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]

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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
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. Infection during pregnancy and the puerperium account for approximately 15% of newborn deaths. Maternal sepsis and infections represent about 10% of the global burden of maternal deaths. 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. Azithromycin can target organisms that may be very frequent pathogens but that historically have not been the target of antimicrobial preventive treatment. 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. While these trials showed heterogenic results, the most apparent benefit has been observed among young infants. Azithromycin has also been used in randomized clinical trials during pregnancy to reduce preterm birth. 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.

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%. Use of this intervention was reported to be highly cost-saving. 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%.

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. 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, 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. These studies evaluated resistance through surveillance activities, and it is unclear this translates to resistant infections.

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. Macrolides administered to neonates have been associated with infantile hypertrophic pyloric stenosis in some observational studies, 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. 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.

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.

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. The BMGF-funded ‘Sauver avec Azithromycine en Traifiant les Femmes Enceintes et les Enfants’ 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. The PregAnZI-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 PregAnZI-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. |
|---------------------------|---------------------------|---------------------------|
| **Population** | PregAnZI-2 | A-PLUS | SANTE |
| **Intervention** | 2 g of oral intrapartum azithromycin | 2 g of oral intrapartum azithromycin | 2 g of oral azithromycin, twice during pregnancy and once intrapartum |
| **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 stillbirth and infant death through 6–12 months of age (maternal 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. |
|---------------------------|---------------------------|---------------------------|
| **Main Inclusion Criteria** | PregAnZI-2 | A-PLUS | SANTE |
| **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) |
Table 3
tics to treat infection as already shown in other trials. To evaluate outcomes among sub-groups. The three trials have assessed the effect of azithromycin on maternal, newborn and child survival, and 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.

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.

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<th>PregAnZI-2</th>
<th>A-PLUS</th>
<th>SANTE</th>
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<td><strong>Maternal Outcomes</strong></td>
<td>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 localized 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.</td>
<td>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</td>
<td>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)</td>
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<td><strong>Neonatal Outcomes</strong></td>
<td>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.</td>
<td>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</td>
<td>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</td>
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<td><strong>Infant/child Outcomes</strong></td>
<td>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.</td>
<td>Neurologic (BSID) outcomes at 24-mos postpartum for sub-set of infants</td>
<td>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)</td>
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<td><strong>Microbiologic secondary outcomes (and others)</strong> For infants: <em>S. pneumoniae</em> and <em>Klebsiella spp</em> in the nasopharynx; <em>E. coli, Pseudomonas spp, Klebsiella spp</em> from rectal swab and <em>S. aureus, GBS, GAS</em> in the oropharynx. For mothers: prevalence of <em>S. aureus, GBS, GAS, E. coli, Pseudomonas spp, Klebsiella spp</em> in the nasopharynx and <em>S. pneumoniae, Klebsiella spp</em> in the nasopharynx. Resistance to AZI, oxacillin and amoxicillin. Microbiome analysis in nasopharyngeal samples, rectal swabs (babies) and breast milk (women)</td>
<td>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</td>
<td><em>Streptococcus pneumoniae</em> in the nasopharynx (pregnant women and infants) <em>Escherichia coli</em> 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)</td>
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<td><strong>Safety endpoints</strong></td>
<td>SAEs in mothers and infants Infantile hypertrophic pyloric stenosis</td>
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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


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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.