Mass Administration of Azithromycin to Prevent Pre-school Childhood Mortality: Boon or Bane?

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SUMMARY

A group of American researchers funded by the Bill and Melinda Gates Foundation examined the effect of mass administration of azithromycin, on mortality in pre-school children. This was done through a community-based randomized controlled trial (RCT) designated MORDOR-I, conducted in Malawi, Niger, and Tanzania [1]. MORDOR is an acronym for the French title of the study. Community clusters of children (1 month to 5-year-old) were randomized to receive either azithromycin (single dose 20 mg/kg, administered twice a year for 2 years) or identical placebo (in the same dosage schedule). The overall mortality rate (expressed as deaths per 1000 person years) was 13.5% lower in the treatment arm, with 95% confidence interval 6.7% to 19.8% (hence statistically significant). However, detailed analysis showed that only communities in Niger had statistically significant mortality reduction to the extent of 18% (95% CI 10%, 25.5%), whereas those in Malawi and Tanzania did not. Thus, the overall mortality reduction was largely due to the reduction in Niger. This significant inter-country difference was partly attributed to higher baseline mortality in Niger, and stronger effect of mass azithromycin administration in such settings [2]. The investigators then evaluated the administration of two doses of azithromycin (6 months apart) in children from both groups of communities in Niger only. Thus, communities in the original Azithromycin group (in MORDOR-I) received a total of 6 doses, whereas those in the original placebo group received 2 doses. This part of the study has been designated MORDOR-II [3], and is examined in detail here. Communities in Malawi and Tanzania that did not show mortality decline were not evaluated any further.

The primary outcome in MORDOR-II [3] was the same as in MORDOR-I *viz*. all-cause mortality at the community level. Secondary outcomes included intra-group comparison of mortality. Although safety data were mentioned in the manuscript [3], the data were not presented. The results showed a comparable mortality rate (expressed as deaths per 1000 person-years) among children who received 6 doses of azithromycin over three years *versus* those who received 2 doses over 1 year. In contrast, the mortality after administration of 2 doses and 4 doses of azithromycin (*versus* similar doses of placebo) was 16.0% and 20.3% lower respectively, in the azithromycin group. Intra-group comparison showed that mortality in the original placebo group was 26.3 at the end of year 1 of MORDOR-I, 28.0 at the end of year 2 of MORDOR-I, and 24.0 at the end of MORDOR-II. This translated to an overall (statistically significant) 13.5% reduction in mortality between pre-MORDOR-I and post-MORDOR-II. In contrast, the intra-group comparison in the azithromycin group showed a 3.6% higher mortality after MORDOR-II, compared to before MORDOR-I (although the difference was not statistically significant). The authors reiterated their original conclusion that mass administration of azithromycin reduced mortality among pre-school children in Niger [1,3], and additional administration of two doses did not appear to wane this effect. However, there was no additional benefit on mortality with the third year of mass azithromycin administration.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Azithromycin was discovered in 1980, and has broad antimicrobial activity. Researchers are intrigued, if mass administration of Azithromycin is capable of decreasing mortality in children. Trachoma Amelioration in Northern Amhara (TANA) trial, conducted in Ethiopia, showed that mass administration of azithromycin for trachoma halved all-cause mortality among children 1 to 9 years of age in communities that received azithromycin. Similarly, mass administration of azithromycin had shown to reduce morbidity associated

with infectious diseases in Gambian children. MORDOR trail is another attempt to answer the complex questions associated with mass administration of Azithromycin.

Critical appraisal

Study design and procedures: In the MORDOR-I trial [1], community clusters in each country were randomized by assigning one of ten alphabets to each. These ten alphabets were randomly coded to azithromycin or placebo. Thus, the sequence generation was unpredictable and hence acceptable. However, since block randomization (with variable block sizes) was not used, there is a theoretical possibility of predictability towards the end of the randomization procedure, and unequal number of communities in each group. The process of allocation concealment is unclear; although, it appears that centralized allocation was done. Blinding of participating communities, outcome assessors and most investigators was adequately done. MORDOR-II [3] continued with the original allocation and involved the administration of two doses of azithromycin to both groups of communities. Hence in that sense, although it was a component of the original RCT, it is an observational study comparing the effect of three years' azithromycin administration *versus* one year; as well as intra-group mortality estimates over time.

The investigators' *a priori* sample size calculation required 624 community clusters to be included [3], whereas only 594 were eventually included. However, *post-hoc* analysis suggested adequate power.

Strengths and limitations: This study had several strengths including robust design, community-based randomization, and inclusion of a highly meaningful outcome (relevant to individual children, communities and policy-makers). Sophisticated study procedures were deployed to minimize selection and ascertainment biases inherent in this type of study. The investigators also acknowledged salient limitations in their study, and did not try to over-sell the implications of their findings.

