Child Health Outcomes After Presumptive Infection Treatment in Pregnant Women: A Randomized Trial

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abstract

BACKGROUND AND OBJECTIVES: We showed earlier that presumptive infection treatment in pregnancy reduced the prevalence of neonatal stunting in a rural low-income setting. In this article, we assess how these gains were sustained and reflected in childhood growth, development, and mortality.

METHODS: We enrolled 1320 pregnant Malawian women in a randomized trial and treated them for malaria and other infections with either 2 doses of sulfadoxine-pyrimethamine (SP) (control), monthly SP, or monthly sulfadoxine-pyrimethamine and 2 doses of azithromycin (AZI-SP). Child height or length and mortality were recorded at 1, 6, 12, 24, 36, 48, and 60 months and development at 60 months by using Griffith's Mental Development Scales.

RESULTS: Throughout follow-up, the mean child length was 0.4 to 0.7 cm higher ($P < .05$ at 1–12 months), the prevalence of stunting was 6 to 11 percentage points lower ($P < .05$ at 12–36 months), and the 5-year cumulative incidence of stunting was 13 percentage points lower (hazard ratio: 0.70, 95% confidence interval [CI]: 0.60 to 0.83, $P < .001$) in the AZI-SP group than in the control group. The mean developmental score was 3.8 points higher in the AZI-SP group than in the control group (95% CI: 1.1 to 6.4, $P = .005$). Total mortality during pregnancy and childhood was 15.3%, 15.1%, and 13.1% ($P = .60$) in the control, monthly SP, and AZI-SP groups, respectively. Postneonatal mortality (secondary outcome) was 5.5%, 3.3%, and 1.9%, respectively (risk ratio of AZI-SP versus control: 0.34, 95% CI: 0.15 to 0.76, $P = .008$).

CONCLUSIONS: Provision of AZI-SP rather than 2 doses of SP during pregnancy reduced the incidence of stunting in childhood. AZI-SP during pregnancy also had a positive effect on child development and may have reduced postneonatal mortality.

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WHAT'S KNOWN ON THIS SUBJECT: Stunting is a big global issue and is associated with increased mortality and developmental delay. We showed earlier that presumptive antenatal infection treatment during pregnancy against malaria and reproductive tract infections reduced the prevalence of neonatal stunting in Malawi.

WHAT THIS STUDY ADDS: Gains obtained among children whose mothers received monthly sulfadoxine-pyrimethamine with 2 doses of azithromycin rather than 2 doses of sulfadoxine-pyrimethamine during pregnancy were sustained for 5 years and reflected in the prevalence of childhood stunting, development, and (possibly) neonatal mortality.

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Poor linear growth in childhood is common, especially in sub-Saharan Africa and in southern Asia. It is associated with increased mortality and developmental delay. Reducing its prevalence is a key global health target.[1,2] To date, most public health interventions to prevent growth failure have been based on the promotion of a healthy diet and effective infection control in early childhood. This approach may, however, be insufficient because linear growth retardation often commences during the fetal period.[3,4] Maternal dietary supplementation with energy and/or nutrients during pregnancy has in some contexts resulted in modestly increased mean birth size, but gains in infant length have typically been lost within a year after birth.[5,6]

We have previously reported results from the Lungwena Antenatal Intervention Study (LAIS) in rural Malawi, in which pregnant women received intermittent preventive treatment in pregnancy (IPTp), either with 2 doses of sulfadoxine-pyrimethamine (SP) (control group), monthly SP, or monthly sulfadoxine-pyrimethamine and 2 doses of azithromycin (AZI-SP). SP is primarily an antimalarial with additional activity on many bacteria,[7] and azithromycin is a broad-spectrum antibacterial drug that also has anti-inflammatory and antimalarial activity.[8]

In the LAIS trial sample, the incidence of preterm birth and low birth weight and the prevalence of stunting at 1 month after delivery were 35% to 40% lower, and mean length 1 month after delivery was 6 mm higher, among infants born to women receiving AZI-SP compared with those born to women in the control group.[9,10] Because of these results, we suggest that intensified infection and inflammation control during pregnancy can, in the Malawian context, promote fetal growth and increase length at 1 month after delivery. In this follow-up study, we aimed to assess the sustainability and consequences of these gains. Our primary hypothesis was that the difference in mean length would be retained throughout the first 5 years of life and would be reflected in a permanently lower incidence and prevalence of stunting among infants born to women treated with AZI-SP. We also hypothesized that these children would have a higher mean developmental score at the age of 5 years and a lower mortality by 5 years than children born to women in the control group.

METHODS

Background

This study was a 5-year follow-up to the LAIS trial, a single-center, randomized, partially placebo-controlled, outcome assessor–blinded, 3-arm clinical trial conducted in rural Malawi.[9] The main outcome of the original trial was the incidence of preterm delivery, and the predefined secondary outcomes included birth weight and infant size at 1 month.[9,10]

Participants and Follow-up

The LAIS trial enrolled women with uncomplicated second-trimester pregnancies (14–26 weeks' gestation by ultrasound assessment) who had felt movements of the fetus, had commenced antenatal care at Lungwena Health Centre, Southern Malawi, and had provided informed consent. Exclusion criteria included multiple pregnancy, severe illness, receipt of azithromycin during the current pregnancy or SP within the preceding 28 days, allergy to study drugs, and any previous serious allergic reaction.[9]

