ORIGINAL ARTICLE

Oral azithromycin given during labour decreases bacterial carriage in the mothers and their offspring: a double-blind randomized trial

A. Roca[1,2], C. Oluwalana[1], A. Bojang[1], B. Camara[1], B. Kampmann[1], R. Bailey[2], A. Demba[3], C. Bottomley[2] and U. D'Alessandro[1,2,4]

1) *Medical Research Council Unit The Gambia,* 2) *London School of Hygiene and Tropical Medicine, London, UK,* 3) *Ministry of Health and Social Welfare, Gambia and* 4) *Institute of Tropical Medicine, Antwerp, Belgium*

Abstract

Bacterial sepsis remains a leading cause of death among neonates with *Staphylococcus aureus*, group B streptococcus (GBS) and *Streptococcus pneumoniae* identified as the most common causative pathogens in Africa. Asymptomatic bacterial colonization is an intermediate step towards sepsis. We conducted a phase III, double-blind, placebo-controlled randomized trial to determine the impact of giving one oral dose of azithromycin to Gambian women in labour on the nasopharyngeal carriage of *S. aureus*, GBS or *S. pneumoniae* in the newborn at day 6 postpartum. Study participants were recruited in a health facility in western Gambia. They were followed for 8 weeks and samples were collected during the first 4 weeks. Between April 2013 and April 2014 we recruited 829 women who delivered 843 babies, including 13 stillbirths. Sixteen babies died during the follow-up period. No maternal deaths were observed. No serious adverse events related to the intervention were reported. According to the intent-to-treat analysis, prevalence of nasopharyngeal carriage of the bacteria of interest in the newborns at day 6 was lower in the intervention arm (28.3% versus 65.1% prevalence ratio 0.43; 95% CI 0.36–0.52, p <0.001). At the same time-point, prevalence of any bacteria in the mother was also lower in the azithromycin group (nasopharynx, 9.3% versus 40.0%, p <0.001; breast milk, 7.9% versus 21.6%, p <0.001; and the vaginal tract, 13.2% versus 24.2%, p <0.001). Differences between arms lasted for at least 4 weeks. Oral azithromycin given to women in labour decreased the carriage of bacteria of interest in mothers and newborns and may lower the risk of neonatal sepsis.

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Corresponding author: A. Roca, Disease Control & Elimination—Theme Coordinator, Medical Research Council Unit The Gambia, Atlantic Road, Fajara, PO Box 273 Banjul, Gambia
E-mail: aroca@mrc.gm

Background

There are more than 4 million neonatal deaths annually and a third are caused by severe bacterial disease, which mainly presents as sepsis [1]. In sub-Saharan Africa, the limited available data show that neonatal sepsis is caused by both Gram-positive and Gram-negative bacteria [2–4], although more than half of the cases are attributable to the former, particularly *Staphylococcus aureus* [1], *Streptococcus pneumoniae* and group B streptococcus (GBS) [3].

Early-neonatal sepsis is mainly due to intrapartum bacterial vertical transmission [2] during delivery (in the birth canal) or during the first weeks of life as a result of the close physical contact with the mother if she carries pathogenic bacteria [1,5–7]. If newborns are mainly infected by their mother, an intervention that is able to reduce maternal bacterial carriage should prevent vertical transmission and consequently neonatal sepsis.

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Azithromycin is a macrolide with a wide antimicrobial spectrum [8] currently licensed for use in children >6 months of age for a wide range of infections [9,10]. As part of the WHO-recommended trachoma control strategy, mass azithromycin treatment campaigns in countries where trachoma is endemic [11–13] decreased both the nasopharyngeal pneumococcal carriage [14] and the overall childhood mortality [15].

