Mass Distribution of Azithromycin Reduces Mortality in African Children

Kara Middleton

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Abstract

Background: Sub-Saharan Africa remains the region with the highest child mortality rate in the world. Most commonly, pneumonia, diarrhea, and malaria rank among the leading causes of preventable deaths in this population. The World Health Organization (WHO) recommends mass drug administration (MDA) of azithromycin, a broad-spectrum macrolide antibiotic, for the treatment of trachoma. Some studies suggest that MDA of azithromycin for this purpose has the added benefit of protection against other illnesses including malaria, diarrheal episodes, and respiratory infections. The aim of this review is to investigate the effect of MDA of azithromycin on mortality rates in African children.

Methods: An exhaustive search of available medical literature was performed using MEDLINE-Ovid, CINHAL, and Web of Science databases. Relevant search terms included 'azithromycin,' 'child*,' 'mortality,' and 'mass.' The quality of relevant articles was assessed using the GRADE Working Group guidelines.

Results: A total of 3 studies, 2 randomized control trials (RCT) and 1 observational analysis, were included in this review. One RCT conducted in Malawi, Niger, and Tanzania showed that all-cause mortality rates declined in children ages 1-59 months after azithromycin administration, with the greatest benefit seen in children ages 1-5 months. Another RCT revealed similar findings, with decreased all-cause mortality rates in children ages 1-9 years in Ethiopia after MDA of azithromycin. A retrospective observational analysis also suggested reduced all-cause and infectious mortality rates in children ages 1-5 years in Ethiopia after azithromycin treatment.

Conclusion: MDA of azithromycin in African communities decreases all-cause mortality rates in children ages 1-5 years. Additional studies are needed to assess short and long-term adverse outcomes of MDA and the effect of MDA on antibiotic resistance.

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Keywords
Africa, azithromycin, child*, MDA, mortality

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Mass Distribution of Azithromycin Reduces Mortality in African Children

Kara Middleton
Biography

Kara Middleton is from Wausau, Wisconsin and received her Bachelor of Science degree in Biology at Cornell College. After completing her undergraduate degree, she moved to Baltimore, Maryland where she worked in research at the National Institute on Aging for two years. Prior to PA school, she worked as a CNA, caring for patients with dementia. Kara enjoys traveling the world and hopes to incorporate this love into her career.
Abstract

**Background:** Sub-Saharan Africa remains the region with the highest child mortality rate in the world. Most commonly, pneumonia, diarrhea, and malaria rank among the leading causes of preventable deaths in this population. The World Health Organization (WHO) recommends mass drug administration (MDA) of azithromycin, a broad-spectrum macrolide antibiotic, for the treatment of trachoma. Some studies suggest that MDA of azithromycin for this purpose has the added benefit of protection against other illnesses including malaria, diarrheal episodes, and respiratory infections. The aim of this review is to investigate the effect of MDA of azithromycin on mortality rates in African children.

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**Conclusion:** MDA of azithromycin in African communities decreases all-cause mortality rates in children ages 1-5 years. Additional studies are needed to assess short and long-term adverse outcomes of MDA and the effect of MDA on antibiotic resistance.

**Keywords:** Africa, azithromycin, child*, MDA, mortality
Acknowledgements

To my family, friends, and classmates- thank you for your unwavering support during these past two years. I am eternally grateful for all of your love and encouragement.
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List of Abbreviations
GRADE Grading of Recommendations, Assessment, Development, and Evaluation
MDA Mass drug administration
RCT Randomized control trial
WHO World Health Organization
Mass Distribution of Azithromycin Reduces Mortality in African Children

BACKGROUND

Pneumonia, diarrhea, and malaria rank among the most common preventable causes of death in children worldwide. Combined, these infectious diseases account for over 30 percent of deaths in children less than 5 years old, with most deaths occurring in sub-Saharan Africa and South Asia. In 2013, the World Health Organization (WHO) even created a global action plan outlining measures to end child deaths due to pneumonia and diarrhea by 2025. Such measures include improving sanitation and hygiene, ensuring vaccination against respiratory illnesses, and proper treatment of diarrhea via oral rehydration salts and zinc supplements. In addition, insecticide-treated bed nets have been introduced to countries endemic to malaria, which accounts for 7 percent of under-five deaths each year.

