality Collaborators: **Global, regional, and national progress towards Sustainable Development Goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019.** *Lancet.* 2021; **398**(10303): 870–905.
PubMed Abstract | Publisher Full Text | Free Full Text
2. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, *et al.*: **Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.** *Lancet.* 2014; **384**(9947): 980–1004.
PubMed Abstract | Publisher Full Text | Free Full Text
3. Liu L, Oza S, Hogan D, *et al.*: **Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis.** *Lancet.* 2015; **385**(9966): 430–40.
PubMed Abstract | Publisher Full Text
4. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, *et al.*: **The global burden of paediatric and neonatal sepsis: a systematic review.** *Lancet Respir Med.* 2018; **6**(3): 223–230.
PubMed Abstract | Publisher Full Text
5. Keenan JD, Arzika AM, Maliki R, *et al.*: **Longer-Term Assessment of Azithromycin for Reducing Childhood Mortality in Africa.** *N Engl J Med.* 2019; **380**(23): 2207–14.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Kimani J, Phiri K, Kamiza S, *et al.*: **Efficacy and Safety of Azithromycin-Chloroquine versus Sulfadoxine-Pyrimethamine for Intermittent Preventive Treatment of *Plasmodium falciparum* Malaria Infection in Pregnant Women in Africa: An Open-Label, Randomized Trial.** *PLoS One.* 2016; **11**(6): e0157045.
PubMed Abstract | Publisher Full Text | Free Full Text
7. Tita AT, Szychowski JM, Boggess K, *et al.*: **Adjunctive Azithromycin Prophylaxis for Cesarean Delivery.** *N Engl J Med.* 2016; **375**(13): 1231–41.
PubMed Abstract | Publisher Full Text | Free Full Text
8. Sutton AL, Acosta EP, Larson KB, *et al.*: **Perinatal pharmacokinetics of azithromycin for cesarean prophylaxis.** *Am J Obstet Gynecol.* 2015; **212**(6): 812.e1–6.
PubMed Abstract | Publisher Full Text | Free Full Text
9. Gladstone RA, Bojang E, Hart J, *et al.*: **Mass drug administration with azithromycin for trachoma elimination and the population structure of *Streptococcus pneumoniae* in the nasopharynx.** *Clin Microbiol Infect.* 2021; **27**(6): 864–870.
PubMed Abstract | Publisher Full Text | Free Full Text
10. Keenan JD, Arzika AM, Lietman TM, *et al.*: **Azithromycin and Childhood Mortality in Africa.** *N Engl J Med.* 2018; **379**(14): 1383–1384.
PubMed Abstract | Publisher Full Text
11. Chandramohan D, Dicko A, Zongo I, *et al.*: **Effect of Adding Azithromycin to Seasonal Malaria Chemoprevention.** *N Engl J Med.* 2019; **380**(23): 2197–2206.
PubMed Abstract | Publisher Full Text
12. Pierson RC, Gordon SS, Haas DM: **A retrospective comparison of antibiotic regimens for preterm premature rupture of membranes.** *Obstet Gynecol.* 2014; **124**(3): 515–519.
PubMed Abstract | Publisher Full Text | Free Full Text
13. Unger HW, Ome-Kaius M, Wangnapi RA, *et al.*: **Sulphadoxine-pyrimethamine plus azithromycin for the prevention of low birthweight in Papua New Guinea: a randomised controlled trial.** *BMC Med.* 2015; **13**: 9.
PubMed Abstract | Publisher Full Text | Free Full Text
14. Basu S, Smith S: **Macrolides for the prevention and treatment of feeding intolerance in preterm low birth weight infants: a systematic review and meta-analysis.** *Eur J Pediatr.* 2021; **180**(2): 353–378.
PubMed Abstract | Publisher Full Text
15. Harper LM, Kilgore M, Szychowski JM, *et al.*: **Economic Evaluation of Adjunctive Azithromycin Prophylaxis for Cesarean Delivery.** *Obstet Gynecol.* 2017; **130**(2): 328–34.
PubMed Abstract | Publisher Full Text | Free Full Text
16. Oluwalana C, Camara B, Bottomley C, *et al.*: **Azithromycin in Labor Lowers Clinical Infections in Mothers and Newborns: A Double-Blind Trial.** *Pediatrics.* 2017; **139**(2): e20162281.
PubMed Abstract | Publisher Full Text
17. Lietman TM, Doan T, Keenan JD: **Macrolide Resistance and Longer-Term Assessment of Azithromycin in MORDOR I. Reply.** *N Engl J Med.* 2019; **381**(22): 2184–2185.
PubMed Abstract | Publisher Full Text
18. O'Brien KS, Emerson P, Hooper PJ, *et al.*: **Antimicrobial resistance following mass azithromycin distribution for trachoma: a systematic review.** *Lancet Infect Dis.* 2019; **19**(1): e14–e25.
