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Effectiveness of intrapartum azithromycin to prevent infections in planned vaginal births in low-income and middle-income countries: a post-hoc analysis of data from a multicentre, randomised, double-blind, placebo-controlled trial

*Waldemar A Carlo, Alan T N Tita, Janet L Moore, Musaku Mwenechanya, Elwyn Chomba, Jennifer J Hemingway-Foday, Avinash Kavi, Mrityunjay C Metgud, Shivaprasad S Goudar, Richard J Derman, Adrien Lokangaka, Antoinette Tshefu, Melissa Bauserman, Jackie K Patterson, Poonam Shivkumar, Manju Waikar, Archana Patel, Patricia L Hibberd, Paul Nyongesa, Fabian Esamai, Osayame Austine Ekhaguere, Sherri Bucher, Saleem Jessani, Shiyam Sunder Tikmani, Sarah Saleem, Robert L Goldenberg, Sk Masum Billah, Ruth Lennox, Rashidul Haque, William Petri, Manolo Mazariegos, Nancy F Krebs, Denise C Babineau, Elizabeth M McClure, Marion Koso-Thomas, on behalf of the A-PLUS Trial Group**

Summary

Background In 2023, the Azithromycin Prevention in Labor Use (A-PLUS) trial showed intrapartum azithromycin reduces maternal sepsis or death in women with planned vaginal delivery in low-resource settings, but whether it reduces maternal infection is unknown. We aimed to evaluate the effectiveness of intrapartum azithromycin in reducing maternal infection.

Methods We performed a post-hoc analysis of the multicentre, facility-based, randomised, double-blind, placebo-controlled A-PLUS trial. This trial compared prophylactic intrapartum single oral dose of 2 g azithromycin versus placebo on maternal morbidity and mortality in low-resource settings in southeast Asia and Africa from Sept 9, 2020, to Aug 18, 2022. The trial enrolled women in labour at 28 weeks' gestation (or later) at eight sites in the Democratic Republic of the Congo, Kenya, Zambia, Bangladesh, India, Pakistan, and Guatemala and found that azithromycin reduced the incidence of maternal sepsis or death. The primary outcome of the present analysis was the incidence of any maternal infection in the azithromycin versus placebo groups, which was defined as one or more of these infections after randomisation: chorioamnionitis, endometritis, perineal or caesarean wound infection, abdominopelvic abscess, mastitis or breast abscess, and other infections. Any neonatal infection was also analysed. All analyses were by intention to treat in all those with data available for that outcome. Relative risks (RRs) and 95% CIs were estimated with a Poisson model adjusted for treatment group and site. Subgroup analyses included a two-way interaction test between intervention group and subgroup. A-PLUS was registered at ClinicalTrials.gov, number NCT03871491.

Findings 29 278 women were randomly assigned to groups: 14 590 to receive azithromycin, 14 688 to receive placebo. Baseline characteristics were similar between the azithromycin and placebo groups (43·3% *vs* 43·4% primiparous, 8·5% *vs* 8·7% high risk for infection). The presence of any maternal infection occurred less often in the azithromycin group (580 [4·0%] of 14 558) compared with the placebo group (824 [5·6%] of 14 661 women; RR 0·71, 95% CI 0·64–0·79, p<0·0001). Any neonatal infection did not differ between treatment groups. Adverse events were not detected.

Interpretation Among women planning vaginal delivery, this analysis provides evidence indicating that intrapartum azithromycin is associated with a lower incidence of maternal infections than placebo.

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For the French translation of the abstract see **Online** for appendix 1

For the Spanish translation of the abstract see **Online** for appendix 2

*Members of the A-PLUS Trial Group are provided in appendix 3 pp 13–15

University of Alabama at Birmingham, Birmingham, AL, USA (Prof W A Carlo MD, Prof A T N Tita PhD); **RTI International, Durham, NC, USA** (J L Moore MS, J J Hemingway-Foday MPH, D C Babineau PhD, E M McClure PhD); **University Teaching Hospital, Lusaka, Zambia** (Prof M Mwenechanya MD, Prof E Chomba MBChB); **Women's and Children's Health Research Unit, KLE Academy of Higher Education and Research's JN Medical College, Belagavi, India** (A Kavi MD, Prof M C Metgud MD, Prof S S Goudar MD); **Thomas Jefferson University, Philadelphia, PA, USA** (Prof R J Derman MD); **Kinshasa School of Public Health, Kinshasa, Democratic Republic of the Congo** (A Lokangaka MD, Prof A Tshefu PhD); **University of North Carolina at Chapel Hill, Chapel Hill, NC, USA** (M Bauserman MD, J K Patterson MD); **Mahatma Gandhi Institute of Medical Sciences, Sevagram, India** (Prof P Shivkumar MD); **Government Medical College, Nagpur, India** (M Waiker MD);

Introduction

Maternal infections occur in 5–8% of pregnancies,[1,2] accounting for approximately 11% of the global burden of maternal deaths, the third most common cause of maternal death worldwide.[3] Neonatal infections are the third most common cause of neonatal mortality and account for about 16% of neonatal mortality worldwide.[4] Severe infections that lead to life-threatening organ dysfunction are classified as sepsis. Maternal sepsis is defined by WHO as "the presence of suspected or confirmed infection plus signs of mild to moderate organ dysfunction (eg, tachycardia, low blood pressure, tachypnoea, altered mental status, reduced urinary output)".[5] Maternal and neonatal deaths from infections