Despite these efforts, sub-Saharan Africa remains the region with the highest child mortality rate in the world. In fact, 1 in every 13 children will die before their fifth birthday. With such high child mortality rates, the need for further research regarding prevention and treatment of preventable diseases continues to be a top public health priority in the realm of global health.

The WHO already recommends mass drug administration (MDA) of azithromycin, a broad-spectrum macrolide antibiotic, for the treatment of trachoma. Trachoma is an infection of the eye caused by Chlamydia trachomatis that causes permanent blindness. Although found in rural and poor regions worldwide, trachoma is most prevalent in Africa, with more than 26 affected countries on the continent.
studies suggest that MDA of azithromycin for the purpose of trachoma control has the added benefit of protection against other illnesses including malaria and diarrheal episodes. Another study showed that azithromycin may also reduce infection by *S. pneumoniae* in Gambian children, thereby decreasing mortality rates due to pneumonia.

The mechanism by which azithromycin prevents against these diseases is still unknown, however, its use as prophylactic agent against high-mortality diseases warrants investigation. The purpose of this review is to determine the effect of mass distribution of azithromycin on child mortality rates in Africa and to contrast the risks and benefits of this protocol.

**METHODS**

An exhaustive search of available medical literature was performed using MEDLINE-Ovid, CINHAL, and Web of Science databases. Relevant search terms included azithromycin, child*, mortality, and mass. Included studies were those involving children in Africa, evaluating MDA of azithromycin compared to placebo or no treatment, and assessing child mortality rates. Other inclusion criteria included English language articles, articles published within the past 10 years (2008-2018), and age of children (e.g. 0-12 yo). References listed in the included articles were searched for additional articles. Relevant articles were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guidelines.
RESULTS

The initial search resulted in 39 articles. Application of inclusion criteria and removal of duplicate articles yielded 3 relevant studies: two cluster-randomized clinical trials (RCT)\textsuperscript{12,13} and one cohort observational analysis.\textsuperscript{14}

Keenan et al (2018)

This cluster RCT\textsuperscript{12} assessed all-cause mortality rates between children who received MDA of azithromycin compared to those who received placebo in Malawi, Niger, and Tanzania. Communities in each country were allocated to either the azithromycin treatment or placebo group. Within these communities, children ages 1-59 months weighing at least 3800 g who had not previously received azithromycin for trachoma control purposes, or otherwise, were eligible to participate. Children with known macrolide allergies were excluded. Children were provided either a weight-based dose of azithromycin or placebo twice each year, during the length of this 2-year study. Randomization was concealed and participants, observers, investigators, and data collectors were blinded to group allocation.\textsuperscript{12}

The primary outcome of this study was all-cause mortality rate, which was assessed during a twice-yearly census conducted by the investigators. The status of each participant was recorded as alive, dead, or unknown at each census. Verbal autopsies were attained in order to assess cause of death.\textsuperscript{12}

Between the 3 countries, 1533 communities were included, totaling 190,238 children, or 323,302 person-years over the course of 2 years. The study showed that mortality amongst all 3 countries was 13.5\% lower in children treated with azithromycin
compared to the placebo group (95% CI, 6.7 to 19.8). The overall annual mortality rate was 16.5 deaths per 1000 person-years in children receiving placebo and 14.6 deaths per 1000 person-years in azithromycin treated children. These findings were most significant in Niger. In this country, the azithromycin treated group exhibited a mortality rate 18.1% lower compared to children who received placebo (P<0.001). This finding was notable enough to prompt the investigators to offer azithromycin to all participants in Niger at the end of the study.¹²

