ORIGINAL ARTICLE

Effect of Adding Azithromycin to Seasonal Malaria Chemoprevention

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ABSTRACT

BACKGROUND

Mass administration of azithromycin for trachoma control led to a sustained reduction in all-cause mortality among Ethiopian children. Whether the addition of azithromycin to the monthly sulfadoxine–pyrimethamine plus amodiaquine used for seasonal malaria chemoprevention could reduce mortality and morbidity among African children was unclear.

METHODS

We randomly assigned children 3 to 59 months of age, according to household, to receive either azithromycin or placebo, together with sulfadoxine–pyrimethamine plus amodiaquine, during the annual malaria-transmission season in Burkina Faso and Mali. The drug combinations were administered in four 3-day cycles, at monthly intervals, for three successive seasons. The primary end point was death or hospital admission for at least 24 hours that was not due to trauma or elective surgery. Data were recorded by means of active and passive surveillance.

RESULTS

In July 2014, a total of 19,578 children were randomly assigned to receive seasonal malaria chemoprevention plus either azithromycin (9735 children) or placebo (9843 children); each year, children who reached 5 years of age exited the trial and new children were enrolled. In the intention-to-treat analysis, the overall number of deaths and hospital admissions during three malaria-transmission seasons was 250 in the azithromycin group and 238 in the placebo group (events per 1000 child-years at risk, 24.8 vs. 23.5; incidence rate ratio, 1.1; 95% confidence interval [CI], 0.88 to 1.3). Results were similar in the per-protocol analysis. The following events occurred less frequently with azithromycin than with placebo: gastrointestinal infections (1647 vs. 1985 episodes; incidence rate ratio, 0.85; 95% CI, 0.79 to 0.91), upper respiratory tract infections (4893 vs. 5763 episodes; incidence rate ratio, 0.85; 95% CI, 0.81 to 0.90), and nonmalarial febrile illnesses (1122 vs. 1424 episodes; incidence rate ratio, 0.79; 95% CI, 0.73 to 0.87). The prevalence of malaria parasitemia and incidence of adverse events were similar in the two groups.

CONCLUSIONS

Among children in Burkina Faso and Mali, the addition of azithromycin to the antimalarial agents used for seasonal malaria chemoprevention did not result in a lower incidence of death or hospital admission that was not due to trauma or surgery than antimalarial agents plus placebo, although a lower disease burden was noted with azithromycin than with placebo. (Funded by the Joint Global Health Trials scheme; ClinicalTrials.gov number, NCT02211729.)

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Malaria transmission is concentrated during a few months of the year in much of the Sahel and sub-Sahel regions of Africa. In these areas, seasonal malaria chemoprevention — the administration of sulfadoxine–pyrimethamine plus amodiaquine to children at monthly intervals three or four times during the malaria-transmission season — has been a highly effective approach to malaria control.[1] Seasonal malaria chemoprevention is now being implemented widely across these regions.[2] The frequent contact between children and health care workers that is needed for seasonal malaria chemoprevention provides an opportunity for the delivery of other health interventions.

Mass administration of azithromycin has been a highly effective approach to trachoma control.[3] Reductions in the incidences of skin, gastrointestinal, and respiratory infections have been recorded after mass administration of azithromycin.[4-8] Nevertheless, the finding in Ethiopia of a 49% reduction in all-cause mortality among children 1 to 9 years of age during the year after mass administration of a single dose of azithromycin — a reduction that was sustained during a 26-month follow-up period — was surprising.[9,10] Consequently, we conducted a randomized, double-blind, placebo-controlled trial to determine whether the addition of azithromycin to the sulfadoxine–pyrimethamine plus amodiaquine given for seasonal malaria chemoprevention could have a similar effect on overall child mortality and morbidity.

Methods

Trial Oversight

The trial was approved by the ethics committees of the London School of Hygiene and Tropical Medicine, London; the Malaria Research and Training Center, University of Bamako, Bamako, Mali; the Ministry of Health, Ouagadougou, Burkina Faso; and the national regulatory authorities of Burkina Faso and Mali. A data and safety monitoring board reviewed serious adverse events, monitored the overall progress of the trial, approved the statistical analysis plan, and archived the locked database before the data were unmasked. A steering committee reviewed the protocol (available with the full text of this article at NEJM.org) and provided overall advice. The authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol.

Sites and Population

The trial was conducted in the Houndé district of Burkina Faso and in the Bougouni district of Mali (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Information about these communities and the children who live in them is provided in the protocol and the Supplementary Appendix.