Lata Medical Research Foundation, Nagpur, India (A Patel PhD); **Datta Meghe Institute of Medical Sciences, Wardha, India** (A Patel); **Boston University School of Public Health, Boston, MA, USA** (Prof P L Hibberd PhD); **Moi University School of Medicine, Eldoret, Kenya** (Prof P Nyongesa PhD, Prof F Esami PhD); **Indiana School of Medicine, University of Indiana, Indianapolis, IN, USA** (O A Ekhaguere MBBS, S Bucher PhD); **Aga Khan University, Karachi, Pakistan** (S Jessani MD, S S Tikmani MD, S Saleem MD); **Columbia University School of Medicine, New York, NY, USA** (Prof R L Goldenberg MD); **International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh** (S M Billah PhD, R Haque MD); **University of Sydney, Sydney, NSW, Australia** (S M Billah); **LAMB Hospital, Parbatipur, Bangladesh** (Prof R Lennox MBChB); **University of Virginia, Charlottesville, VA, USA** (Prof W Petri PhD); **Instituto de Nutrición de Centroamérica y Panamá, Guatemala City, Guatemala** (M Mazariegos MD); **University of Colorado—Anschutz Medical Campus, Denver, CO, USA** (Prof N F Krebs MD); **Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA** (M Koso-Thomas MD)

Correspondence to: Prof Waldemar A Carlo, University of Alabama at Birmingham, Birmingham, AL 35233, USA **wacarlo@uabmc.edu**

See **Online** for appendix 3

Research in context

Evidence before this study

Intrapartum azithromycin might reduce maternal and neonatal infections in low-resource settings but two of the large trials focused on sepsis and death rather than infections. The A-PLUS trial reported that intrapartum azithromycin reduces sepsis or death in low-income and middle-income countries (LMICs) but did not analyse maternal or neonatal infections. A 2024 meta-analysis concluded that intrapartum azithromycin administration reduces postpartum infections, but few types of infections were included. We searched PubMed on Dec 3, 2024 for manuscripts on maternal and neonatal infections after intrapartum azithromycin without date or language restriction using the search terms: "azithromycin" AND ("labor" OR "intrapartum" OR "pregnancy") AND ("infection" OR "sepsis" OR "maternal mortality" OR "neonatal mortality"). Our search yielded 1041 articles, of which five were randomised controlled trials and four were meta-analyses that reported data from women with intended vaginal deliveries in LMICs.

Added value of this study

Our study showed that maternal infections of any type occurred less often in the azithromycin group compared with the placebo group, and that the effect was greater against any maternal infection than maternal sepsis or death. Intrapartum azithromycin was not associated with a lower rate of meeting accepted criteria for maternal sepsis if there was no suspicion of an additional infection.

Implications of all the available evidence

The reduction of maternal infections affirms and expands our understanding of the benefits of intrapartum azithromycin in planned vaginal deliveries beyond maternal sepsis. The expanded antimicrobial coverage provided by azithromycin might be particularly beneficial to prevent maternal infections, as adjunctive prophylactic azithromycin was also effective in reducing maternal infections in caesarean deliveries. Future research could assess the effectiveness of the implementation of intrapartum azithromycin in selected geographical or practice settings (eg, in Africa) or could test azithromycin against other frequently used antibiotics in settings of high antibiotic use. Ongoing studies are evaluating the association of the single dose with azithromycin resistance.

are not decreasing.[6,7] The available preventive or treatment strategies have had little effect, and WHO grades the evidence generally as low or very low quality.[8] Data on appropriate perinatal antibiotic use are scarce, and many factors can determine how health-care providers use or abuse antiseptic and antibiotic treatments to prevent or treat maternal infections, according to a systematic review.[9] Prophylaxis with antibiotics is recommended in selected clinical situations[8] but it is not recommended to reduce infections in the vast majority of the deliveries. A 2024 systematic review and meta-analysis concluded that there is a need to develop local and international guidelines for the treatment of maternal infections.[10]

Intrapartum oral azithromycin prophylaxis (2 g) is a promising intervention that has been tested to reduce infections in four randomised controlled trials in low-income and middle-income countries (LMICs).[11–14] Two single-country pilot trials of intrapartum azithromycin conducted in The Gambia and Cameroon reported large reductions in any maternal[9,11] or any neonatal infection[9] associated with this antibiotic, but the small number of participants in both trials precluded reliable estimates of infection rates, confidence in the results, and analysis of major outcomes including deaths. In the largest trial to date (Azithromycin Prevention in Labor Use Study [A-PLUS]),[13] which included 29 278 women in seven countries, maternal sepsis or death was decreased in the azithromycin group compared with the placebo group (1·6% *vs* 2·4%; relative risk [RR] 0·67, 95% CI 0·56–0·79; number needed to treat 125), due to decreased incidence of sepsis. Although some individual types of maternal infections were decreased in the A-PLUS trial, a composite outcome of any type of maternal infection was not reported in the A-PLUS trial. By contrast, in the second largest trial of intrapartum azithromycin, which was conducted in The Gambia and Burkina Faso and enrolled 11 983 women, a composite outcome of maternal sepsis or death was not reduced and the outcome of any maternal infection was low in both groups (0·4% azithromycin *vs* 0·7% placebo).[14] A composite of neonatal sepsis or death was not reduced in either of the trials, but the trials in The Gambia and Burkina Faso reported a reduction in any neonatal infection from 4·4% to 3·0% with the introduction of azithromycin.[13,14] A composite outcome that included any neonatal infection was not reported in the A-PLUS trial. A 2024 meta-analysis concluded that intrapartum azithromycin administration reduces postpartum infections but the type of infections included was limited.[15] Given the importance of maternal and neonatal infections but the scarce data on the composite outcome of any infections in the intrapartum azithromycin trials, we aimed to perform a post-hoc analysis to test the hypothesis that a single oral dose of intrapartum azithromycin in women in labour planning a vaginal delivery was associated with a lower incidence of any maternal infection.