The researchers also studied mortality rates by age group. Children ages 1-5 months experienced the highest mortality rates among all 3 countries. This age group also exhibited the greatest benefit from treatment with azithromycin. Mortality rates were 24.9% lower in the azithromycin treated group compared to children who did not receive the antibiotic (95% CI, 10.6 to 37.0; P=0.001).¹²

**Porco et al (2009)**

This cluster RCT¹³ evaluated mortality rates in children ages 1-9 years who received annual, biannual, or quarterly administration of azithromycin for trachoma control compared to children who received no treatment. The study took place over the course of 1 year in Ethiopia. Whole communities, not just children, were randomized to 1 of the 3 treatment groups or the control group. Participants who were pregnant or had known macrolide allergies were excluded.¹³

The primary outcome was mortality risk. This was assessed by personnel who conducted a census at the onset of the trial and another after 1 year’s time to address absent participants. Causes of death were evaluated by verbal autopsy.¹³
A total of 48 communities, comprised of 18,415 children ages 1-9 years old, were included in the analysis. The authors concluded that, in 1-9 year-olds, the overall mortality rate in the control group was 8.3 per 1000 person-years (95% CI, 5.3-13.1) compared to 4.1 per 1000 person-years (95% CI, 3.0-5.7) in the azithromycin treated group. Using negative binomial regression, this equates to a 50% lower mortality rate in children treated with MDA. Analysis of children ages 1-5 years who received treatment revealed a similar reduction in mortality. The mortality rate in the untreated group was 12.1 per 1000 person-years (95% CI, 7.4-19.6) compared to the 5.7 per 1000 person-years (95% CI, 4.1-8.0) in azithromycin treated group. While the authors did not explicitly address the effect size of each treatment limb, the lowest mortality rate was observed in children receiving only the annual dose of azithromycin compared to biannual or quarterly MDA (3.2, 4.9, and 4.7 per 1000 person-years, respectively).  

Keenan et al (2011)

This observational analysis is based on a subset of 24 Ethiopian communities in Porco et al’s (2009) RCT, which examined the use of azithromycin in the setting of trachoma control. In that study, individuals over the age of 1 year were eligible to receive a single dose of azithromycin. Approximately 89% of the entire cohort, and 83% of children ages 1-5 received MDA of azithromycin. Individuals who did not receive treatment included those were ill during the time of administration, those who received topical tetracycline (due to pregnancy or macrolide allergy), individuals who refused treatment, or those who were alive but did not receive treatment for some other reason.
Keenan et al (2011) analyzed a total of 35,052 participants, including 5,507 children ages 1-5 years old. The primary outcomes were all-cause and infectious mortality rates (defined as deaths per 1000 person-years). These outcomes were assessed by census workers 26 months after the treatment dose. Verbal autopsies were conducted to assess causes of death, which were classified as respiratory illness, diarrhea, malaria, old age, accidental, or unknown.

The authors examined all-cause and infectious mortality rates by age group. All-cause mortality rates were lower in children ages 1-5 who received azithromycin (2.79 deaths per 1000 person-years, CI, 1.90-4.09) compared to children in the same age group who did not receive treatment (8.18 deaths per 1000 person-years, CI, 4.34-15.34). This finding was statistically significant (P=0.006). Similarly, mortality due to infection was significantly lower in children ages 1-5 who received MDA of azithromycin (0.89 deaths per 1000 person years , CI, 0.36-2.15) as opposed to those who did not (4.86 deaths per 1000 person years, CI 2.09-11.27). In all other age groups (6-10 years, 10-20 years, and >20 years), participants who received azithromycin actually had higher all-cause mortality rates (OR 1.42, 1.40, and 1.26, respectively). Mortality rates due to infectious causes, however, were lower in all other age groups, although these findings were not significant.