The details of randomization are available in the original trial publication[9] and in the Methods section of the Supplemental Information. In brief, we randomly allocated 1320 women to either a control group or to 1 of the 2 intervention groups: monthly SP or AZI-SP. Women in the control group received standard Malawian antenatal care, which at the time of the study included IPTp with SP (3 tablets orally, each containing 500 mg of sulfadoxine and 25 mg of pyrimethamine) administered twice: once at enrollment and once between 28 and 34 weeks' gestation. At these visits, they also received a placebo in lieu of azithromycin. Women in the monthly SP group received SP monthly from enrollment until 37 weeks' gestation and a placebo in lieu of azithromycin. Women in the AZI-SP group received monthly SP and active azithromycin (2 tablets orally, each containing 500 mg of azithromycin) twice: once at enrollment and once between 28 and 34 weeks' gestation. Active azithromycin and its placebo were manufactured and donated by Pfizer Inc (New York, NY). SP tablets were obtained from Malawi Central Medical Stores that only made purchases from companies with Good Manufacturing Practice certification and quality assurance. We did not perform any pharmacological tests on the study drugs.

All children received standard Malawian care during follow-up; HIV-positive mothers and their newborns received nevirapine for prevention of mother-to-child transmission of HIV.

Child length or height was assessed at the study clinic visits at 1, 6, 12, 24, 36, 48, and 60 months. Details about the measuring equipment and inclusion criteria for length measurements are presented in the Methods section of the Supplemental Information. If the child did not come for a scheduled study clinic visit, the study team traced and interviewed the caretaker and completed a structured verbal autopsy questionnaire if the child had died.

Child development was assessed at 60 months of age by using the Griffith's Mental Development

Scales, Extended Revised: 2–8 Years (GMDS-ER 2–8), which covers 6 domains: locomotor, personal-social, language, eye and hand coordination, performance, and practical reasoning.[11]

Both the original trial and the follow-up were performed according to Good Clinical Practice and the ethical standards of the Declaration of Helsinki. The protocol was approved by the College of Medicine Research and Ethics Committee, Malawi, and the Ethical Committee of Pirkanmaa Hospital District, Finland.

Outcomes

In the present analysis, primary outcomes were child length or height and stunting at 6, 12, 24, 36, 48, and 60 months of age; the total developmental score at 5 years; and the total number of abortions, stillbirths, and child deaths combined. Secondary mortality outcomes included the number of abortions and stillbirths, early neonatal deaths, late neonatal deaths, postneonatal deaths, and child deaths until 5 years of age. Secondary developmental outcomes included the 6 individual subscale scores from the GMDS-ER 2–8.[11]

We calculated age- and sex-standardized height-for-age *z* scores (HAZs) using the World Health Organization Child Growth Standards.[12,13] Values <−2 and <−3 for *z* scores were considered to indicate stunting and severe stunting, respectively.

We calculated a raw score for each subscale in GMDS-ER 2–8 as the sum of the passed items. We calculated a total developmental score as the sum of the subscale scores.

We defined spontaneous abortion as noninduced loss of pregnancy before 22.0 completed weeks' gestation and stillbirth as fetal death at or after 22.0 weeks' gestation, early neonatal death as death of a live-born infant within 7 days of birth, late neonatal death as death within 8 to 28 days of birth, postneonatal death as death between 29 and 365 days, and child death as death between 366 days and 5 years of age. Mortality rates were calculated with standard definitions.[14,15]

Because of delays in starting the developmental assessments, some children were older than 5 years when assessed (range: 59–74 months, except 1 at 48 months). We did not exclude any participants from the analyses but included child age at the time of the assessment and child sex as covariates in the statistical analyses. International guidelines[16,17] highlight the importance of presenting the main results as per a predefined plan. Hence, all main results, besides developmental outcomes, are shown without covariate adjustment, as per the predefined statistical analysis plan.

Statistical Analysis

The sample size of 440 pregnant women per group was planned to give 80% power at a 5% level of significance to detect a 40% reduction in the rate of preterm delivery, which was the trial's main hypothesis.[9]

Group codes for the study were broken for the analysis of the trial's main hypothesis. The statistician for this follow-up was different from the 1 doing the analyses for the main hypothesis. For this follow-up study, the statistician (L.H.) obtained and merged the intervention code with follow-up data only after data were cleaned, the analysis plan was written, and the syntax for the analysis was completed with a mock code. The analysis was based on the principle of intention to treat. We conducted statistical analyses with Stata 13.1 (StataCorp, College Station, TX).

For prevalence of stunting and mortality outcomes, we calculated percentages and used a log-binomial regression model to estimate risk ratios (RRs) or used a modified Poisson regression in case the log-binomial regression did not converge.[18] For absolute length or height, HAZ and developmental scores were calculated as group means, and we used least squares regression to estimate differences between groups. We used Cox regression to estimate hazard ratios (HRs) for mortality, and competing-risks regression[19] to estimate the cumulative incidence of stunting under the competing risk of death. The main analysis for development was done with multiple imputed subscale data (details in the Methods section of the Supplemental Information).