Methods

Trial design and participants

This study was a post-hoc analysis of the A-PLUS trial,[11] a placebo-controlled randomised clinical trial of 2 g of azithromycin given orally to women in labour at 28 weeks or later of pregnancy in health facilities of the eight sites

(Bangladesh, the Democratic Republic of the Congo, Guatemala, Kenya, two sites in India, Pakistan, and Zambia) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Global Network for Women's and Children's Health Research. Participants were assigned (1:1) by random allocation sequence using sequentially numbered envelopes and participants, care providers, research personnel, and outcome assessors were masked to the intervention group. All participants provided informed consent before enrolment. The full methods and procedures of the trial (including randomisation), the algorithm for maternal and neonatal sepsis, and the protocol have been previously reported.[11,16] An interim analysis that was conducted when 76% of participants were randomly assigned indicated maternal benefit; consequently, the trial was stopped for efficacy at the recommendation of the independent data monitoring committee. Participants in this post-hoc analysis were all participants who were included in the intention-to-treat population in the A-PLUS trial. The current post-hoc analysis was prespecified after the initial study was completed but before this analysis was conducted. The institutional review boards and ethics review committees at each participating Global Network for Women's and Children's Health Research site and their partner US institutions and the data coordinating centre approved the A-PLUS trial protocol.[11] A steering committee and an independent data monitoring committee appointed by NICHD provided safety and monitoring of the trial. A-PLUS was registered at ClinicalTrials.gov, number NCT03871491.

Outcomes

Any maternal infection was defined as one or more of the following: chorioamnionitis, endometritis, wound infection, abdominopelvic abscess, mastitis or breast abscess or infection, pyelonephritis, pneumonia, and other suspected infection documented in the clinical record (appendix 3 p 23). The WHO definition for maternal sepsis was operationalised as suspected or confirmed infection based on the presence of fever (>100·4°F or >38°C) or hypothermia (<96·8°F or <36°C) plus one or more signs of mild to moderate organ dysfunction including tachycardia (≥120 beats per min), low blood pressure (systolic <90 mm Hg), tachypnoea (>24 breaths per min), altered mental status or confusion, reduced urinary output (<500 mL over 24 h), jaundice, or renal failure (>1·2 mg/dL). The combinations of the presence or absence of maternal sepsis and any maternal infection were classified as sepsis with another infection, sepsis without other infection, and maternal infection without sepsis.

Any neonatal infection included neonatal sepsis and other infections. Neonatal sepsis was defined as proven (positive bacterial blood culture) or possible serious bacterial infection, pneumonia, or meningitis. Possible serious bacterial infection required one or more of the following WHO criteria: severe chest in-drawing, fever (≥100·4°F or ≥38·0°C), hypothermia (<95·9°F or <35·5°C), no movement or movement only on stimulation, poor or no feeding, or convulsions. Other neonatal infections included urinary infection, omphalitis, eye infection with swelling or drainage, skin infection with 10 or more pustules or bullae, pyelonephritis or kidney infection, other infection documented in the clinical record, or respiratory rate more than 60 breaths per min.

Infection was classified as any infection, sepsis plus another infection, sepsis without another infection, infection without sepsis, and a composite of maternal death, sepsis, or infection. In the infants, analyses compared the incidence of stillbirth, neonatal death between birth and 28 days postpartum, or at least one neonatal infection between birth and 28 days postpartum between treatment groups. Types of infection were neonatal sepsis, neonatal infection, and neonatal infection without sepsis. Any outcome involving infection was broken down also by type of infection. Subgroup analyses of each of these outcomes were also conducted in the following subgroups: high risk and low risk for infection (high risk if membrane ruptured ≥8 h or in labour ≥18 h before randomisation), region (Africa or Asia), prophylactic antibiotic, delivery mode, type of labour, and preterm and term status.

Safety monitoring of harms or unintended effects was based on surveillance of maternal side-effects (eg, nausea, vomiting, and diarrhoea, abdominal pain, vaginitis, and dizziness) potentially associated with azithromycin during labour and postpartum. For infants, findings suggestive of pyloric stenosis were assessed during the follow-up visits. Maternal and neonatal surveillance also included assessment of unintended medical visits and death from any cause. Additional maternal and neonatal risks monitored included anaphylaxis, allergic reactions, liver failure, and arrhythmias.