However, there are a number of issues that warrant closer attention. The investigators reported neither the pre-study baseline mortality rate in each country [1] nor its relationship to the pre-trial baseline mortality rate in each group. This would have been helpful to understand whether the communities participating in the trial reflected the baseline status of each country as a whole. Unfortunately, it is difficult to obtain this information from other sources as well.

The authors did not present the mortality data by the number of doses administered. MORDOR-I showed that infants younger than 6 months had the greatest mortality reduction in all three countries [1] suggesting that one dose alone may have been sufficient. However, it is possible that similar reductions in mortality were not observed in older age groups because the benefit was counter-balanced by increasing bacterial resistance with greater number of doses. Thus, it would be important to examine the relationship between the number of doses administered and mortality pattern.

Safety issues: Mass administration of azithromycin in trachoma control programs (wherein infants older than 6 months are included) have been associated with side effects. In young infants, hypertrophic pyloric stenosis is one of the more serious side effects associated with azithromycin [4]. Among adults, cardiac event related deaths have also been reported [5]. A recent systematic review [6] reported that macrolides in general increased the risk of myocardial infarction, but not arrhythmia. This effect was greater with erythromycin and clarithromycin than azithromycin. The safety of azithromycin in children is still under investigation [7].

In MORDOR-I [1], parents of children were expected to approach village leaders for any suspected adverse event; they in turn passed on the information up the chain of command till the Data Coordinating Centre in San Francisco. Naturally, this passive surveillance could miss potentially important adverse events.

In addition, a component of limited active surveillance for side effects was built in, but only for infants <6 months old, and that too in 30 randomly chosen community clusters [8]. This component was thus restricted to only about 1700 of several thousand participating infants. The investigators found no differences between the azithromycin and placebo groups for the most frequent adverse events such as diarrhea, vomiting, and skin rash. Additional symptoms solicited were abdominal pain, nausea, dyspepsia, constipation, and haemorrhoids – although it is unclear how the first three of these were detected in infants <6 months old. No serious adverse events (notably infantile hypertrophic pyloric stenosis) were detected. A systematic review of 183 studies including over 2.5 lakh participants reported additional unpleasant adverse events including taste disturbances and hearing loss [9]; these were not examined in the trial [1,3]. Comparison of "any health problem" and "any health problem requiring clinic visit" also showed similar distribution between azithromycin and placebo recipients. From these data, the investigators concluded that azithromycin was safe in young infants.

However, it is important to note that despite comparable event frequency in the two groups, the absolute proportion of affected children was fairly high. At

least one adverse event was reported in nearly one-third of infants, and over a third of these required clinic visits. Almost one in five infants had diarrhea – a condition thought to be treated by azithromycin. This raises an important issue whether the comparability of adverse event frequency in the two groups actually translate to safety? One wonders whether the vehicle in which azithromycin was dispersed (which incidentally was the placebo preparation) could independently contribute to side effects. This is important because though azithromycin itself may be safe, its administration may not be as safe. This issue could have tremendous implications for policy-makers and program managers considering mass azithromycin in their communities. The only way to resolve this would have been to record the frequency of adverse events in an additional arm of the trial wherein infants did not receive either azithromycin or placebo. This would be especially relevant because the comparator used in this trial (placebo) is not the usual standard of care, hence could be easily omitted in control group children. This also raises the ethical issue of whether infants in the trial were exposed to potentially undesirable adverse events through their participation in the trial.

From the research angle, an important lesson is that although placebo administration to control group participants is the ideal way to minimize bias while testing efficacy of interventions, it may not be the ideal comparator to test safety.

The investigators attempted to suggest additional safety of azithromycin by emphasizing that mortality was lower in those who received it (than those who received placebo) [1,10]. This argument is untenable for two reasons. First, morality was recorded over six months after administration. If mortality related to the intervention was an outcome of interest for evaluating safety, it should have been separately recorded within the timeframe of minutes to days after administration. Only this would enable capturing allergy/anaphylaxis mediated mortality, as well as the effect of somewhat delayed serious side effects. Second, the confidence intervals of mortality reduction estimates in Tanzania and Malawi in MORDOR-I overlapped zero, suggesting that azithromycin could increase (rather than decrease) mortality in these communities. A separate analysis of mortality data [10] suggested that in all three participating countries, children were less likely to have died early in the treatment arm relative to the control arm. Although this could be interpreted to mean that azithromycin was safe, it could also suggest that placebo was unsafe.