We took intragroup correlation due to twin pregnancies into account using robust SEs for clustered data.[20] To prevent inflated type I errors due to testing between multiple groups, we began hypothesis testing with a global null hypothesis of no difference between any groups.[21] Pairwise null hypotheses were rejected only if the global null hypothesis was also rejected. We rejected a null hypothesis if 2-sided $P < .05$. We thus controlled the familywise error rate at 5%. For developmental assessment, we considered the differences in the total score between groups the primary hypothesis and did not apply multiplicity adjustment for multiple subscales.

A number of sensitivity analyses were performed: an analysis with multiple imputation for missing data for growth outcomes,[22] an analysis of raw data without imputations for developmental outcomes, an analysis with adjustment for covariates selected on the basis of predefined criteria as per the statistical analysis plan (covariates listed in the Methods section of the Supplemental Information), and a post-hoc analysis stratified by maternal HIV status. Finally, we built Heckman

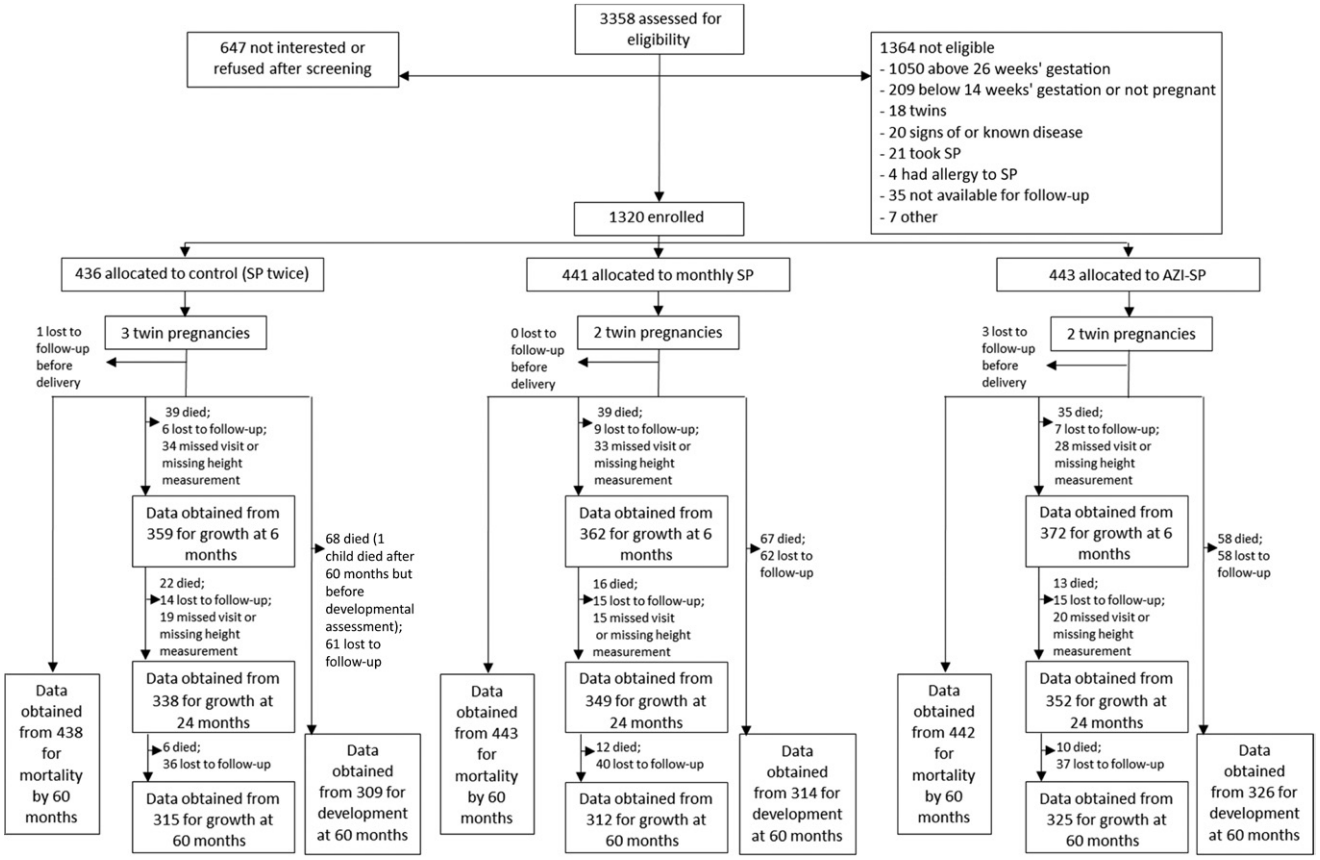

FIGURE 1
Enrollment, randomization, and follow-up.

selection models to estimate whether differences between groups in child growth at 60 months might have been affected by the higher mortality of stunted children in some groups[23,24] (Methods section of the Supplemental Information).

RESULTS

Of the 3358 pregnant women invited to participate in the study, 1320 (39.3%) were enrolled between December 1, 2003, and October 11, 2006, and were randomly assigned to the control (436), monthly SP (441), and AZI-SP groups (443) (Fig 1). Enrolled and nonenrolled women were approximately the same mean age (25 and 26 years, respectively) and had the same mean number of previous pregnancies (2.3 and 2.5, respectively). At enrollment, the intervention groups were similar except for small differences in the prevalence of malaria parasitemia and the number of previous pregnancies (Table 1). We inadvertently assigned 3, 2, and 2 twin pregnancies to the control, monthly SP, and AZI-SP groups, respectively, resulting in 1327 fetuses for follow-up (Fig 1).