Statistical methods

All analyses were performed in the intention-to-treat population, defined as all women who were randomly assigned and their infants, in all those with data available for each outcome. Baseline characteristics and outcomes in each treatment group were summarised with frequencies and percentages. The analyses were done to compare the incidence of at least one maternal infection diagnosed between delivery and 42 days postpartum (except chorioamnionitis, which is before delivery) between treatment groups. The RR and 95% CI of each outcome comparing the azithromycin group to the placebo group was obtained by fitting a generalised linear model with a Poisson distribution and log link and adjusting for site and treatment group as fixed effects. Subgroup analyses were performed by including fixed

	Azithromycin (n=14 590)	Placebo (n=14 688)
Region		
Africa	5779/14 590 (39·6%)	5801/14 688 (39·5%)
Asia	8017/14 590 (54·9%)	8084/14 688 (55·0%)
Latin America	794/14 590 (5·4%)	803/14 688 (5·5%)
Median maternal age (IQR), years	24·0 (21·0–28·0)	24·0 (21·0–28·0)
Married	13 729/14 589 (94·1%)	13 834/14 687 (94·2%)
Maternal education		
No formal schooling	3457/14 565 (23·7%)	3476/14 665 (23·7%)
1–6 years of schooling	2002/14 565 (13·7%)	2022/14 665 (13·8%)
7–12 years of schooling	7308/14 565 (50·2%)	7325/14 665 (49·9%)
≥13 years of schooling	1798/14 565 (12·3%)	1842/14 665 (12·6%)
Primiparous	6311/14 588 (43·3%)	6376/14 687 (43·4%)
Multiple birth	99/14 588 (0·7%)	95/14 687 (0·6%)
Any maternal infection during pregnancy*	797/14 589 (5·5%)	821/14 687 (5·6%)
Any maternal condition during pregnancy†	1017/14 589 (7·0%)	955/14 687 (6·5%)
Gestational age <37 weeks	1841/14 583 (12·6%)	1895/14 684 (12·9%)
Labour induction	2651/14 581 (18·2%)	2724/14 677 (18·6%)
High risk for sepsis before randomisation	1247/14 588 (8·5%)	1283/14 687 (8·7%)
Prolonged labour ≥18 h before randomisation	670/14 588 (4·6%)	698/14 687 (4·8%)
Prolonged rupture of membranes ≥8 h before randomisation	615/14 588 (4·2%)	632/14 687 (4·3%)

Data are n/N (%), unless otherwise specified. *Any maternal infection during pregnancy includes group B streptococcus, pneumonia, pyelonephritis, rubella, chlamydia, herpes, syphilis, gonorrhoea, HIV, hepatitis B, malaria, urinary tract infection, or other infection. †Any maternal condition during pregnancy includes diabetes, chronic hypertension, hypertensive disorders of pregnancy, or other condition.

Table 1: **Baseline, labour, and delivery characteristics by treatment group**

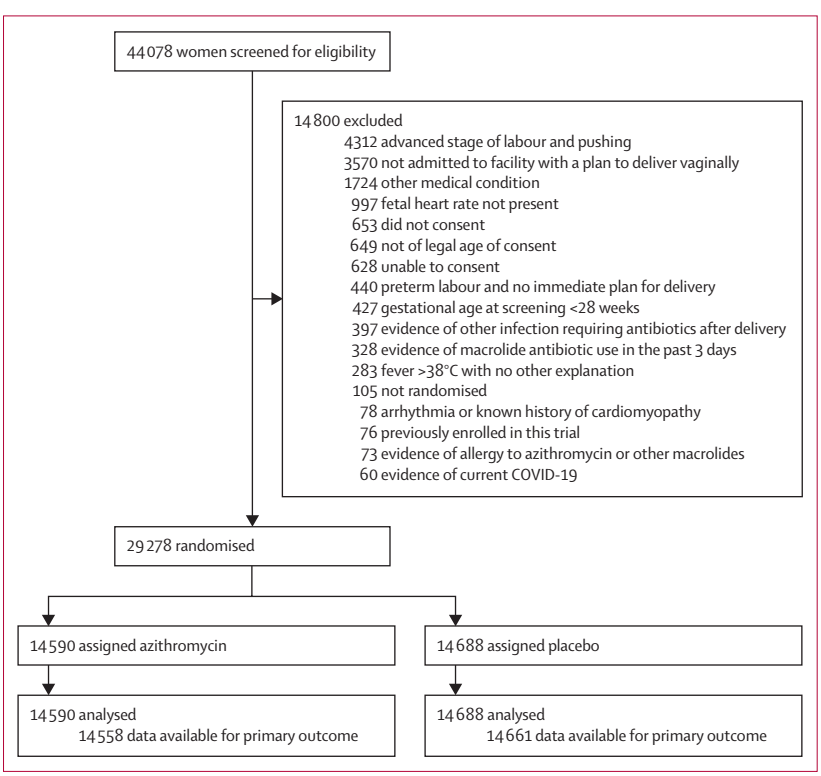

Figure 1: **Participant flow diagram**

effects for the subgroup and a two-way interaction between treatment group and subgroup to find out if the effect of intrapartum azithromycin on the incidence of each outcome was modified by the subgroup.

Models for neonatal outcomes used a generalised estimating equation approach with a compound symmetry covariance structure to account for correlation of responses within multiple births. Due to the small number of participants that were lost to follow-up, the percentage of participants with missing outcomes was negligible across all outcomes (<0·5%) and so all analyses were performed by assuming any missing data were completely at random. All analyses were exploratory in nature and so no adjustment was made for multiple comparisons arising from analyses of multiple outcomes or subgroups and p values and CIs were provided for descriptive purposes only. All analyses were conducted with SAS version 9.4 and figures were produced using R version 4.4.0.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

29 278 participants were randomly assigned to either the azithromycin group (14 590 women with 14 687 neonates or stillbirths) or to the placebo group (14 688 women with 14 782 neonates or stillbirths) from Sept 9, 2020 up to

Aug 18, 2022. Baseline characteristics of the two groups did not differ (table 1; figure 1). Maternal participants were followed up between 7 days and 7 months after birth and neonatal participants were followed up between 7 days and 8 months after birth.