Enrollment and Randomization

A household census was conducted in June 2014, and children of either sex who were 3 to 59 months of age on August 1, 2014, were eligible for enrollment in the trial. After written informed consent was obtained from the child's parent or guardian, the child received a long-lasting insecticide-treated bed net. Children were excluded if they had a chronic disease or a known allergy to sulfadoxine–pyrimethamine, amodiaquine, or azithromycin or if they were taking cotrimoxazole. The household census was repeated in May 2015 and in May 2016 to recruit additional eligible children and to detect any deaths that had been missed through the surveillance system. Each year, children who were still younger than 60 months of age on August 1 remained in follow-up for the subsequent trial year, and children who had reached 5 years of age on or before July 31 exited the trial on that date. Enrollment of children in the trial started on August 25, 2014, in Mali and on August 28, 2014, in Burkina Faso.

Randomization was performed according to household to avoid the potential effect of within-household transmission of infection; all eligible children who shared a kitchen were assigned to the same trial group. To mask the trial-group assignments for the trial team and caregivers, a placebo for azithromycin of identical appearance was used.

Interventions

Children who were enrolled in the trial received the assigned preventive regimen during the annual peak malaria-transmission season (August to November). The drug combinations were administered in four 3-day cycles, at monthly intervals, for three successive seasons. Infants 3 to 11 months of age received a combined 250 mg of sulfadoxine and 12.5 mg of pyrimethamine plus 75 mg of amodiaquine on day 1 and received 75 mg of amodiaquine on days 2 and 3 (Guilin Pharmaceutical, Shanghai, China). In addition, they were randomly assigned to receive either 100 mg of

azithromycin or matching placebo on days 1, 2, and 3 (Cipla, Mumbai, India). Children 1 to 4 years of age received double these doses. All doses were based on age and administered by trial staff. All trial drugs were purchased from the manufacturers with the use of a grant provided by the U.K. Medical Research Council and were provided to the children free of cost.

Each year, the drug combinations were prepacked in resealable plastic bags by pharmacists who were not part of the trial team. Each child was assigned one large bag that contained four smaller bags, each of which contained the sulfadoxine–pyrimethamine, amodiaquine, and either azithromycin or placebo for one of the four cycles. The child received a photo identification card that had a quick response code (known as a QR code) that encoded the child's name, the mother's name, the child's date of birth, the census number, and a randomization number with a check digit. A label on the large bag also had a QR code that encoded the same variables. On the day of administration of the trial drugs, the QR codes on the identification card and on the large bag were scanned with a tablet computer to link the child to the correct bag. The trial drugs were kept at the trial office and were administered under direct observation by trial staff.

When the child was seen for administration of the trial drugs, if a diagnosis of malaria was confirmed with the use of a rapid diagnostic test, the child was not given the assigned regimen and instead received a dose of artemether–lumefantrine. Children with other illnesses were referred to a local health center for investigation and treatment.

END POINTS

The primary end point was death or hospital admission for at least 24 hours that was not due to trauma or elective surgery during the intervention period. The intervention period was defined as the period from the administration of the first dose of the first cycle of the trial drugs until 30 days after the administration of the first dose of the last cycle. For children who did not receive the first dose of the first or last cycle, the date that the dose was scheduled to be administered was used.

The prespecified secondary end points were the individual components of the primary end point; death or hospital admission for at least 24 hours during the entire trial period; parasitologically confirmed malaria, which was defined as a febrile illness (a history of fever within 24 hours or a measured temperature of ≥37.5°C) and either a positive rapid diagnostic test or a positive blood smear; radiographically confirmed pneumonia; clinically diagnosed pneumonia or lower respiratory tract infection; gastrointestinal infection; nonmalarial fever, which was defined as a febrile illness that was not due to malaria, lower or upper respiratory tract infection, or gastrointestinal infection; and anemia (hemoglobin level, <10 g per deciliter) or severe anemia (hemoglobin level, <7 g per deciliter) at the end of the malaria-transmission season. An exploratory analysis was performed to investigate the incidence of skin diseases.

SURVEILLANCE

Deaths and hospital admissions were recorded throughout the trial period, but only events that occurred during the intervention period contributed to the primary end point. Data regarding vital status were updated during an annual census and during an exit census that was conducted in March 2017. Deaths that occurred outside a health facility were assessed with the use of the World Health Organization verbal autopsy questionnaire.[11] The trial-group assignments were masked for all assessments. Data regarding adverse events that occurred during the week after administration of the trial drugs were solicited from 800 children (a random selection of 200 children from each trial group in each country) on day 7 after each cycle in the first year of the trial. Details regarding surveillance are provided in the Supplementary Appendix.