The mean (SD) number of scheduled SP treatments received was 2.0 (0.2) in the control group, 4.0 (1.0) in the monthly SP group, and 4.0 (0.9) in the AZI-SP group. Women in the AZI-SP group received a mean (SD) of 2.0 (0.2) azithromycin doses.

The last follow-up visit was completed on June 6, 2012, with data from 1323 children (99.7%) at 5 years for mortality outcomes and from 949 (71.5%) for development. Growth data at 2 and 5 years of age were obtained from 1039 (78.3%) and 952 (71.7%) participants, respectively (Fig 1). Success of follow-up was similar between the groups ($P = .72$ and $P = .69$ for growth at 2 and 5 years; $P = .60$ for development). Maternal background characteristics were mostly similar for children lost to follow-up by 5 years compared with those who remained in the study, except for a higher number of HIV-positive (23.4% vs 10.3%, $P < .001$) and malaria-positive (12.2% vs 7.9%, $P = .017$) mothers.

The mean (SD) length or height of children in the study cohort was 63.8 cm (2.8 cm) at 6 months, 80.6 cm (3.3 cm) at 24 months, and 101.9 cm (4.4 cm) at 60 months of age, corresponding to a mean (SD) HAZ of −1.38 (1.22), −2.11 (1.05), and −1.68 (0.94), respectively (Supplemental Fig 5). The mean difference in absolute length or height between AZI-SP and the

TABLE 1 Baseline Characteristics of the Participating Women at Enrollment, by Study Group

Characteristic	Control (SP Twice) ($N = 436$), n (%)	Monthly SP, ($N = 441$), n (%)	AZI-SP ($N = 443$), n (%)
Age, y, mean (SD)	25 (7)	25 (7)	25 (6)
Height, cm, mean (SD)	155.0 (5.5)	154.8 (5.4)	155.3 (5.6)[a]
BMI, kg/m^2, mean (SD)	21.7 (2.2)	21.8 (2.1)	21.9 (2.1)[a]
Gestational age at enrollment, wk, mean (SD)	20.3 (3.0)	20.0 (3.2)	20.0 (3.0)
Primiparous	110 (25.2%)	107 (24.3%)	89 (20.1%)
HIV-positive	48/396 (12.1%)	64/400 (16.0%)	49/398 (12.3%)
Positive syphilis status	18/433 (4.2%)	27/435 (6.2%)	21/440 (4.8%)
Blood Hb concentration, g/L, mean (SD)	110 (19)	111 (17)	110 (20)
Moderate or severe anemia, Hb < 100 g/L	116 (26.6%)	106 (24.0%)	129 (29.1%)
Severe anemia, Hb < 70 g/L	9 (2.1%)	2 (0.5%)	9 (2.0%)
Microscopic peripheral blood malaria parasitemia	49/435 (11.3%)	41 (9.3%)	27 (6.1%)
Literate participants	116 (26.6%)	129 (29.3%)	139 (31.4%)
Years of schooling completed, mean (SD)	2.1 (2.7)[a]	2.2 (2.6)	2.4 (2.8)

Hb, hemoglobin.
[a] Value missing for 1 participant.

control group varied between 0.4 and 0.7 cm between 1 and 60 months of age (Fig 2, Supplemental Table 3). After covariate adjustment, the mean difference varied between 0.3 and 0.6 cm (Supplemental Table 3). The difference in mean HAZ between the AZI-SP group and the control group was 0.25 at 6 and 12 months, 0.17 at 24 months, 0.13 at 36 months, and 0.15 at 48 and 60 months, with statistically significant differences at 6 and 12 months (each $P < .05$) (Supplemental Table 4). After covariate adjustment, the mean difference in HAZ varied between 0.11 and 0.21, with statistically significant differences at 12 months ($P = .008$) (Supplemental Table 3).

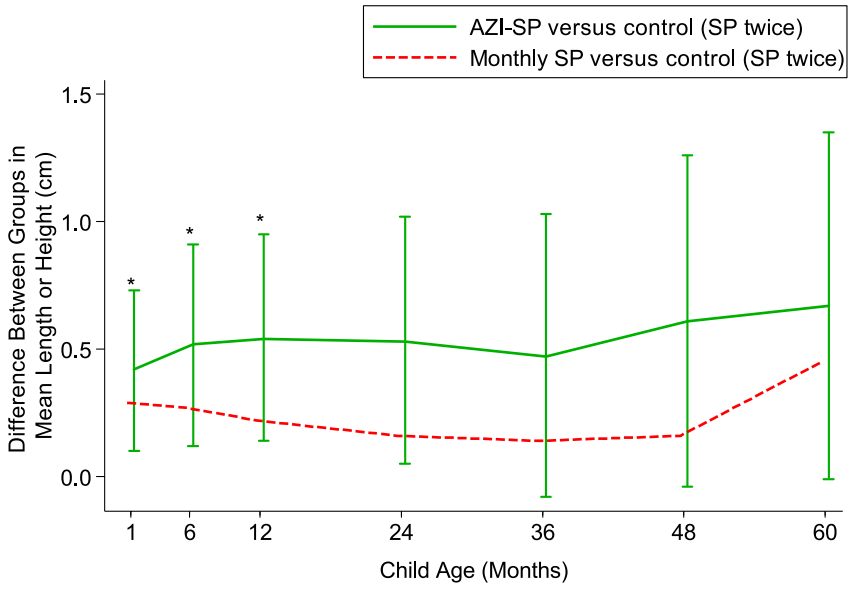

FIGURE 2
Differences between groups and 95% CI for AZI-SP versus control in height (centimeters) at 1, 6, 12, 24, 36, 48, and 60 months. * $P < .05$.]