Any maternal infection occurred less often in the azithromycin group compared with the placebo group (4·0% *vs* 5·6%; RR 0·71, 95% CI 0·64–0·79; p<0·0001; table 2). Sepsis plus another infection and any infection without sepsis occurred less often in the azithromycin group. By contrast, there was no evidence of a statistically significance difference in the incidence of sepsis without another infection between groups. The results for the specific type of infections are in table 2. The composite outcome of any maternal infection or death occurred less often in the azithromycin group compared with the placebo group (4·0% *vs* 5·7%; RR 0·72, 95% CI 0·64–0·80; table 2).

There was no evidence of a statistically significant difference between groups with respect to the incidence of any neonatal infection, any neonatal infection without sepsis, or the composite outcome of any infection, stillbirth, or neonatal death (table 2). Skin infections with ten or more pustules or bullae were lower in the azithromycin group than in the placebo group (0·4% *vs* 0·6%; RR 0·67, 95% CI 0·49–0·93). There was also no evidence of a statistically significant difference between groups in the incidence of other neonatal infections (table 2).

In the prespecified subgroup analyses of maternal outcomes, the effect of azithromycin on reducing the incidence of any maternal infection was stronger in Africa than Asia (p<0·0001; figure 2), maternal sepsis plus another infection (p<0·0001; figure 3), and any maternal infection or death (p<0·0001; appendix 3 p 9). There was no evidence that geographical region modified the effect of azithromycin on the incidence of maternal sepsis without another infection (p=0·23; figure 4) or maternal infection without sepsis (p=0·21; appendix 3 p 9). There was also no evidence that the cohort at high risk, prophylactic antibiotic use during labour, type of delivery (caesarean or vaginal), type of labour (ie, spontaneous labour or induction), or preterm delivery modified the effect of azithromycin on any of the maternal outcomes.

In the subgroup analyses for the neonatal outcomes, including any infection, infection without sepsis, and the composite outcome of any infection, stillbirth, or neonatal death, there was no evidence of effect modification by any of the subgroups considered (appendix 3 pp 10–12). There were no harms or unintended effects reported in the A-PLUS Trial.[11]

Discussion

In this post-hoc analysis of the A-PLUS trial, a single dose of intrapartum azithromycin was associated with a lower incidence of any maternal infection than placebo regardless of whether the maternal infection was associated with sepsis or not, without evidence of harm. This post-hoc analysis supports the results of the primary publication of the A-PLUS Trial[13] and also shows that the analysis of a composite of infections, including infections not reported in the original manuscript from the randomised trial, showed a larger reduction compared

	Azithromycin	Placebo	Relative risk (95% CI)
Maternal outcome			
Any infection	580/14 558 (4·0%)	824/14 661 (5·6%)	0·71 (0·64–0·79)
Sepsis without another infection	69/14 558 (0·5%)	76/14 658 (0·5%)	0·91 (0·66–1·26)
Sepsis plus another infection	150/14 558 (1·0%)	261/14 658 (1·8%)	0·58 (0·47–0·71)
Chorioamnionitis	1/14 558 (<0·1%)	3/14 662 (<0·1%)	··
Endometritis	118/14 558 (0·8%)	205/14 659 (1·4%)	0·58 (0·46–0·73)
Wound infection	24/14 557 (0·2%)	46/14 655 (0·3%)	0·53 (0·32–0·86)
Other maternal infection	56/14 558 (0·4%)	79/14 657 (0·5%)	0·71 (0·51–1·01)
Abdominopelvic abscess	2/14 558 (<0·1%)	3/14 657 (<0·1%)	0·67 (0·11–4·01)
Mastitis or breast abscess or infection	21/14 558 (0·1%)	27/14 655 (0·2%)	0·78 (0·44–1·38)
Pyelonephritis	5/14 558 (<0·1%)	23/14 655 (0·2%)	0·22 (0·08–0·58)
Pneumonia	29/14 558 (0·2%)	27/14 657 (0·2%)	1·09 (0·64–1·83)
Infection without sepsis	361/14 558 (2·5%)	485/14 658 (3·3%)	0·75 (0·66–0·86)
Chorioamnionitis	4/14 558 (<0·1%)	5/14 662 (<0·1%)	··
Endometritis	73/14 558 (0·5%)	89/14 659 (0·6%)	0·83 (0·61–1·13)
Wound infection	202/14 557 (1·4%)	276/14 655 (1·9%)	0·74 (0·61–0·88)
Other maternal infection	93/14 558 (0·6%)	138/14 657 (0·9%)	0·68 (0·52–0·89)
Abdominopelvic abscess	2/14 558 (<0·1%)	3/14 657 (<0·1%)	··
Mastitis or breast abscess or infection	17/14 558 (0·1%)	30/14 655 (0·2%)	0·57 (0·32–1·04)
Pyelonephritis	6/14 558 (<0·1%)	20/14 655 (0·1%)	0·30 (0·12–0·76)
Pneumonia	0/14 558	4/14 657 (<0·1%)	··
Other bacterial infection	68/14 558 (0·5%)	81/14 657 (0·6%)	0·85 (0·61–1·17)
Death or infection	588/14 526 (4·0%)	829/14 640 (5·7%)	0·72 (0·64–0·80)
Newborn outcome			
Any infection	2196/14 573 (15·1%)	2205/14 657 (15·0%)	1·01 (0·96–1·06)
Infection without sepsis	763/14 573 (5·2%)	798/14 657 (5·4%)	0·97 (0·88–1·07)
Eye infection with swelling or drainage	152/14 573 (1·0%)	124/14 657 (0·8%)	1·23 (0·98–1·56)
Skin infection with ≥10 pustules or bullae	61/14 573 (0·4%)	92/14 657 (0·6%)	0·67 (0·49–0·93)
Omphalitis	29/14 573 (0·2%)	36/14 657 (0·2%)	0·81 (0·50–1·32)
Urinary tract infection	1/14 573 (<0·1%)	5/14 657 (<0·1%)	0·20 (0·02–1·72)
Pyelonephritis or kidney infection	0/14 573	0/14 657	··
Pneumonia or lung infection	15/14 573 (0·1%)	11/14 657 (0·1%)	1·37 (0·63–2·99)
Meningitis	0/14 573	0/14 657	··
Other infection in clinical record	128/14 573 (0·9%)	140/14 657 (1·0%)	0·92 (0·72–1·16)
Respiratory rate ≥60 breaths per min	435/14 573 (3·0%)	448/14 657 (3·1%)	0·99 (0·87–1·12)
Stillbirth, death, or infection	2300/14 658 (15·7%)	2319/14 757 (15·7%)	1·00 (0·95–1·06)

