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Back to the drawing board: still looking for a simple, effective prevention measure for neonatal sepsis in high-mortality settings

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The Decade of Vaccines¹ contributed to notable global declines in mortality among children <5 years of age, but mortality in the neonatal period remains a stubborn problem.² Most neonatal deaths occur in the first week of life. The causes of such deaths are difficult to characterize. Evidence suggests complications of labor and delivery play a major role in deaths in the first hours after birth, and that preterm delivery and infections also each cause approximately 1/3 of deaths in the first week of life.³ Many neonatal deaths are a result of multiple conditions, such as preterm birth in combination with sepsis.⁴ Primary prevention of preterm delivery remains a holy grail, but prevention of early-life infections feels more tractable--though often just out of our grasp.

To this end, it is with great interest that we read the results of the PregnAnZI-2 trial by Roca et al⁵ of 12,000 enrolled delivering women in the Gambia and Burkina Faso who were randomized upon admission for labor to receive either placebo or intrapartum oral azithromycin in a widely available formulation. Despite the inherent challenges of conducting research in a high neonatal mortality setting, further compounded by the COVID-19 pandemic, the trial was conducted with rigor by experienced investigators. The outcomes of the over 11,800 live born infants point to a clear, strong, but disappointing result: the intervention (intrapartum oral azithromycin) did not prevent neonatal sepsis and total mortality, the trial's composite primary endpoint

Why did the investigators think the intervention might work? Since the publication of the MORDOR trial results,⁶ in which twice-annual community administration of azithromycin showed an unexpected but notable reduction in mortality among infants aged 1-5 months in the high-mortality Niger trial site, the potential life-saving benefits of azithromycin have been of great interest. Azithromycin's safety and tolerability have been established and the medicine has been used at scale among children for trachoma prevention.⁷ Since few interventions actually reduce child mortality, any notable positive effects, even if the causal pathways are not fully understood, merit attention. Because the MORDOR trial and its

extensions excluded infants <1 month of age, efforts to explore the potential of azithromycin early in life motivated the PregnAnZI-2 trial. The authors conducted a smaller scale ‘proof of concept’ trial before embarking on the full trial presented here. The smaller trial showed significant reductions in vertical transmission of key neonatal sepsis pathogens, as measured using nasopharyngeal swabs in the newborns, and fewer bacteria of any kind in specimens from mothers’ nasopharynges and genital tracts.⁸ Follow-up of the cohort of enrolled infants at 11 months of age hinted at lower prevalence of malnutrition in those who had received intrapartum azithromycin.⁹ Another West African trial evaluating azithromycin use at antenatal, intrapartum, and postnatal routine visits is currently recruiting participants.¹⁰

On the other hand, there are many reasons *a priori* to question the intervention. The etiologic agents causing neonatal sepsis in West Africa are not well described (and difficult to isolate, as evidenced by the high rate of contamination even in this trial setting⁵). In addition, azithromycin is not a preferred agent for prevention of group B *Streptococcus* (GBS) or *Escherichia coli*, two known and leading causes of early-onset neonatal infections. Growing evidence suggests late-onset neonatal sepsis is caused by a range of Gram-negative pathogens, and azithromycin is likely neither an optimal agent nor sustained at adequate levels after an intrapartum maternal dose to prevent such infections. Pharmacokinetic analyses of oral azithromycin in pregnant women show peak maternal serum levels within 6 hours of administration with tissue levels sustained for up to 72 hours; however, levels in the fetus and newborn, as measured by umbilical artery and venous serum, are very low, even during the first 72 hours after administration.¹¹ Oral antibiotic formulations have not been effective in the prevention of early-onset GBS disease, which requires at least 4 hours of intravenous administration of a beta-lactam agent during labor—an intervention often impractical in the high mortality settings with limited resources where most of the world’s newborns die. Finally, an intervention administered after admission for delivery in a setting where women often present late in labor may not have sufficient opportunity to prevent *in utero* transmission of infections. A substantial portion of early-onset infections occur at or very shortly after birth, with some newborns clearly ill at delivery.¹²

