

## Azithromycin for child survival: digging without getting too dirty into the differential effect on cause-specific mortality



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A decade ago, the astonishing and unexpected results of a trachoma trial in Ethiopia<sup>1</sup> hinted at the exciting potential of mass azithromycin distribution to significantly reduce all-cause mortality in children by approximately 50%. In 2018, the Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) multi-country study,<sup>2,3</sup> designed to investigate the effect of mass biannual azithromycin distribution on all-cause mortality in children aged 1–59 months in sub-Saharan African communities, corroborated these results—although with more modest and credible findings than the trachoma trial.<sup>1</sup> The greatest reduction in all-cause mortality was observed in Niger, the site with the highest baseline mortality, where biannual mass distribution of azithromycin to children aged 1–59 months decreased all-cause mortality by 18% compared with placebo.<sup>2</sup> The results of the MORDOR trial,<sup>2</sup> however, raised many questions about the mechanisms by which azithromycin could have such an effect on child mortality. The direct and indirect (ie, herd protection) therapeutic and chemoprophylactic effects of macrolides against a series of pathogens (either carried asymptotically or overtly causing disease), their immunomodulatory benefits, or their effect on the human microbiome by promoting a so-called protective composition (ie, against superinfections), are all plausible explanations; the contributions of which remain a matter of scientific speculation. There were high expectations of the MORDOR trial<sup>2</sup> to clearly establish the necessary mechanisms underlying the effects of mass azithromycin distribution in reducing all-cause mortality in children.

In this issue of *The Lancet Global Health*, Jeremy D Keenan and colleagues<sup>3</sup> report verbal autopsy results for childhood deaths that occurred in communities located at the Niger site of the MORDOR trial and analyse the distribution of deaths among the two study groups in an effort to understand the mechanisms underlying the effects of mass azithromycin distribution. In total, the cause of death for 1566 children in the azithromycin group and 1735 children in the placebo group (91.3% of all child deaths reported by population censuses)

were ascertained by verbal autopsy interviews. The results indicated that mass azithromycin distribution protected against deaths due to infectious diseases, with a third fewer deaths due to meningitis and dysentery in the azithromycin group versus the placebo group, and a fifth fewer deaths due to pneumonia and malaria. Notably, azithromycin did not appear to alter the overall distribution of causes of death when compared with placebo. Keenan and colleagues<sup>3</sup> concluded that, in a setting where the epidemiological transition (ie, the dominant burden of disease transitioning from infectious to non-communicable causes) had not yet occurred and where infections remain the major determinants of child survival, the broad antimicrobial activity of azithromycin would suffice to cause a general reduction in the number of child deaths due to infectious diseases, and consequently overall mortality.

One of the fundamental caveats of the study<sup>3</sup> is the method used to ascertain cause of death—the verbal autopsy, which is a notably unreliable method.<sup>4</sup> In the verbal autopsy, the probable cause of death of a child is ascertained by interviewing the child's caregiver by use of a standardised questionnaire, the results of which are analysed by clinicians or inputted into an automated software programme. The 2007 version of the WHO verbal autopsy questionnaire was used at the Niger site of the MORDOR study.<sup>2,3</sup> Verbal autopsies can reasonably depict trends in the distribution of causes of death at a community level, but cause of death can be misclassified at the individual level, especially for children with unspecific and overlapping symptomatology. In addition, verbal autopsies generally include only a few syndromic diagnoses (17 diagnoses were included in the version used in the MORDOR study<sup>2,3</sup>), and they fail to request information about coexisting morbidities or about the series of events that led to the death. The advent of the minimally invasive autopsy,<sup>5</sup> which is a robust method for ascertaining cause of death post mortem that was introduced within the past 5 years, has surpassed the verbal autopsy interview as a reference for ascertaining cause of death of individuals from any age group in

low-income and middle-income settings. Although the minimally invasive autopsy is not a feasible option beyond 24–48 h post mortem, which is a severe limitation, this method has already been implemented for mortality surveillance as part of the ambitious Child Health and Mortality Prevention Surveillance network programme, with high acceptability.<sup>6,7</sup> Using the minimally invasive autopsy for at least a subset of child deaths in the MORDOR study<sup>2,3</sup> could have provided more information and invaluable samples to identify the pathophysiological causes of death and investigate the potential reasons underlying the effects azithromycin on reducing overall mortality. Nevertheless, randomisation should have guaranteed that, irrespective of its weaknesses, the verbal autopsy method applied remained valid, at least for an initial depiction of the distribution of causes of death and for the differential effect of mass azithromycin distribution.

The subanalysis of the MORDOR study results by Keenan and colleagues<sup>3</sup> raises further questions. The authors found no effect of mass azithromycin distribution on child deaths due to malnutrition, nor did they explore the neonatal period, in which nearly half of all deaths in children younger than 5 years currently occur.<sup>8</sup> It is now imperative to study the potential effect of such a preventive intervention on these two high-risk and susceptible groups. In addition, the long-term consequences of using a mass antibiotic administration approach on the emergence of antimicrobial resistance is an issue that remains unresolved. After trachoma control programmes, macrolide-resistant strains of *Streptococcus pneumoniae* and *Escherichia coli* were documented,<sup>9</sup> and there is also evidence to suggest that the prevalence of macrolide resistance is increased with mass azithromycin distribution.<sup>10</sup> Although Keenan and colleagues<sup>3</sup> hypothesise that mass drug administration to children younger than 5 years might lead to less macrolide resistance than trachoma programmes in adults, it would be negligent to overlook the consequences of this life-saving intervention in potentially increasing the prevalence of life-threatening antimicrobial resistance in the aforementioned

pathogens and other pathogens, which are the main causes of death among neonates and children in sub-Saharan Africa.

In the current era of big data, in which the global health community is largely focused on attaining a better understanding of the causes of deaths in children, large randomised trials, such as the MORDOR study,<sup>2,3</sup> that aim to ascertain causes of child death in high mortality settings are welcomed and praised; however, we encourage the authors of the study<sup>3</sup> to dig more profoundly into the precious opportunities that such trials provide.

We declare no competing interests.

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