Data are n/N (%), unless otherwise specified. Estimates were obtained by fitting a Poisson model to each outcome adjusting for site and treatment. Models for neonatal outcomes account for correlation among multiples assuming an exchangeable covariance structure. Models for skin infection, urinary tract infection, and pneumonia had convergence issues, so models are fit without the adjustment for correlation among multiples. Models for chorioamnionitis, pyelonephritis or kidney infection, and meningitis did not converge.

Table 2: **Maternal and newborn outcomes by treatment**

	Azithromycin (n=14 558)	Placebo (n=14 661)	Relative risk (95% CI)	$p_{interaction}$
Any infection within 6 weeks	580/14 588 (4·0%)	824/14 661 (5·6%)	0·71 (0·64–0·79)	
Cohort at high risk				
Yes	65/1245 (5·2%)	88/1280 (6·9%)	0·75 (0·54–1·03)	0·73
No	515/13 312 (3·9%)	736/13 381 (5·5%)	0·71 (0·63–0·79)	
Geographical region				
Africa	108/5777 (1·9%)	222/5794 (3·8%)	0·49 (0·39–0·61)	0·0002
Asia	458/7989 (5·7%)	582/8066 (7·2%)	0·79 (0·70–0·90)	
Prophylactic antibiotic use during labour				
Yes	149/2042 (7·3%)	205/2038 (10·1%)	0·73 (0·59–0·90)	0·81
No	431/12 516 (3·4%)	619/12 623 (4·9%)	0·70 (0·62–0·80)	
Type of delivery				
Caesarean delivery	173/2038 (8·5%)	254/2063 (12·3%)	0·69 (0·57–0·84)	0·76
Vaginal delivery	407/12 520 (3·3%)	570/12 598 (4·5%)	0·72 (0·63–0·82)	
Type of labour				
Spontaneous labour	387/11 909 (3·2%)	577/11 938 (4·8%)	0·67 (0·59–0·76)	0·13
Induction	192/2641 (7·3%)	247/2713 (9·1%)	0·80 (0·66–0·97)	
Preterm				
Yes	71/1834 (3·9%)	106/1893 (5·6%)	0·67 (0·50–0·90)	0·68
No	509/12 719 (4·0%)	718/12 765 (5·6%)	0·72 (0·64–0·80)	

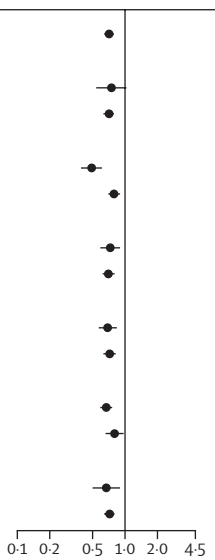

Figure 2: **Any maternal infection subgroup analyses**
Forest plot displaying the estimated relative risk (95% CI) of maternal sepsis or infection comparing mothers randomly assigned to azithromycin versus placebo overall and within selected subgroups. Overall estimates were obtained by fitting a Poisson model adjusting for site and treatment. Subgroup estimates were obtained by fitting a Poisson model adjusting for site, treatment, subgroup, and the interaction of treatment and subgroup.

	Azithromycin (n=14 558)	Placebo (n=14 658)	Relative risk (95% CI)	$p_{interaction}$
Sepsis plus additional infection within 6 weeks	150/14 558 (1·0%)	261/14 658 (1·8%)	0·58 (0·47–0·71)	
Cohort at high risk				
Yes	16/1245 (1·3%)	20/1279 (1·6%)	0·79 (0·41–1·52)	0·34
No	134/13 312 (1·0%)	241/13 379 (1·8%)	0·56 (0·45–0·69)	
Geographical region				
Africa	55/5777 (1·0%)	138/5793 (2·4%)	0·40 (0·29–0·55)	<0·0001
Asia	94/7989 (1·2%)	122/8064 (1·5%)	0·78 (0·60–1·02)	
Prophylactic antibiotic use during labour				
Yes	28/2042 (1·4%)	51/2038 (2·5%)	0·56 (0·35–0·88)	0·84
No	122/12 516 (1·0%)	210/12 620 (1·7%)	0·59 (0·47–0·73)	
Type of delivery				
Caesarean delivery	39/2038 (1·9%)	79/2061 (3·8%)	0·53 (0·36–0·77)	0·51
Vaginal delivery	111/12 520 (0·9%)	182/12 597 (1·4%)	0·61 (0·48–0·77)	
Type of labour				
Spontaneous labour	102/11 909 (0·9%)	191/11 936 (1·6%)	0·54 (0·42–0·68)	0·22
Induction	48/2641 (1·8%)	70/2712 (2·6%)	0·71 (0·49–1·02)	
Preterm				
Yes	24/1834 (1·3%)	46/1893 (2·4%)	0·53 (0·32–0·87)	0·71
No	126/12 719 (1·0%)	215/12 762 (1·7%)	0·59 (0·47–0·73)	