Because the PregnAnZI-2 trial elected to evaluate as the primary outcome measure a composite endpoint of neonatal sepsis (based on a defined set of signs) and mortality, a positive effect of intrapartum azithromycin administration on neonatal infections could have been masked by inclusion of the non-sepsis specific mortality endpoint. Forty percent of the endpoints were neonatal deaths, which might not have been sepsis related. Inclusion of mortality in the composite endpoint in theory increased the power of the trial to detect an effect. Moreover, early neonatal infections in these settings are expected to result in a meaningful portion of mortality. Nonetheless, approximately half of neonatal deaths in the trial occurred in the first two days of life and could have resulted from a range of causes other than sepsis. The report’s supplemental materials show that many deaths were attributed to delivery complications (“birth asphyxia”) in both sites, and sudden death and aspiration were commonly cited as causes of death in the Gambia.⁵ Causes of death were attributed based on verbal autopsy or clinical assessments with presumably little diagnostic testing, so the accuracy of these assigned causes is unclear. The investigators attempted to exclude deaths with congenital anomalies, but some defects, including heart abnormalities, are not evident from external examination.

Regardless of a theoretical benefit, there are reasons to approach any potential antibiotic intervention with caution. Antibiotics can, rarely, lead to serious adverse events, such as prolongation of the cardiac QT interval and sudden death reported among a subset of susceptible persons taking azithromycin.¹³ Emerging antibiotic resistance poses a threat to the treatment and control of key pathogens and global efforts to combat resistance are gaining traction. Unintended consequences of mass azithromycin prophylaxis for trachoma have been evaluated and include increases in the proportion of macrolide-resistant *Streptococcus pneumoniae* and *E. coli*,¹⁴ pathogens of importance that contribute to childhood and neonatal mortality. Moreover, there is growing evidence that early disruption of the maternal and newborn microbiome, just at the time of initial microbiome establishment after birth, can have lasting health effects ranging from increased risk of obesity to allergies and asthma.^{15,16} In this light, even though the trial did report reductions in some secondary endpoints including skin infections in newborns and mastitis and puerperal fever in mothers, the failure of the intervention to prevent the primary outcome provides compelling information that intrapartum azithromycin is not likely a solution for preventing neonatal sepsis and its associated mortality. Other studies evaluating related interventions should take Roca's findings into account.

Thus, while the discouraging results of the PregnAnZI-2 trial may be sending neonatal sepsis prevention researchers back to the drawing board, several ongoing efforts hold promise to move the field forward. Efforts to more accurately describe the causes of early neonatal mortality are ongoing, in spite of the challenges of conducting such studies. Platforms such as Child Health and Mortality Prevention Surveillance (CHAMPS; www.champshealth.org) that investigate causes of stillbirths and neonatal deaths in the first week of life through rigorous specimen capture and evaluation may facilitate the identification and design of better prevention measures. Additionally, with a maternal respiratory syncytial virus (RSV) vaccine in late stages of phase 3 evaluation and the launch of a phase 3 maternal group B streptococcal vaccine trial, planned for 2023, new interventions may soon be available that can prevent mortality early in life by providing protective antibodies to fetuses before delivery. Antenatal vaccination may be more amenable to integration into healthcare delivery systems than intrapartum interventions; high neonatal mortality settings have already built platforms around maternal tetanus immunization that could incorporate new vaccines. While the burden of RSV and GBS pathogens has proven challenging to uncover in some regions, the availability of a licensed vaccine may pave the way for probe studies to reveal the full neonatal and maternal burden associated with these pathogens. Finally, a focus on efforts to improve maternal access to and quality of care for non-crying and non-breathing infants at birth will improve neonatal survival. Better application of existing tools and methods would go a long way towards reducing neonatal mortality while new approaches are evaluated.

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