DISCUSSION

Overall, the 3 studies evaluated in this review suggest that MDA of azithromycin reduces mortality in children, although the effect size differed greatly (Table 2). Keenan et al (2018) found that all-cause mortality rates decreased 13.5% in
children aged 1-5 years treated with azithromycin, although the greatest mortality reduction was observed in children ages 1-5 months. In comparison, Porco et al (2009)\textsuperscript{13} and Keenan et al (2011)\textsuperscript{14} noted a 47% and 65% decrease, respectively, in all-cause mortality rates in children ages 1-5. Keenan et al (2011)\textsuperscript{14} also noted that mortality due to infectious causes was 80% less likely in azithromycin-treated children compared to children receiving placebo.

This difference in effect may, in part, be due to the fact that these studies were conducted in different countries. Keenan et al (2018)\textsuperscript{12} analyzed the mortality rates of children in Malawi, Niger, and Tanzania, while Porco et al (2009)\textsuperscript{13} and Keenan et al (2011)\textsuperscript{14} based their studies in Ethiopia. Inherent differences between populations and health risks specific to each country could have impacted mortality rates. As such, care should be taken when extrapolating the results of one study to all African countries, or even other regions of the world.

One of the major limitations of all 3 studies\textsuperscript{12-14} is the lack of individual health indices recorded for participants. Both RCTs\textsuperscript{12,13} were cluster-randomized trials, which can inherently introduce bias through an imbalance of variables at baseline.\textsuperscript{15} Both Keenan et al (2018)\textsuperscript{12} and Porco et al (2009)\textsuperscript{13} adjusted for this using clustered logistic regression and negative binomial regression in their statistical analyses. Porco et al (2009)\textsuperscript{13} also addressed some community factors that could influence individual mortality rates. For example, altitude of each community was analyzed, as a particular fly known to transmit infections favors higher altitudes. Despite these adjustments, a comparison of health indices would be useful in evaluating the similarity between
treatment and control groups to account for any baseline imbalances, as well as to compare populations across studies.

All 3 studies\textsuperscript{12-14} determined causes of death by verbal autopsies, which were conducted by census personnel. The accuracy of verbal autopsies is questionable, as conclusions were drawn from a constellation of symptoms prior to death and may not have correctly identified the actual cause of death in some cases. Regardless, all 3 articles cited\textsuperscript{12-14} pneumonia, diarrhea, and respiratory illness as the 3 primary infectious causes of child deaths, albeit in differing proportions. These findings are consistent with the leading causes of childhood mortality identified worldwide.\textsuperscript{1}

Although Keenan et al (2011)\textsuperscript{14} published the largest reduction in childhood mortality after azithromycin administration, this observational analysis was downgraded to very low quality evidence due to poor methodology. Azithromycin treatment was not randomly allocated. Rather, participants were only allotted to the no-treatment group if they refused treatment, were pregnant, allergic to macrolides, or were ill or not present during the time of administration. The authors acknowledged that lack of randomization is a source of bias in this study. In particular, refusal to receive antibiotic treatment may be correlated with other factors that increase mortality, including poverty and lack of healthcare. Therefore, the findings of this study should not be weighted as heavily as the findings of other 2 RCTs in this review.

The study conducted by Porco et al (2009)\textsuperscript{13} also has its limitations, including a lack of blinding throughout the study. As a result, this RCT was downgraded to moderate quality evidence. Census personnel were unaware of treatment allocations and community randomization was concealed initially. However, field teams were ultimately
unmasked to treatment protocols. Additionally, participants were not blinded. Dose regimens were apparent and placebo doses were not provided for participants receiving annual or biannual administration to coincide with quarterly administration. Placebo antibiotic was not provided to the control group either. This study design makes it difficult to assess a placebo effect on mortality rates. Lastly, the short duration of the study makes it difficult to extrapolate these findings beyond one year and prompts further investigation to address the stability of these findings long-term.

Keenan et al (2018) reported that cause of death varied between countries included in their trial. Malaria was the leading cause of death in Niger, while pneumonia was the main cause of death in Tanzania. This, combined with the fact that Niger had the most significant reduction in mortality with treatment, suggests that azithromycin may play a larger role in malaria prevention compared to prevention of other infectious diseases. Further investigation into the mechanism of azithromycin is needed to better understand which diseases are most susceptible to the antibiotic. In turn, this may help us target populations that would benefit most from MDA of azithromycin.