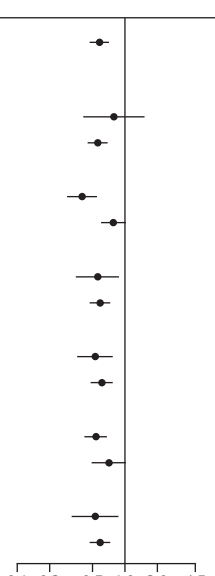

Figure 3: **Maternal sepsis plus another infection subgroup analyses**
Forest plot displaying the estimated relative risk (95% CI) of maternal sepsis with infection comparing mothers randomly assigned to azithromycin versus placebo overall and within selected subgroups. Overall estimates were obtained by fitting a Poisson model adjusting for site and treatment. Subgroup estimates were obtained by fitting a Poisson model adjusting for site, treatment, subgroup, and the interaction of treatment and subgroup.

with the reduction in sepsis previously reported.[13] Furthermore, this analysis also found that, in the absence of another identified or suspected infection, azithromycin was not associated with a lower incidence of maternal sepsis, as defined by WHO, compared with placebo. These findings support the likelihood that the mechanism of action of intrapartum azithromycin is an antibiotic-mediated effect, as the positive associations were linked more to maternal infection than maternal sepsis, which was sometimes not associated with proven or suspected infection. The previous reports of azithromycin trials[12,14,16] and a new meta-analysis[15] did not

	Azithromycin (n=14 558)	Placebo (n=14 658)	Relative risk (95% CI)	$p_{interaction}$
Sepsis without an additional infection within 6 weeks	69/14 558 (0·5%)	76/14 658 (0·5%)	0·91 (0·66–1·26)	
Cohort at high risk				
Yes	7/1245 (0·6%)	16/1279 (1·3%)	0·45 (0·19–1·10)	0·091
No	62/13 312 (0·5%)	60/13 379 (0·4%)	1·03 (0·73–1·48)	
Geographical region				
Africa	26/5777 (0·5%)	36/5793 (0·6%)	0·72 (0·44–1·20)	0·23
Asia	43/7989 (0·5%)	40/8064 (0·5%)	1·08 (0·70–1·67)	
Prophylactic antibiotic use during labour				
Yes	13/2042 (0·6%)	7/2038 (0·3%)	1·79 (0·71–4·49)	0·12
No	56/12 516 (0·4%)	69/12 620 (0·5%)	0·82 (0·58–1·17)	
Type of delivery				
Caesarean delivery	25/2038 (1·2%)	17/2061 (0·8%)	1·48 (0·80–2·74)	0·067
Vaginal delivery	44/12 520 (0·4%)	59/12 597 (0·5%)	0·75 (0·51–1·11)	
Type of labour				
Spontaneous labour	44/11 909 (0·4%)	57/11 936 (0·5%)	0·77 (0·52–1·15)	0·18
Induction	24/2641 (0·9%)	19/2712 (0·7%)	1·27 (0·70–2·32)	
Preterm				
Yes	15/1834 (0·8%)	13/1893 (0·7%)	1·21 (0·57–2·54)	0·41
No	54/12 719 (0·4%)	63/12 762 (0·5%)	0·86 (0·59–1·23)	

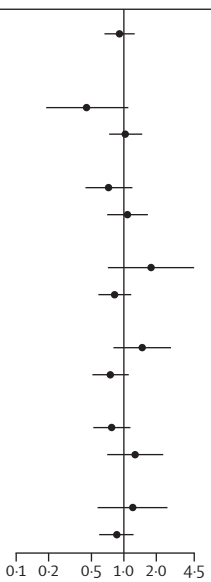

Figure 4: **Maternal sepsis without an additional infection subgroup analyses**
Forest plot displaying the estimated relative risk (95% CI) of maternal sepsis without infection comparing mothers randomly assigned to azithromycin versus placebo overall and within selected subgroups. Overall estimates were obtained by fitting a Poisson model adjusting for site and treatment. Subgroup estimates were obtained by fitting a Poisson model adjusting for site, treatment, subgroup, and the interaction of treatment and subgroup.

report a composite of any maternal or any neonatal infection so this study reports unique data.