The cumulative incidence of stunting with competing risk of death by 60 months was 76.9% (control), 74.0% (monthly SP), and 64.2% (AZI-SP), with statistically significant differences between the AZI-SP group and the control group (HR: 0.70, 95% confidence interval [CI]: 0.60 to 0.83, $P < .001$) (Fig 3A). Similarly, the incidence of severe stunting was significantly lower in the AZI-SP group than in the control group (HR: 0.64, 95% CI: 0.50 to 0.81, $P < .001$) (Fig 3A). Covariate adjustment did not markedly change the results (HR for stunting between AZI-SP and control: 0.74, 95% CI: 0.62 to 0.88, $P = .001$, global $P = .003$; severe stunting between AZI-SP and control: 0.68; 95% CI: 0.52 to 0.88, $P = .004$, global $P = .01$).

The prevalence of stunting varied from 27.4% (at 6 months) to 55.3% (at 24 months), and the prevalence of severe stunting varied from 7.5% (at 60 months) to 18.3% (at 24 months). Compared with the control group, the prevalence of stunting in the AZI-SP group was 5.5 to 10.9 percentage points, and the prevalence of severe stunting was 0.5 to 4.5 percentage points lower throughout the follow-up period (Fig 3B, Supplemental Table 5), corresponding to a RR from 0.75 to 0.84 for stunting and 0.73 to 0.93 for severe stunting (Supplemental Table 5). Differences in the prevalence of stunting between the AZI-SP group and the control group were statistically significant at 12, 24, and 36 months (each $P < .05$) (Supplemental Table 5). The differences in the prevalence of severe stunting between the AZI-SP group and the control group were not

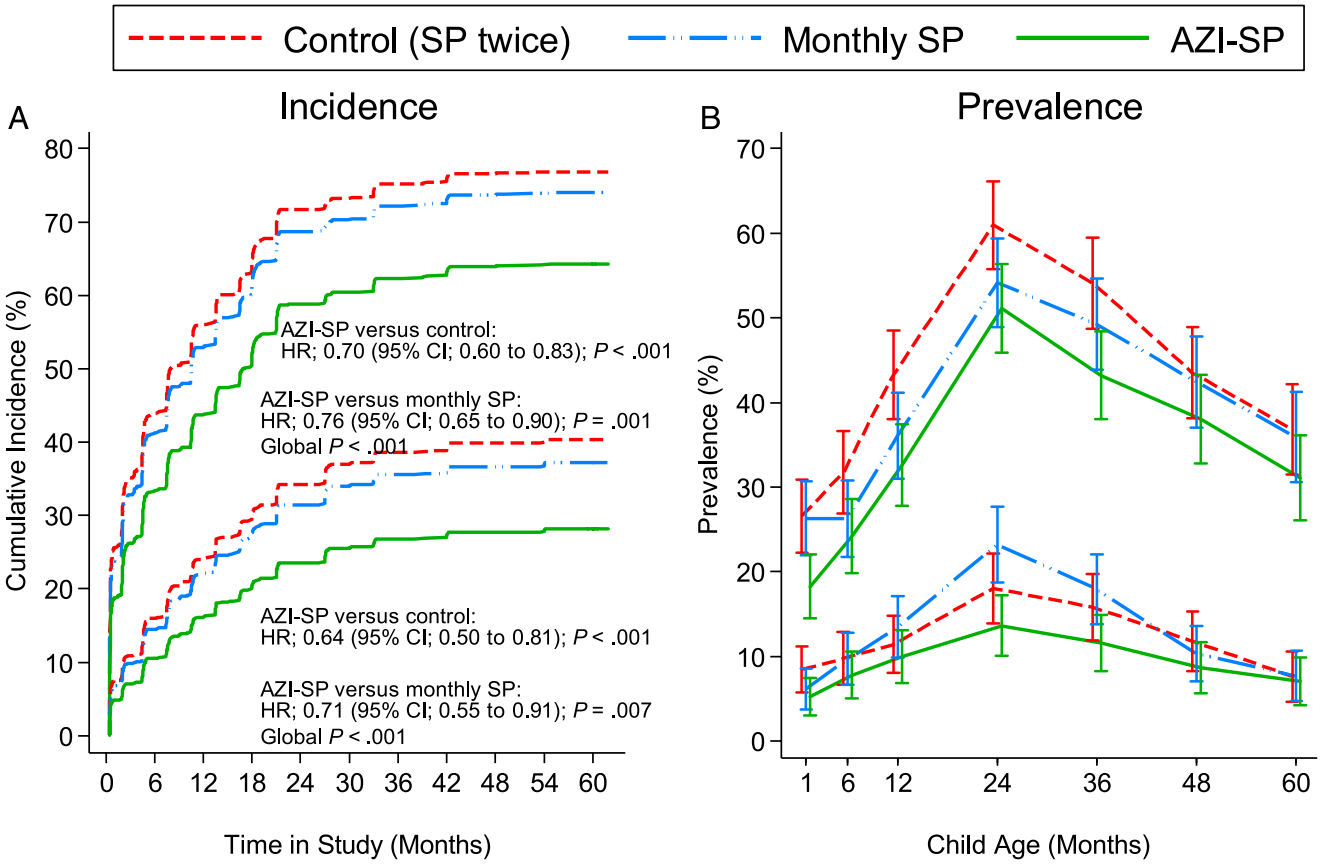

FIGURE 3

A, Cumulative incidence of stunting and severe stunting by 60 months of age by intervention group. B, Prevalence of stunting and severe stunting with 95% CIs by intervention group. Stunting (HAZ < −2, upper set of lines) and severe stunting (HAZ < −3, lower set of lines) are shown.