Azithromycin has also been used in pregnant women in sub-Saharan Africa in several trials designed to reduce the incidence of maternal malaria and preterm deliveries and low-birthweight, but a meta-analysis found no effect of these outcomes [16]. However, a recent study conducted in Papua New Guinea showed 25% reduction of low-birthweight infants after including monthly azithromycin (4 g) for 3 months to the standard sulphadoxine-pyrimethamine during the last months of pregnancy [17]. Blocking vertical transmission has already been used successfully in the context of GBS, the main bacterium causing neonatal sepsis in developed countries, in Europe [18] and USA [19]. But whereas in Europe and the USA treatment is targeted at women with GBS vaginal carriage, in sub-Saharan Africa systematic treatment may be more feasible, since half of pregnant women are carriers of bacteria associated with neonatal sepsis in the region [20]. In a first proof-of-concept assessing the potential of a new intervention to prevent neonatal sepsis, we evaluated the efficacy of one oral dose of azithromycin administered to women in labour in decreasing bacterial carriage (*S. aureus*, GBS and *S. pneumoniae*) both in the mother and her newborn.

Methods/Design

The study protocol has been published elsewhere [21]. Briefly, this was a phase III, double-blind, placebo-controlled, randomized trial in which women in labour were randomized to receive a single dose of oral azithromycin (2 g) or placebo.

The packaging and labelling of the interventional medical product was conducted by IDIFARMA. Azithromycin and placebo were provided as tablets packed in blisters. IDIFARMA created the randomization list (permuted blocks) and numbered the blisters according to the list. One blister pack of interventional medical product contained four tablets each of 0.5 g of azithromycin or placebo (2 g). The active drug and the placebo looked identical. The statistician of the Data Safety Monitor Board (DSMB) kept the list until the final database was locked. The investigators were blinded to the patient's allocation until the database was locked, when the code was broken.

The study was based at the Jammeh Foundation for Peace (JFP), a government-run health centre located in western Gambia that manages 4500 deliveries/year. The population in the catchment area is representative of The Gambia and it covers the main ethnic groups. Approximately 70% of deliveries in the country occur in health facilities (Jasseh *et al.* personal communication). The climate of the area is typical of the sub-Sahel region. Illiteracy is high [22].

Between April 2013 and April 2014, women in labour aged 18–45 years were recruited when attending the JFP labour ward. They had signed consent to participate in the study during their antenatal visits. Eligibility was re-assessed in the JFP labour ward based on the exclusion criteria: (i) known human immunodeficiency virus infection; (ii) any acute or chronic condition that could interfere with the study as judged by the research clinicians; (iii) planned travel out of the catchment during the follow up; (iv) known risk of caesarean section; (v) likely referral during labour (eclampsia or severe anaemia); (vi) known multiple pregnancy; (vii) known severe congenital malformation or intrauterine death confirmed before randomization; (ix) known allergy to macrolides; (x) consumption of antibiotic within the previous week.

Pre-intervention samples were collected during labour (nasopharyngeal swab (NPS) and vaginal swab (VS)). An NPS was collected from the baby within 6 h after birth. After discharge, mothers and babies were visited at home for 2 months, daily during the first week and weekly thereafter. NPS and breast milk samples were collected at days 3, 6, 14 and 28. In addition, a VS was collected between days 8 and 10 after delivery at the postnatal check visit at JFP.

The primary end point was prevalence of carriage of *S. aureus*, GBS or *S. pneumoniae* in the NPS sample of the newborn at day 6. Secondary end points included: (i) bacterial carriage in the NPS of the baby and the mother; (ii) carriage in the VS and breast milk during the first 4 weeks after delivery; and (iii) prevalence of carriage of any of the study bacteria non-susceptible to azithromycin.

To evaluate the safety of the intervention on mothers and newborns, adverse events were monitored and assessed throughout the follow up. Diagnoses were based on clinical judgement according to the study clinicians.

A local safety monitor (LSM) and a DSMB reviewed serious adverse events during the trial, and the trial was monitored by an independent clinical trials monitor. The study was approved by the joint Gambia Government/Medical Research Council (MRC)/Ethics Committee.

Sample collection and laboratory analysis

The NPS, low VS and breast milk samples were collected as part of the trial; see details elsewhere [24].

Laboratory procedures

Samples were processed following standard microbiological procedures [21].

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