

## PERSPECTIVE

# Priorities in reducing child mortality: Azithromycin and other interventions

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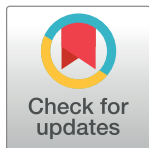
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According to World Health Organization (WHO) estimates, the global under-5 mortality rate decreased by 59% between 1990 and 2018, from 93 to 39 deaths per 1,000 live births [1]. This remarkable reduction was achieved largely by increasing the coverage of vaccination against measles and other childhood infections, rolling out new vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, and introducing artemisinin combination treatment and long-lasting, insecticide-treated bed nets for the treatment and prevention of malaria.

In 2018, a randomised trial conducted in Niger, Tanzania, and Malawi—the Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR; “Oral macrolides to reduce death with an eye on resistance”) study—showed that twice yearly, community-based mass treatment with a single dose of azithromycin reduced all-cause under-5 mortality by 13.5% (95% CI 6.7–19.8) [2]. In children aged between 1 and 6 months, mortality was 24.9% lower in those who received azithromycin. Azithromycin is a long-acting, broad spectrum antibiotic that also has antimalarial, anti-inflammatory, and possibly antiviral properties [3,4]. At the study site in Niger, where the impact of azithromycin on mortality was greatest, verbal autopsy revealed fewer deaths from malaria, dysentery, meningitis, and pneumonia in communities treated with azithromycin, the prevalence of malaria parasitaemia was reduced, and the gut pathogen load was reduced after the fourth biannual azithromycin distribution [5–7]. Given that severe malnutrition increases the risk of life-threatening infectious diseases and is an important contributor to under-5 mortality, it seemed likely that the impact of azithromycin on mortality would be enhanced in malnourished children.

The paper by Kieran O’Brien and colleagues in this issue of *PLOS Medicine* investigates the question, comparing the impact of azithromycin mass treatment in malnourished (underweight) versus well-nourished children at the Niger study site of MORDOR [8]. The reduction in mortality in the azithromycin arm of the study (12.6 fewer deaths, 95% CI 6.9–18.5, per 1,000 person-years overall) was greater in malnourished than in well-nourished children, but not significantly so. The authors conclude that azithromycin mass treatment given to all children will have a greater impact on mortality than targeting treatment to malnourished children. While this is not unexpected, the potential impact of treating 10 times as many children on the antimicrobial susceptibility of important bacterial pathogens is an important consideration.

Bacterial infections remain a major cause of mortality among newborns [9] with *Staphylococcus aureus*, *S. pneumoniae*, and group B streptococcus (GBS) among the major pathogens [10]. Although the MORDOR trial excluded newborns, a recent study showed that



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**Abbreviations:** GBS, group B streptococcus; MORDOR, Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance; WHO, World Health Organization.

administration of oral azithromycin during labour significantly reduced maternal and neonatal nasopharyngeal carriage of *S. pneumoniae*, *S. aureus*, and GBS as well as maternal and neonatal infections, with a short-term increase in the prevalence of azithromycin-resistant *S. aureus* among newborns of mothers who had received azithromycin [11,12].

A major target of the sustainable development goals is to end preventable deaths of newborns and children under 5 years of age by 2030, with all countries reducing under-5 mortality to less than 25 per 1,000 live births. While 120 WHO member states already meet this target, achieving it in all countries will be challenging. Whether and in what circumstances azithromycin mass treatment should be recommended remains debatable, and further research is needed to better understand the mechanisms by which the drug reduces mortality and the settings in which its impact is likely to be greatest while also evaluating the impact of this intervention on antimicrobial resistance.

What other interventions could help to achieve this target? Neonatal mortality has declined very little in the past 30 years, and almost 50% of childhood deaths are now in neonates, making interventions to reduce neonatal mortality and prevent stillbirths a high priority. More than 80% of all newborn deaths result from 3 preventable and treatable conditions—complications due to prematurity, intrapartum-related deaths (including birth asphyxia), and neonatal infections; a third of these deaths occur on the day of birth and nearly three-quarters in the first week of life. In 2014, WHO and UNICEF launched the Every Newborn Action Plan, which was endorsed by all 194 member states and which focuses on improving the quality of care around the time of birth [13]. It set out a clear vision of how to improve newborn health and prevent stillbirths. The target for 2035 is for all countries to reach the target of 10 or fewer newborn deaths and fewer than 10 stillbirths per 1,000 live births. How can this ambitious target be achieved?

Focusing on the critical periods before and immediately following birth is essential. The packages of care with greatest impact on neonatal deaths and stillbirths include care during labour, childbirth, and the first week of life and care for the small and sick newborn child. Recommended interventions include skilled care at birth, basic and comprehensive obstetric care (including parenteral administration of uterotonics, anticonvulsants, and antibiotics for preterm or prolonged rupture of membranes), management of preterm births (including the use of antenatal corticosteroids), a clean birth environment, and essential newborn care (i.e., hygienic care, thermal control, support for breastfeeding, and—if required—newborn resuscitation). It is important that the interventions for mother and newborn are seen as a functional unit delivered in a narrow time window by the same healthcare providers in the same place, with referral for management of complications including mother and baby together. These packages could, with universal access, prevent more than 1.9 million maternal and newborn deaths and stillbirths by 2025. The package of care for small and sick newborn babies includes interventions to deal with complications arising from preterm birth and/or small for gestational age and neonatal infections (sepsis, meningitis, pneumonia, and those causing diarrhoea), such as extra thermal care and support for feeding for small or preterm babies, including kangaroo mother care, antibiotic treatment for infections, and full supportive facility care. Focusing on small or sick newborns could prevent almost 600,000 newborn deaths by 2025 [14,15].

Antenatal care provides an opportunity for integrated service delivery for pregnant women, including obstetric services, and also provides the opportunity to treat and prevent malaria and syphilis in pregnancy, prevent mother-to-child transmission of HIV, and reduce harmful lifestyle practices such as smoking and alcohol use. Ensuring that all pregnant women are screened for syphilis using a point of care test, and that those who test positive are treated with a single dose of benzathine penicillin, would prevent an estimated 140,000 stillbirths and more

than 60,000 neonatal deaths annually and is one of the most cost-effective health interventions [16,17]. Maternal immunisation also presents a specific opportunity to prevent neonatal infections, especially GBS. The use of antibiotics remains, therefore, an important intervention with a high impact on preventing stillbirths as well as reducing newborn and maternal deaths. However, increasing global antimicrobial resistance has the potential to erode the hard-won gains in maternal and newborn survival. Global commitment to antimicrobial stewardship is crucial to reverse this trend.

Mass treatment with azithromycin can reduce childhood mortality in some settings, but further research is needed to identify where it is likely to have an impact. Its blanket use to reduce childhood mortality remains fraught with unanswered questions [18]. Improvements in water, sanitation, and hygiene; provision of adequate health care; and improved coverage of immunisation and other effective interventions—as well as community participation in the planning, implementation, and monitoring of policies and programmes that affect them—remain the cornerstone of efforts to achieve health-related sustainable development goal targets.

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