statistically significant at any time point (Supplemental Table 5). The covariate-adjusted RR varied from 0.76 to 0.86 ($P < .05$ at 12 and 24 months) for stunting and from 0.76 to 1.09 ($P > .05$ at all time points) for severe stunting (Supplemental Table 5).

A detailed description of growth in the AZI-SP group compared with the monthly SP group and of growth in the monthly SP group compared with the control group is reported in the Results section of the Supplemental Information. In general, the AZI-SP group had a higher mean length or height and a lower incidence and prevalence of stunting at all time points compared with the monthly SP group (Figs 2 and 3, Results section of the Supplemental Information, Supplemental Tables 4 and 5). The monthly SP group had higher mean length or height and a lower incidence and prevalence of stunting at almost all time points compared with the control group. However, the differences between groups were smaller than between the AZI-SP and control groups (Figs 2 and 3, Results section of the Supplemental Information, Supplemental Tables 4 and 5).

The mean (SD) total developmental score was 108.6 (17.1) in the control group, 110.2 (17.0) in the monthly SP group, and 112.4 (17.7) in the AZI-SP group ($P = .02$). The AZI-SP group had a mean total developmental score that was 3.8 (95% CI: 1.1 to 6.4, $P = .005$) points higher than that of the control group. After covariate adjustment, the difference was 3.3 points (95% CI: 0.7 to 5.9, $P = .01$, global $P = .05$) (Supplemental Table 6). The difference in means between the monthly SP and control groups was 1.6 (95% CI: −1.1 to 4.3, $P = .24$) points (covariate-adjusted difference: 1.4, 95% CI: −1.2 to 4.1, $P = .28$) (Supplemental Table 6). The difference between the AZI-SP group and the control group was mostly due to a higher mean score in the performance subscale in the AZI-SP group ($P < .001$). There were no significant differences in the other subscales between groups (Table 2, Supplemental Table 6).

The proportion of abortions, stillbirths, and children who died during the follow-up was 15.3%, 15.1%, and 13.1% in the control, monthly SP, and AZI-SP groups respectively ($P = .60$) (Supplemental Table 7). There were no statistically significant differences between the groups in the cumulative 5-year mortality found by using

TABLE 2 Total Developmental Score and 6 Subscale Scores by Intervention Group at 60 Months of Age Using Multiple Imputed Data

Outcome	Control (SP Twice) (N = 371), Mean (SD)[a]	Monthly SP (N = 376), Mean (SD)[a]	AZI-SP (N = 387), Mean (SD)[a]	Global P	Comparison Between AZI-SP Group and Control Group		Comparison Between AZI-SP Group and Monthly SP Group		Comparison Between Monthly SP Group and Control Group	
					Difference in Means (95% CI)	P	Difference in Means (95% CI)	P	Difference in Means (95% CI)	P
Total score	108.6 (17.1)	110.2 (17.0)	112.4 (17.7)	.02	3.8 (1.1 to 6.4)	.005	2.2 (−0.4 to 4.8)	.10	1.6 (−1.1 to 4.3)	.24
Locomotor score	24.6 (3.8)	24.8 (3.5)	24.8 (3.9)	.88	0.1 (−0.5 to 0.7)	.67	0.0 (−0.6 to 0.6)	.97	0.1 (−0.5 to 0.7)	.64
Personal-social score	27.0 (3.9)	27.4 (3.9)	27.4 (3.8)	.27	0.4 (−0.2 to 1.0)	.17	0.0 (−0.6 to 0.6)	.95	0.4 (−0.2 to 1.0)	.16
Language score	14.7 (4.9)	15.1 (5.1)	15.6 (4.8)	.09	0.8 (0.1 to 1.6)	.03	0.5 (−0.3 to 1.2)	.24	0.4 (−0.4 to 1.2)	.34
Eye and hand coordination score	8.4 (3.1)	8.9 (3.2)	8.6 (3.0)	.14	0.3 (−0.2 to 0.7)	.28	−0.2 (−0.7 to 0.2)	.32	0.5 (0.0 to 1.0)	.05
Performance score	15.1 (6.2)	15.3 (5.9)	16.9 (6.1)	<.001	1.8 (0.8 to 2.8)	<.001	1.5 (0.6 to 2.5)	.001	0.3 (−0.7 to 1.2)	.60
Practical reasoning score	18.8 (3.7)	18.7 (3.7)	19.2 (3.7)	.25	0.3 (−0.2 to 0.9)	.24	0.5 (−0.1 to 1.0)	.10	−0.1 (−0.7 to 0.5)	.67

All models are adjusted for child sex and age at the time of developmental assessment.
[a] SDs for multiple imputed data were each calculated as an average SD from 50 imputations.