Another issue related to safety is the potential impact of enhancing bacterial resistance to azithromycin through mass administration. This has been documented in trachoma control programs (although *C. trachomatis* itself does not appear to have become resistant) [11], hence requires close monitoring, especially when young children are involved. The investigators examined azithromycin resistance in 30 community clusters in Niger, randomly selected from the participating communities in the MORDOR-I trial. The proportion of Pneumococcus (isolated in nasopharyngeal swabs) was compared among pre-school children receiving azithromycin *versus* placebo, after four successive administrations. In addition, rectal specimens were examined for macrolide resistance determinants. The data showed 325% increase in resistance among Pneumococcus, and 50% increase in the prevalence of macrolide resistance determinants in the gut. Thus, the short-term benefits of mass azithromycin administration could be offset by the challenging long-term consequences related to azithromycin resistance. This could pose not only research and programmatic challenges, but ethical challenges as well.

Biological mechanism: What could be the mechanism by which azithromycin reduced mortality in young infants in only one country? This question has worried the investigators also. One explanation could be the anti-microbial efficacy, since azithromycin impacts organisms related to respiratory tract infection, diarrhea and even malaria [12,13]. It is pertinent that a very recent online publication showed that children receiving azithromycin had significantly reduced quantum of 35 bacteria (in particular two *Campylobacter* species) in the gut microbiome, compared to those receiving placebo [14]. On the other hand, since a single dose of 20 mg/kg is unlikely to sustain therapeutic levels beyond a few days, could there be a prophylactic mechanism? This has not been explored in detail. Further, azithromycin is associated with diverse clinically relevant effects, raising the possibility that non anti-microbial effects may be involved [15].

Ethical issues: Does this trial [1] and its subsequent follow-up [3] raise ethical issues? The basis for initiating the trial was the successful mass azithromycin administration program (among older infant, children, and adults) for trachoma control, endorsed by the World Health Organization. This success, aligned to the goal of improving health across the world, made it possible to explore the effect even in younger infants. A group of scientists suggested that it could be inappropriate to withhold mass azithromycin administration on ethical grounds [16] because MORDOR-I demonstrated benefit on mortality, similar mass administration is done to eradicate trachoma as well as yaws, and many

communities have limited access to antibiotics (hence this could be one way of enhancing access). The scientists themselves were averse to this argument because health system deficiencies in some settings should not justify interventions where the balance between benefit *versus* harm is unclear [16].

Another potential ethical issue is whether interventions whose mechanism of action are unclear, could/should be used in apparently healthy infants and children, especially when there could be unclear/ unrecognized long-term consequences in individual children and the community.

Extendibility: Can the results of MORDOR-I and MORDOR-II be applied in any setting outside Niger? Although the significant percentage reduction in mortality is impressive, the absolute reduction of 5 deaths per 1000 person-years [17], necessitates that 200 children be treated for at least one year, to prevent one death. This number-needed-to-treat is 10000 for Tanzania [17]. Viewed in this context, it is clear that individual settings (in different countries, or perhaps even within the same country) have to be examined very carefully before considering any policy of mass azithromycin administration.

Conclusion: Although India does not use mass azithromycin administration for trachoma control, and based on the data presented, there is no reason to consider this intervention in any part of the country, irrespective of the baseline childhood mortality. This is especially because, currently azithromycin resistance among typhoidal and non-typhoidal Salmonella is fairly low [18-20], and disturbing this can have serious consequences in the future.

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JOSEPH L MATHEW
Department of Pediatrics, PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

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Pediatrician's Viewpoint

Under-5 mortality in India continues to remain high at 39/1000 live births [1]. The most important causes are preterm birth complications [2]. The other main causes of death in poor performing states are pneumonia and diarrhoea. The causes are similar in African countries along with a high prevalence of trachoma, and some socio-geographical reasons [3]. Though mass administration of azithromycin has shown some reduction in the childhood mortality in Africa, this is not the correct way to approach the problem as vaccination against pneumococcus, Hemophilus influenzae B and Rotavirus can result in long-term sustained protection with additional benefit of herd immunity. As a clinician, the other issue which bothers me the most is the risk of developing azithromycin-resistant strains of bacteria with such mass administration. There are reports of rising incidence of drug-resistant Salmonella in the Indian sub-continent to the extent that some of the strains are found to be ceftriaxone resistant as well [4,5]. In such situations, azithromycin remains the last choice for us. Moreover, in some other diseases such as scrub typhus, azithromycin is one of the very few drugs which can tackle this emerging infection. Increasing reports of azithromycin resistant of other bacterial strains have already been reported from India [6]. In our institute, 10-50% of the staphylococcus, enterococcus and pneumococcus are resistant to azithromycin (unpublished data). Therefore, I would be very cautious in accepting the study findings, and depend more on public health measures, immunization and restrictive use of azithromycin in my practice.

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RASHNA DAS
Department of Pediatrics
Health City Hospital
Guwahati, India.
rashnadass@gmail.com

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