Does mass drug administration of azithromycin reduce child mortality?

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Child mortality remains prevalent in low-income and middle-income countries, with the sub-Saharan Africa region accounting for the largest under-5 mortality rates.[1] Although under-5 mortality rates have significantly decreased, most countries in sub-Saharan Africa with high mortality rates are unlikely to achieve the Sustainable Development Goal of at least as low as 25 deaths per 1000 livebirths by 2030.[2]

Mass administration of azithromycin is one of the key interventions in trachoma control programmes and potentially reduces child mortality in sub-Saharan Africa.[3,4] Several trials done in sub-Saharan Africa have reported mixed efficacy of mass administration of azithromycin in reducing child mortality at a population level.[4] On the basis of this evidence, WHO, in 2020, recommended against the universal mass administration of azithromycin except for biannual administration for children aged 1–11 months in countries with high child mortality and where existing child survival interventions are also strengthened.[3]

In *The Lancet Global Health*, Patricia Pavlinac and colleagues[5] did an individually randomised, double-blind, placebo-controlled trial to assess the effect of a 5-day course of azithromycin administered at hospital discharge on the risk of death and rehospitalisation in the subsequent 6-month period among children aged 1–59 months.[5] In the study, eligible children from four hospitals in Kenya were randomly assigned to receive either azithromycin (oral suspension 10 mg/kg on day 1, followed by 5mg/kg per day on days 2–5) or placebo, with the first dose being directly observed. Caregivers administered and recorded the subsequent doses and returned the bottles at the 3-month follow-up. They also provided information on the child's medical history during the 3-months and 6-months post-discharge follow-up visits, when whole stool or flocked rectal swabs were also collected to assess for azithromycin resistance in *Escherichia coli* isolates. Pavlinac and colleagues' study is one of the few assessing the effects of mass administration of azithromycin in individual-level randomised trials. The authors found that, despite a high risk of mortality and readmission in the study population, azithromycin did not have beneficial effects on the combined outcome of readmission or mortality, with an incidence of death or rehospitalisation of 20·4 per 100 child-years in the azithromycin group versus 22·5 per 100 child-years in the placebo group (adjusted hazard ratio 0·91, 95·5% CI 0·64–1·29, p=0·58), even after adjusting for medication adherence.[5]

The protective effect of mass administration of azithromycin has only been shown in population-wide cluster randomised trials, with no beneficial effect shown in one trial done in combination with seasonal malaria chemoprophylaxis,[4] which could explain the difference in the findings. Additionally, most children in the study were treated with antibiotics during hospital admission and were discharged home with antibiotics, possibly affecting the potential effect of azithromycin. Regardless, this new evidence does not preclude the potentially beneficial effects of mass administration of azithromycin on child mortality or hospitalisation, as the study was not sufficiently powered to detect these effects independently and at the population level.

Similar to earlier studies showing that mass administration of azithromycin might propagate antimicrobial resistance,[6] Pavlinac and colleagues found a concerningly high rate of azithromycin resistance in commensal *Escherichia coli* at baseline (37·7% in both study groups) and at 3 months post-randomisation, especially in the azithromycin group (26·9%) compared with the placebo group (19·1%; adjusted prevalence ratio 1·41, 95% CI 0·95–2·09, p=0·088).[5] This was despite very low use of azithromycin during hospitalisation and study inclusion restricted to children at high risk of rehospitalisation and mortality. Concerns that mass drug administration will lead to the selection of macrolide-resistant strains of endemic diseases and resistance to macrolides and other classes of antimicrobials in other pathogens are real barriers to further implementation. This reflects the growing evidence of increasing antimicrobial resistance among children[7] and raises concerns because most countries in sub-Saharan Africa do not have robust antimicrobial surveillance systems.

As more research on the potential effects of azithromycin is done, phenotype-drug resistance profiles

for multiple organisms need to be integrated to provide robust evidence on antimicrobial resistance due to the mass administration of azithromycin.[6] Importantly, the issues of community-wide azithromycin resistance should be of concern to policy makers and health practitioners, especially due to the recent use of azithromycin in some settings in sub-Saharan Africa for the management of COVID-19.[8]

It is increasingly clear that more research is needed to understand the specific mechanisms of action of azithromycin in reducing child mortality. Additionally, an assessment of the overall and age-specific effects of azithromycin on child mortality and morbidity in high quality, individually randomised, placebo controlled trials among children younger than 5 years is urgently needed to clarify the continued use of mass administration of azithromycin given the low level of evidence and risk for antibiotic resistance.

In general, child mortality is a complex public health issue, with multiple determinants that affect the health and wellbeing of children. Despite evidence that the mass administration of azithromycin effectively reduces child mortality at the population level for specific treatable endemic diseases such as trachoma,[4] it is unlikely to be the magic pill that can independently reduce child mortality in sub-Saharan Africa. Downstream interventions to improve key determinants of health, including immunisation, nutrition, and access to clean and safe water, need to be strengthened to reduce the persistent disparities in child mortality across and within countries.

We declare no competing interests.

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