Cox regression (Fig 4). During the postneonatal period, the proportion of children who died was lower in the AZI-SP group (1.9%) than in the control group (5.5%; RR: 0.34, 95% CI: 0.15 to 0.76, P = .008; adjusted RR: 0.31, 95% CI: 0.13 to 0.74, P = .009) (Supplemental Table 7). There were no statistically significant differences in the number of abortions and stillbirths or early or late neonatal or child deaths (Supplemental Table 7). Mortality rates are reported in the Results section of the Supplemental Information.

Results from the sensitivity analyses with imputed data for length or height, unimputed data for development, and covariate-adjusted differences in means and RRs were consistent with those from the primary analyses (Supplemental Tables 3 through 7). Among children born to HIV-negative mothers, the results were consistent with those from the primary analyses. Among children born to HIV-positive mothers, the intergroup differences were typically larger than in the full-group analyses, but there was less statistical significance, presumably because of the play of chance in the small number of HIV-positive mothers (Supplemental Tables 8 and 9). Finally, the point estimates for the difference in mean child length between the AZI-SP and control groups were not affected much by the higher mortality observed in the control group (Results section of the Supplemental Information).

DISCUSSION

We tested hypotheses that rural Malawian children would on average be taller, have a lower incidence and prevalence of stunting throughout their first 5 years of life, and have a higher developmental score at 5 years if their mothers received AZI-SP in pregnancy rather than 2 SP doses as a preventive treatment. The study findings were consistent

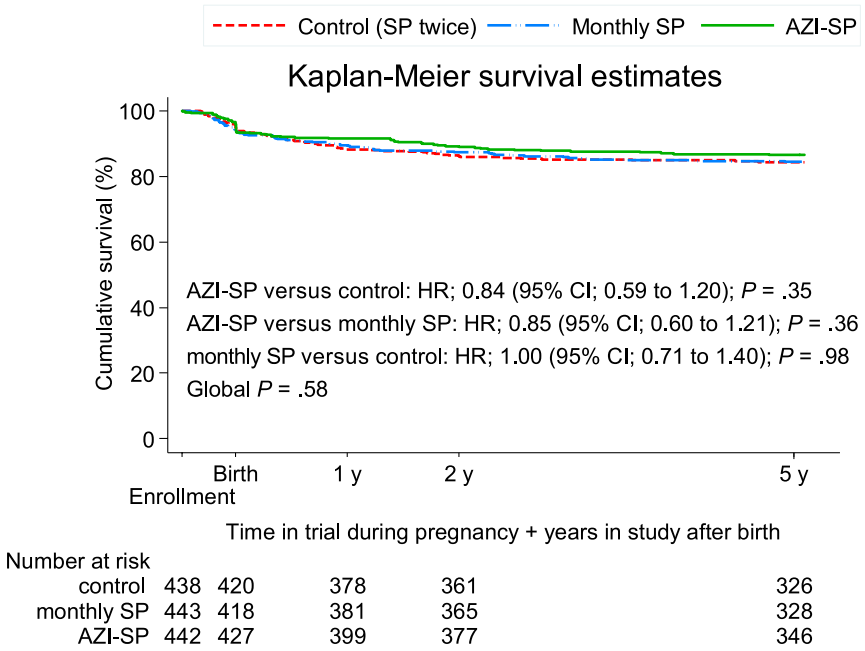

FIGURE 4

Mortality survival curve by intervention groups: Kaplan-Meier survival estimates. The time to death during pregnancy = the time between enrollment and abortion or stillbirth. All pregnancies resulting in live birth were coded to have lasted 25 weeks, and the time in the study after birth was added to that.

with the hypotheses. Children in the AZI-SP group also had a lower postneonatal mortality than children in the control group. It therefore appears that gains obtained among children whose mothers received intensified antenatal infection treatment were sustained for 5 years and reflected in the prevalence of childhood stunting and other health indicators. Differences between the monthly SP group and the control group often trended in the same direction as AZI-SP versus control differences but were smaller and not statistically significant.

The strengths of this trial include random group allocation, broad inclusion criteria, a large sample size, comprehensive follow-up, and blinding of the outcome assessors. Internal validity could have been compromised by missed recordings of child deaths and missing data on anthropometric measurements and developmental items, and we did not have comprehensive information on postnatal exposures that might have affected the outcomes of interest. However, we implemented an active tracing system for defaulters and verified mortality data from multiple sources, and the random allocation was likely to have distributed the nontrial determinants of growth, development, and mortality evenly among the study groups. Furthermore, anthropometric and developmental results were robust to sensitivity analyses, and the baseline characteristics of those lost to follow-up and those who remained in the study were similar. The point estimates for the intergroup differences in mean length and stunting prevalence remained essentially constant throughout the follow-up, and the Heckman selection model suggested that differences in growth were not affected by higher mortality in the control group. The differences in mean length and stunting prevalence were not statistically significant at the older age groups, but this is to be expected if the absolute difference remains constant because of the increasing population variance in length with age.[25] Because of the constant strength of association, the consistency among various indicators, and the biological plausibility of the findings, we consider our findings valid, representative, and indicative of a causal association[26] between the antenatal AZI-SP intervention and the improved and sustained child growth and development outcomes. A positive impact on postneonatal mortality is also biologically plausible, but this finding arose from an exploratory analysis and hence needs further confirmation in future studies.