Although this post-hoc analysis was done strictly by randomisation with data from the large placebo-controlled A-PLUS trial, there are important limitations. First, this analysis was not prespecified in the original protocol, it was proposed after the data on death, sepsis, and some individual infections were analysed but before data on all maternal and neonatal infection were analysed. Still, as a post-hoc analysis of a randomised controlled trial, the best interpretation of the results is of associations rather than causal inferences. Thus, the results can only be considered exploratory. A second important limitation is that the accurate identification of maternal and neonatal infection is difficult, especially in low-resource settings, where incomplete laboratory support is available, and diagnoses are mostly dependent on clinical assessments. In preparation for the A-PLUS trial, capacity was built for improved clinical diagnosis and laboratory testing. Urinalysis and urine cultures were rarely collected, and urinary tract infections were rarely diagnosed. However, the inclusion of data on other maternal infections besides peripartum infections is an important strength of this study as maternal infections, other than peripartum infections, are common and account for many peripartum hospitalisations and deaths.[17] Furthermore, follow-up was done to 42 days postpartum, which is not available in many studies and databases. Importantly, receipt of antibiotics was not solely sufficient to meet criteria for infection. Third, we made no allowance for multiplicity.

The incidence of maternal peripartum infection can vary by risk factors, definitions, and capacity for diagnosis including clinical or laboratory criteria. In the only meta-analysis of peripartum infection, which was published in 2019 and included 111 studies from 46 countries, 3·9% (95% CI 1·8–6·8) of women had chorioamnionitis, 1·6% (0·9–2·5) had endometritis, 1·2% (1·0–1·5) had wound infection, 0·05% (0·03–0·07) had sepsis, and 1·1% (0·3–2·4) had two or more maternal peripartum infections, for a total incidence of 7·8% women having one or more peripartum infections.[1] Despite the limited data from LMICs in the meta-analysis, the incidence of maternal peripartum infection was similar to the data from the WHO-led multi-country (n=52) cross-sectional prospective study published in 2020, in which 7·0% of all women, 7·1% of women participating in low-income countries, and 7·2% of women living in lower-middle-income countries who gave birth were diagnosed with infection.[18] The incidence of any maternal infection in the placebo group of the A-PLUS trial was 5·6%, which was similar to the rates reported (excluding endometriosis and sepsis, as they were excluded in our trial) in the meta-analysis (6·2%) and the cross sectional study (5·9%).[1,17] The incidence of any maternal infection was also similar to the model-based data from the 2017 Global Burden of Diseases, Injuries, and Risk Factors Study.[19]

In preparation for the A-PLUS trial, capacity building was conducted at each site before starting the trial. Capacity building included training in recognition of peripartum and neonatal infections and obtaining the

appropriate laboratory testing, but did not include infection prevention or control. Capacity building probably improved the diagnosis of maternal and neonatal infections. Intrapartum screening and enrolment excluded women with chorioamnionitis and other infections at the time of consent and randomisation, explaining the lower overall peripartum infection in this study compared with the meta-analysis data. In this study, the incidence of other maternal infections besides chorioamnionitis was similar to or higher than that in the meta-analysis, suggesting accurate identification of maternal peripartum infection in the A-PLUS trial. Blood, urine, or other cultures and pathogen identification were obtained from 3·1% of the mothers and 28·7% of the neonates as reported,[13] which is similar to the rates of infections diagnosed, but uptake was not universal if an infection was suspected.

See Online for appendix 4

The intrapartum azithromycin trials reported a wide range of maternal and neonatal infection and sepsis rates. In the initial pilot trial in The Gambia, the incidence of maternal infection (9·2%) and neonatal infection (23·8%) were very high in the control group and decreased significantly in the azithromycin group for both maternal (3·6%) and neonatal (18·1%) infections.[11] The Cameroon trial did not report any maternal or any neonatal infection but reported a reduction in chorioamnionitis (3·2% to 1·2%) and wound infections (4·0% to 0·8%).[12] The trial in The Gambia and Burkina Faso found a low incidence of any maternal infection, with a small reduction in the azithromycin group compared with placebo (0·4% *vs* 0·7%).[14] The incidences of maternal and neonatal infections can vary widely depending on baseline risk factors, definitions, and diagnostic capacity.[17] Despite different baseline incidences of infection in the four randomised controlled trials in LMICs, the findings of lower incidence of any maternal infection in the azithromycin trials could be robust, generalisable, and clinically important. Azithromycin is effective in reducing maternal infections after caesarean delivery[13,20–22] and is recommended for prophylaxis in caesarean delivery during labour.[23] The spectrum of antimicrobial coverage provided by azithromycin might be particularly beneficial to prevent perinatal infections.[24] However, the widespread use of intrapartum antibiotics could lead to antibiotic resistance, a potential threat that makes infections hard to treat and resistant organisms more likely to spread, so the balance between benefits and harms needs to be considered.

In summary, this post-hoc analysis of the A-PLUS trial shows that use of azithromycin in low-resource settings was associated with a lower incidence of any maternal infection but not a difference in any neonatal infections compared with placebo. These data might be useful for epidemiological, programmatic, and research endeavours, as maternal infections are an important cause of maternal mortality and morbidities.[6,17,25]

Contributors

WAC, ATNT, MMw, EC, JJH-F, and EMM conceptualised and designed the study. All authors collected the data. JLM and DCB did the modelling and statistical analysis. WAC and JLM directly accessed and verified the underlying trial data reported in the manuscript. DCB and MK-T interpreted the data. WAC and JLM wrote the first draft of the report with input from ATNT, MMw, EC, JJH-F, DCB, and EMM. All authors critically revised the manuscript. All authors had full access to all the data in the study, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work. All authors had final responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 4). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

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Data sharing

De-identified participant data from the A-PLUS trial are available at the National Institute of Child Health and Human Development data repository (N-DASH): https://dash.nichd.nih.gov/. Data sharing is accessed and governed according to the procedures and policies of N-DASH.

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