PubMed Abstract | Publisher Full Text
19. Ramblière L, Guillemot D, Delarocque-Astagneau E, *et al.*: **Impact of mass and systematic antibiotic administration on antibiotic resistance in low- and middle-income countries? A systematic review.** *Int J Antimicrob Agents.* 2021; **58**(1): 106364.
PubMed Abstract | Publisher Full Text
20. Doan T, Worden L, Hinterwirth A, *et al.*: **Macrolide and nonmacrolide resistance with Mass Azithromycin Distribution.** *N Engl J Med.* 2020; **383**(20): 1941–1950.
PubMed Abstract | Publisher Full Text | Free Full Text
21. Bojang A, Baines SL, Camara B, *et al.*: **Impact of Intrapartum Oral Azithromycin on the Acquired Macrolide Resistome of Infants' Nasopharynx: A Randomized Controlled Trial.** *Clin Infect Dis.* 2020; **71**(12): 3222–3225.
PubMed Abstract | Publisher Full Text | Free Full Text
22. Roca A, Oluwalana C, Bojang A, *et al.*: **Oral azithromycin given during labour decreases bacterial carriage in the mothers and their offspring: a double-blind randomized trial.** *Clin Microbiol Infect.* 2016; **22**(6): 565.e1–9.
PubMed Abstract | Publisher Full Text | Free Full Text
23. Ray WA, Murray KT, Hall K, *et al.*: **Azithromycin and the risk of cardiovascular death.** *N Engl J Med.* 2012; **366**(20): 1881–90.
PubMed Abstract | Publisher Full Text | Free Full Text
24. Eberly ME, Eide MB, Thompson JL, *et al.*: **Azithromycin in Early Infancy and Pyloric Stenosis.** *Pediatrics.* 2015; **135**(3): 483–8.
PubMed Abstract | Publisher Full Text
25. John LN, Beiras CG, Houinei W, *et al.*: **Trial of Three Rounds of Mass Azithromycin Administration for Yaws Eradication.** *N Engl J Med.* 2022; **386**(1): 47–56.
PubMed Abstract | Publisher Full Text | Free Full Text
26. Salman S, Bendel D, Lee TC, *et al.*: **Pharmacokinetics of a novel sublingual spray formulation of the antimalarial drug artemether in African children with malaria.** *Antimicrob Agents Chemother.* 2015; **59**(6): 3208–15.
PubMed Abstract | Publisher Full Text | Free Full Text
27. Camara B, Bognini JD, Nakakana UN, *et al.*: **Pre-delivery administration of azithromycin to prevent neonatal sepsis and death: a phase iii double-blind randomized clinical trial (PregnAnZI-2 trial).** *Int J Clin Trials.* 2022; **9**(1): 34–44.
Publisher Full Text
28. Hemingway-Foday J, Tita A, Chomba E, *et al.*: **Prevention of maternal and neonatal death/infections with a single oral dose of azithromycin in women in labour in low- and middle-income countries (A-PLUS): Study protocol for a multi-national, randomized placebo-controlled clinical trial (submitted)**.
29. Driscoll A, Haidara FC, Tapia MD, *et al.*: **Antenatal, intrapartum and infant azithromycin to prevent stillbirths and infant deaths: study protocol for a 2x2 factorial randomized controlled trial (submitted bmjopen-2022-067581)**.

Open Peer Review

Current Peer Review Status: ✔

Version 1

Reviewer Report 22 May 2023

https://doi.org/10.21956/gatesopenres.15520.r33328

✔ **Patrick Duff**
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, FL, USA

In this letter, the authors provide a clear, concise summary of the current information concerning the value of prophylactic azithromycin in reducing the frequency of maternal and neonatal infection in low and middle resource countries. They carefully illustrate selected problems that might result from widespread use of this antibiotic, namely, alteration of the maternal and neonatal microbiomes, rare maternal/neonatal cardiovascular derangements such as arrhythmias, and birth defects such as pyloric stenosis. They argue convincingly for the need for standardized treatment protocols and consistent definitions of important outcomes. They also point out the need to conduct additional investigations in high resource countries. Overall, the authors present an excellent agenda for future research designed to reduce the alarming frequency of maternal and neonatal sepsis.

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases in obstetrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.