The positive impact of IPTp on birth weight in malaria-endemic areas has been well documented.[27] Similarly, the preventive antenatal provision of broad-spectrum antibiotics has been associated with increased mean duration of pregnancy and birth weight in sub-Saharan Africa, although opposite results have also been reported.[28] Few study authors have, however, reported newborn or infant lengths and none have evaluated the intervention effect beyond infancy. Although the authors of some maternal dietary supplementation studies have suggested a favorable effect on birth or neonate length,[5,6,29,30] this difference disappears within 6 to 12 months after delivery in the few studies with postnatal follow-up.[5,6] This may be due to the fact that the intervention only affected duration of pregnancy, which in turn affected birth size, because longer gestational duration is negatively associated with early postnatal growth velocity. In our trial, approximately two-thirds of the difference in birth weight was attributed to fetal growth velocity, and only one-third was attributed to pregnancy duration.[10]

Fetal length gain has been shown to be regulated by insulin-like growth factors (IGFs) secreted by maternal

tissues, the placenta, and the fetus in reaction to various stimuli.[31,32] The downregulation of IGFs and their cellular receptor expression, increased concentrations of IGF-binding and inactivating proteins in fetal circulation, and reduced placental nutrient transfer have been associated with systemic inflammation elicited by maternal and placental infection.[33] The antenatal intervention that consisted of repeated doses of SP and azithromycin was designed to reduce the burden of malaria and reproductive tract infections in pregnant women.[9] In our trial, the prevalence of maternal peripheral malaria at 32 weeks' gestation and at delivery, as well as the postnatal prevalence of vaginal trichomoniasis, was significantly lower in the AZI-SP group than in the control group.[9,34] Although we have little data on other infections and no data on maternal inflammation, it seems likely that the AZI-SP intervention affected fetal growth and the duration of pregnancy through its impact on infection-mediated inflammation. Besides malaria and trichomoniasis, azithromycin may have affected maternal bacterial vaginosis, oral infections, and chorioamnionitis, all of which are common in Malawi and associated with reduced birth size.[35–37]

Compared with the control group, the AZI-SP group had a total developmental score at 5 years that was 3.8 points higher. The authors of a recent study on extremely low birth weight children using GMDS-ER 2–8 found roughly the same difference at the age of 5 years when comparing children with and without learning disabilities.[38] This study, conducted in Italy, also revealed that assessing children over the age of 2 was most effective in detecting children with learning disabilities. In our sample, most of the differences in the total developmental score were due to differences in the performance subscale, which measures visuospatial skills, including the speed of working and precision. This is consistent with the findings from the Italian study, whose investigators suggested that a lack of cognitive flexibility at preschool age might interfere with intellectual functioning and negatively affect academic attainment. Our results are promising, but further follow-up assessments would be necessary to better understand the significance of the intervention effect on child development.

CONCLUSIONS

Taken together, the results from this study support the hypothesis that the provision of AZI-SP rather than 2 doses of SP during pregnancy reduces the incidence and prevalence of childhood stunting, has a positive effect on child development, and may reduce postneonatal mortality in Malawi. Monthly treatment with SP alone does not seem to have the same effect, although it does reduce the incidence of low birth weight by ~20%.[27] Although encouraging, these results should not be interpreted to promote widespread use of broad-spectrum antibiotics as a routine antenatal treatment. Such practice could theoretically lead to problems with antibiotic resistance and cause detrimental long-term effects on the microbiota of both the mother and her offspring.[39]

There were no major health policy changes or secular trends in child health outcomes in the study area during the trial follow-up. However, after the implementation of our study, the recommendation for IPTp has changed from 2 doses to monthly dosing with SP.[40] Additionally, HIV-positive women nowadays receive antiretroviral therapy during pregnancy, delivery, and lactation, as opposed to the single-dose nevirapine regimen used at the time of our study. Furthermore, childhood mortality rates in Malawi and elsewhere have significantly declined, at least partly because of improved diagnostics and management of malaria and severe acute malnutrition.[41] Although the results from our sample lead us to suggest that azithromycin combined with monthly SP would provide health benefits compared with the monthly SP alone, the recent health trends and policy changes might modify its impact on 1 or more outcomes. Hence, our results should mainly be considered indicative of a causal role of maternal infections and inflammation in fetal growth restriction and its sustained impact on child growth and development. Given the importance of these fetal exposures and the slow progress in stunting reduction in Sub-Saharan Africa and southern Asia,[42–44] it seems warranted to conduct further trials on the effects of prevention and management of infections during pregnancy and to address childhood stunting in low-income contexts through interventions that reduce the prevalence of maternal infections in pregnancy.

ABBREVIATIONS

AZI-SP: monthly sulfadoxine-pyrimethamine and 2 doses of azithromycin
CI: confidence interval
GMDS-ER 2–8: Griffith's Mental Development Scales, Extended Revised 2–8 Years
HAZ: age- and sex-standardized height-for-age *z* score
HR: hazard ratio
IGF: insulin-like growth factor
IPTp: intermittent preventive treatment in pregnancy
LAIS: Lungwena Antenatal Intervention Study
RR: risk ratio
SP: sulfadoxine-pyrimethamine

quality assurance, and critically reviewed the manuscript; Dr P Ashorn conceptualized the study, developed the data collection materials, oversaw the study, data analysis, and interpretation, drafted the initial manuscript, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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