

The Impact of Antenatal Azithromycin and Monthly Sulphadoxine-Pyrimethamine on Child Mortality, Morbidity, Growth, and Development

Background

Public health interventions targeting childhood growth failure and undernutrition have been largely based on the promotion of a healthy diet and effective infection control in early childhood. Recently there has been increased attention to the fetal period and its critical importance for subsequent health. However, there is a relative paucity of empirical data on the impact of pregnancy interventions on child health beyond immediate birth outcomes.

A randomized, controlled trial conducted in rural Malawi from 2003–2006 provided an opportunity to study medium-term effects on children after interventions targeted to pregnant women. The trial enrolled 1,320 pregnant women in three intervention groups. Participants in the control group received standard Malawian antenatal care, which included intermittent preventive malaria treatment in pregnancy with sulphadoxine-pyrimethamine (SP) once at enrollment and once between 28–34 weeks of gestation. Participants in the monthly SP intervention group received SP monthly from enrollment until 37 weeks of gestation. Participants in the azithromycin (AZI)-SP intervention group received monthly SP and two doses of active AZI (once at enrollment and once between 28–34 weeks of gestation) to eradicate possible maternal reproductive tract infections and strengthen the antimalarial effect of SP.

As a follow-up to the trial, we tested the hypotheses that children born to mothers treated during pregnancy with monthly SP, with or without two doses of AZI, would have a lower number of deaths during the first 5 years of life, a lower incidence of non-scheduled (NS) visits to the health center during the first 3 years of life, be taller and otherwise larger in size through the first 5 years of life, and have a higher total developmental score at 5 years of age than children born to mothers who received standard malaria treatment in pregnancy.

Methods

Primary outcomes of the follow-up study were the number of deaths by 5 years of age, the incidence of NS visits by 3 years of age, child length/height at 2



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and 5 years of age, and total developmental score at 5 years of age. For mortality outcomes, we calculated total mortality during the first 5 years of life, number of miscarriages and stillbirths, number of early and late neonatal deaths, number of postneonatal deaths, and number of child deaths. We used the number of NS visits as a proxy for morbidity because we did not have direct data on child morbidity. Child anthropometrics were measured at the age of 1, 3, 6, 9, 12, 15, 18, 24, 30, 36, 48, and 60 months. We calculated age- and sex-standardized anthropometric indices (height-for-age z-score, weight-for-age z-score, weight-for-height z-score, head circumference-for-age z-score, and mid-upper arm circumference [MUAC]-for-age z-score) by using the World Health Organization Child Growth Standards. Values below -2 z-scores were considered indicative of stunting, underweight, wasting, small head circumference, and low MUAC. Child development was measured at 5 years of age with Griffith's Mental Development Scale. We calculated total developmental score as a sum of locomotor, personal-social, language, eye and hand coordination, performance, and practical reasoning subscale scores.

For mortality outcomes and the prevalence of various forms of malnutrition, we calculated percentages and risk ratios. We calculated incidence rate ratios for the total number of NS visits. For anthropometric indices

and developmental scores, we calculated group means and differences between groups. We used log-binomial regression models to estimate risk ratios for binary end-points at a single time point and negative binomial regression adjusted for time in follow-up to estimate incidence rate ratios for total number of NS visits. We used least squares regression to calculate differences in means for continuous outcomes.

Developmental results were adjusted for child age at the time of developmental assessment and child sex, otherwise all main results are shown without covariate adjustments. As a sensitivity analysis, we also estimated coefficients adjusted for a set of covariates. All regression models for the mortality and morbidity outcomes were adjusted for the same set of covariates, based on whether the potential covariate was associated with any mortality or morbidity outcome at $p < 0.05$. All regression models for anthropometric outcomes were adjusted for the same set of covariates, selected based on covariate selection carried out with 24-month outcomes. All regression models for total developmental score were adjusted for covariates associated with total developmental score at $p < 0.05$.

As exploratory analyses we also tested for the presence of an interaction between the intervention and pre-specified maternal and child characteristics. We performed analyses stratified by the respective variables if the interaction term was significant at $p < 0.1$. The purpose of the interaction testing was exploratory rather than confirmatory.

Results

The proportion of children who died during the follow-up was 15.3% in the control group, 15.1% in the monthly SP group, and 13.1% in the AZI-SP group ($p = 0.603$). The proportion of postneonatal deaths was 5.5% in the control group, 3.3% in the monthly SP group, and 1.9% in the AZI-SP group ($p = 0.008$ AZI-SP vs. control). The incidence of NS visits during the first 3 years of life was 0.12 in the control and monthly SP groups and 0.13

in the AZI-SP group ($p = 0.710$). The mean height-for-age z-score was higher in the AZI-SP group than in the control or monthly SP groups at all time points. Mean absolute length/height in the AZI-SP group was 0.4–0.7 cm higher compared to the control group between 1 and 60 months. The AZI-SP group also had a higher mean weight-for-age z-score and head circumference-for-age z-score compared to the control and monthly SP groups at all time points. Differences between groups in mean weight-for-height z-score were not consistently in favor of AZI-SP or any other intervention group over time. Mean MUAC-for-age z-score was higher in the AZI-SP group compared to the control group from 6 to 36 months of age, but at 48 and 60 months, those differences had disappeared. The mean (standard deviation [SD]) total developmental score was 108.8 (17.1) in the control group, 110.3 (17.0) in the monthly SP group, and 112.5 (17.6) in the AZI-SP group ($p = 0.029$), with the AZI-SP group having a 3.7 point higher score compared to the control group ($p = 0.008$). Covariate adjustment did not markedly change these results. Although effect modification was observed for some outcomes, the results did not show a clear pattern in how the effect of the intervention was modified by maternal background variables or child characteristics.

Conclusions

The results of this study support the hypothesis that children born to mothers who receive monthly SP and two doses of AZI during pregnancy are on average taller throughout the first 5 years of life than children born to mothers who receive standard malaria treatment in pregnancy. It is also possible that differences in newborn weight and head size are sustained for 5 years but this was not conclusively confirmed. The results also support a positive effect of the AZI-SP intervention on postneonatal infant mortality and the developmental status of the children at 5 years of age. The results do not support the hypothesis that the intervention would reduce child morbidity during the first 3 years of life in rural areas of Malawi.



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