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Unravelling the potential mortality benefits of mass drug administration with azithromycin in niger

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Unravelling the Potential Mortality Benefits of Mass Drug Administration With Azithromycin in Niger

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Some 5 years following the publication of the landmark Macrolides Oraux pour Réduire les Décès avec un Oeil sur la Résistance (MORDOR) trial, a placebo-controlled, double-masked, cluster-randomized clinical trial of biannual mass azithromycin administration (MAA) among 190 238 children in Niger, Malawi, and Tanzania,[1] debate regarding its mechanisms of effects and implications for policy continues. This study by Chao et al[2] presents secondary analysis of 594 communities from the original cluster-randomized trial in Niger (the only participating country where an impact on mortality was observed), and demonstrates that the impact on mortality increased with distance from primary care facilities and was largely restricted to mortality among children younger than 5 years living more than 5 km (reduction, 16%; 95% CI, 7%-23%) or 10 km (reduction, 28%; 95% CI, 17%-38%) away from primary care facilities.

There are several missing elements to the analysis by Chao et al[2] that could have shed further light on the effect of MAA. We do not have information on care-seeking patterns of families by distance, childhood immunization rates, and burden of common illnesses, which could have explained the gradient of mortality benefit. Information on health worker density (especially paid Agents de Santé Communautaire and Relais volunteers) in the area[3] and their coverage at population level could have provided insight into availability of primary care services for common illnesses, such as malaria, diarrhea, and acute respiratory infections, all possibly impacted by MAA.

Several efforts have been made to assess potential pathways for benefit with MAA, and the current thinking is that benefits would be largely related to reduction in the risk of common childhood infections. A study by Keenan et al[4] using verbal autopsies found that the MAA was associated with fewer deaths in children aged 1 to 59 months due to meningitis, dysentery, malaria, and pneumonia. However, the causes of deaths did not differ between the treatment and placebo groups in the analysis by Keenan et al,[4] leaving the selective impact of azithromycin on certain types of infections unclear. Regardless, the fact remains that in many high–mortality burden countries with limited health system functionality, MAA might be the only means for children with potentially life-threatening clinical and subclinical infections to receive effective antibiotics.

Large-scale blanket antibiotic use at the population level still poses a major risk for the emergence of antimicrobial resistance. Careful follow-up studies of nasopharyngeal specimens among recipients of MAA in Niger show an increase in macrolide resistance among *Streptococcus pneumoniae* nasopharyngeal isolates, although this was not shown to persist by 36 months.[5] Given that no impact of MAA has been shown on ocular trachoma in Niger,[6] the original reason for mass azithromycin use, questions have to be asked as to the viability of this approach in the country, especially compared with other investments. No country has rolled out this strategy, more than 3 years following the conditional recommendation by the World Health Organization,[7] and findings from replication trials are still awaited. If the fundamental reason for the use of MAA is that it helps reduce child mortality in settings with limited access to antibiotics or outreach services for children at high risk of death by treatable infection, perhaps a more sustainable, impactful, and beneficial alternative would be to strengthen health systems and improve community delivery strategies and outreach programs. Surely children in these high-risk settings also have other needs, including undernutrition and early childhood adversities, which could also be averted by strengthening primary care services. This was likely the reason behind the lack of apparent benefits in Malawi and

Tanzania and is corroborated by no benefit of the strategy in Niger among populations living less than 5 km from a primary care facility.

Targeted and limited use of MAA could still be considered in special circumstances among populations with limited mobility or in humanitarian settings. Fixing fundamental lacunae in health systems, scaling up childhood immunizations, and strengthening outreach systems should be prioritized regardless and may be better longer term strategies.

ARTICLE INFORMATION

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REFERENCES

1. Keenan JD, Bailey RL, West SK, et al; MORDOR Study Group. Azithromycin to reduce childhood mortality in Sub-Saharan Africa. *N Engl J Med*. 2018;378(17):1583-1592. doi:10.1056/NEJMoa1715474

2. Chao DL, Arzika AM, Amza A, et al. Distance to health centers and effectiveness of azithromycin mass administration for children in Niger: a secondary analysis of the MORDOR cluster randomized trial. *JAMA Netw Open*. 2023;6(12):e2346840. doi:10.1001/jamanetworkopen.2023.46840

3. Strodel R. Niger's program of agents de santé communautaire and relais volunteers. *CHW Central*. June 5, 2018. Accessed November 14, 2023. https://chwcentral.org/nigers-program-of-agents-de-sante-communautaire-and-relais-volunteerso/

4. Keenan JD, Arzika AM, Maliki R, et al; MORDOR-Niger Study Group. Cause-specific mortality of children younger than 5 years in communities receiving biannual mass azithromycin treatment in Niger: verbal autopsy results from a cluster-randomised controlled trial. *Lancet Glob Health*. 2020;8(2):e288-e295. doi:10.1016/S2214-109X(19)30540-6

5. Hazel A, Arzika AM, Abdou A, et al. Temporal trends in phenotypic macrolide and nonmacrolide resistance for *Streptococcus pneumoniae* nasopharyngeal samples up to 36 months after mass azithromycin administration in a cluster-randomized trial in Niger. *Am J Trop Med Hyg*. 2023;109(5):1107-1112. doi:10.4269/ajtmh.23-0431

6. Arzika AM, Mindo-Panusis D, Abdou A, et al; Macrolides Oraux pour Réduire les Décés Avec un Oeil sur la Resistance (MORDOR)–Niger Study Group. Effect of biannual mass azithromycin distributions to preschool-aged children on trachoma prevalence in Niger: a cluster randomized clinical trial. *JAMA Netw Open*. 2022;5(8):e2228244. doi:10.1001/jamanetworkopen.2022.28244

7. World Health Organization. WHO guideline on mass drug administration of azithromycin to children under five years of age to promote child survival. Accessed November 14, 2023. https://www.who.int/publications/i/item/9789240009585