Furthermore, Keenan et al (2018) included children ages 1-59 months in their study. Although the greatest benefit of treatment was noted in children ages 1-5 months, administration of azithromycin for trachoma control is not currently recommended by the WHO, nor is the antibiotic approved by the FDA, for use in this age group. Some studies suggest that azithromycin increases the risk of hypertrophic pyloric stenosis in infants. Because this age group has the most to gain from MDA of azithromycin, additional studies are needed to address this risk and other potential consequences of azithromycin administered to infants.
The studies assessed in this review did not address the side effects of MDA of azithromycin. Keenan et al (2018) advised participants to report adverse events that occurred during the course of the trial. Although 20 hospitalizations and serious conditions were reported, it could not be determined whether they were caused by azithromycin. Some studies suggest a link between azithromycin and deaths due to cardiac events in adults. Although this data may not be applicable to the population addressed in this review, future studies should consider adverse effects and long-term outcomes of MDA of azithromycin to assess the safety of this protocol.

Perhaps one of the most significant implications of MDA of azithromycin is its impact on antibiotic resistance, which remains largely unknown. One study observed that azithromycin-resistant strains of Streptococcus pneumoniae increased after treatment with azithromycin for trachoma control. Another study suggested that MDA of azithromycin in the setting of trachoma control did not contribute to azithromycin-resistant strains of Chlamydia trachomatis two months after treatment. Keenan et al (2018) also noted that the reduction in mortality rates actually increased during the course of the trial, providing little evidence to support the emergence of azithromycin-resistant strains. Studies with longer follow-up periods are needed to fully assess whether this increase in mortality reduction is reproducible and sustainable.

Separately, the results from Keenan et al (2011) suggest that the lowest mortality rate was observed in children receiving only the annual dose of azithromycin compared to biannual or quarterly MDA. Although this finding should be taken lightly due to the very low quality of this study, it suggests that minimizing the number of
azithromycin doses given is actually more effective in protecting against infectious diseases and may help reduce the risk of antibiotic resistance.

**CONCLUSION**

MDA of azithromycin for trachoma control in African children appears to have additional benefits. Specifically, the studies examined in this systematic review showed that all-cause mortality rates decreased in children ages 1-5 years who received azithromycin treatment. Considering MDA of azithromycin is already recommended by the WHO for trachoma control in endemic regions in Africa, reduced mortality among children is an added benefit of this protocol. Although the results of this research is promising, further investigation is needed to address adverse outcomes and antibiotic resistance related to MDA of azithromycin.
References


### Table 1: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Quality</th>
</tr>
</thead>
</table>

aLack of blinding of field team and participants; no mention of blinding of investigators
bFailure to identify all known prognostic factors in participants and rule out as confounding variables

### Table 2: Mortality Rates* amongst Children Receiving Azithromycin vs. Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range</th>
<th>Country</th>
<th>Azithromycin Treated</th>
<th>Placebo</th>
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</thead>
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<tr>
<td>Keenan et al (2018)</td>
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<td>9.6</td>
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<td></td>
<td></td>
<td>Niger</td>
<td>22.5</td>
<td>27.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tanzania</td>
<td>5.4</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall</td>
<td>14.6</td>
<td>16.5</td>
</tr>
<tr>
<td>Porco et al (2009)</td>
<td>1-5 years old</td>
<td>Ethiopia</td>
<td>5.7</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-9 years old</td>
<td>4.1</td>
<td>8.3</td>
</tr>
<tr>
<td>Keenan et al (2011)</td>
<td>1-5 years old</td>
<td>Ethiopia</td>
<td>2.79</td>
<td>8.18</td>
</tr>
</tbody>
</table>

*Mortality rates reported as deaths per 1,000 person-years