In addition, 200 children (a random selection of 50 children from each trial group in each country) were visited each week during the malaria-transmission season for active detection of malaria infection. At the end of each malaria-transmission season (≥30 days after the administration of the first dose of the last cycle of the trial drugs), 4000 children (a random selection of approximately 1000 children from each trial group in each country) were included in a cross-sectional survey to assess the prevalence of malaria parasitemia. In addition, at the end of each malaria-transmission season, blood slides were obtained from 500 primary school children 5 to 12 years of age who lived in each trial area to provide data on the prevalence of malaria parasitemia among

children who did not receive seasonal malaria chemoprevention.

STATISTICAL ANALYSIS

On the basis of data from previous seasonal malaria chemoprevention trials performed in Burkina Faso[12] and Mali,[13] we assumed that the incidence of death or hospital admission that was not due to trauma or elective surgery during the malaria-transmission season would be approximately 15 per 1000 children who received seasonal malaria chemoprevention plus placebo and the rate of loss to follow-up would be 10% per year. On the basis of these assumptions, we calculated that the enrollment of 19,200 children (9600 per country) for three malaria-transmission seasons would give the trial 90% power to detect a 25% lower incidence of the primary end point with azithromycin than with placebo.

The primary analysis was an intention-to-treat analysis of deaths and hospital admissions that occurred during the 4-month intervention period each year. The intention-to-treat population included all the children who had been screened and enrolled in the trial. A per-protocol analysis of the primary end point was also performed. Children who were seen on the first day of administration of the trial drugs for all four cycles of a particular year were included in the per-protocol population for that year. All analyses of secondary end points were performed on an intention-to-treat basis; these analyses were not adjusted for multiple comparisons, and thus P values are not reported for secondary end points.

For each child, person-time at risk was calculated as the time from the date of enrollment until 30 days after the date that the first dose of the last cycle was scheduled to be administered. If applicable, the following end dates were used instead: if the child was lost to follow-up, the date that the child was last seen; if the child emigrated, the date of permanent emigration; if the child died, the date of death; or if the child reached 5 years of age, the last day of the trial year in which the child reached 5 years of age.

The incidence rate ratio of the primary end point was estimated with the use of Poisson regression models, with a gamma-distributed random effect to account for clustering of episodes within households. Regression models were adjusted for trial site and stratified according to follow-up time with the use of Lexis expansion. As prespecified in the statistical analysis plan, effect modification according to trial site and year of age was assessed with the use of the likelihood ratio test, without adjustment for multiple comparisons, since only these two subgroup analyses were performed. Prevalence rate ratios were estimated with the use of Poisson regression models, with a robust standard error to account for randomization according to household.[12]

RESULTS

CHILDREN AND COVERAGE WITH SEASONAL MALARIA CHEMOPREVENTION

In July 2014, a total of 19,578 children from 9618 households were randomly assigned to receive seasonal malaria chemoprevention plus either azithromycin (9735 children) or placebo (9843 children) (Fig. 1). Each year, additional children in the specified age range were enrolled (6287 in the second year and 5748 in the third year), and children who were 5 years of age on August 1 exited the trial. Because of establishment of new households in the trial areas and migration of children into households that were originally included in the trial, the overall number of children in the trial increased each year. At the last follow-up visit, there were 10,885 children in the group that received seasonal malaria chemoprevention plus azithromycin and 10,852 in the group that received seasonal malaria chemoprevention plus placebo.

The two trial groups were well matched with regard to baseline characteristics (Table S1 in the Supplementary Appendix). Coverage with long-lasting insecticide-treated bed nets was high and similar in the two groups. The percentage of children who received at least three directly observed cycles of the assigned regimen was 92.8% in the first year, 86.8% in the second year, and 84.3% in the third year (Table S2 in the Supplementary Appendix).

EFFICACY

In the intention-to-treat analysis, the overall number of deaths and hospital admissions that were not due to trauma or elective surgery was similar in the two trial groups: 250 in the azithromycin group and 238 in the placebo group (events per 1000 child-years at risk, 24.8 vs. 23.5; incidence rate ratio, 1.1; 95% confidence interval [CI], 0.88 to 1.3) (Table 1). In the per-protocol analysis, the

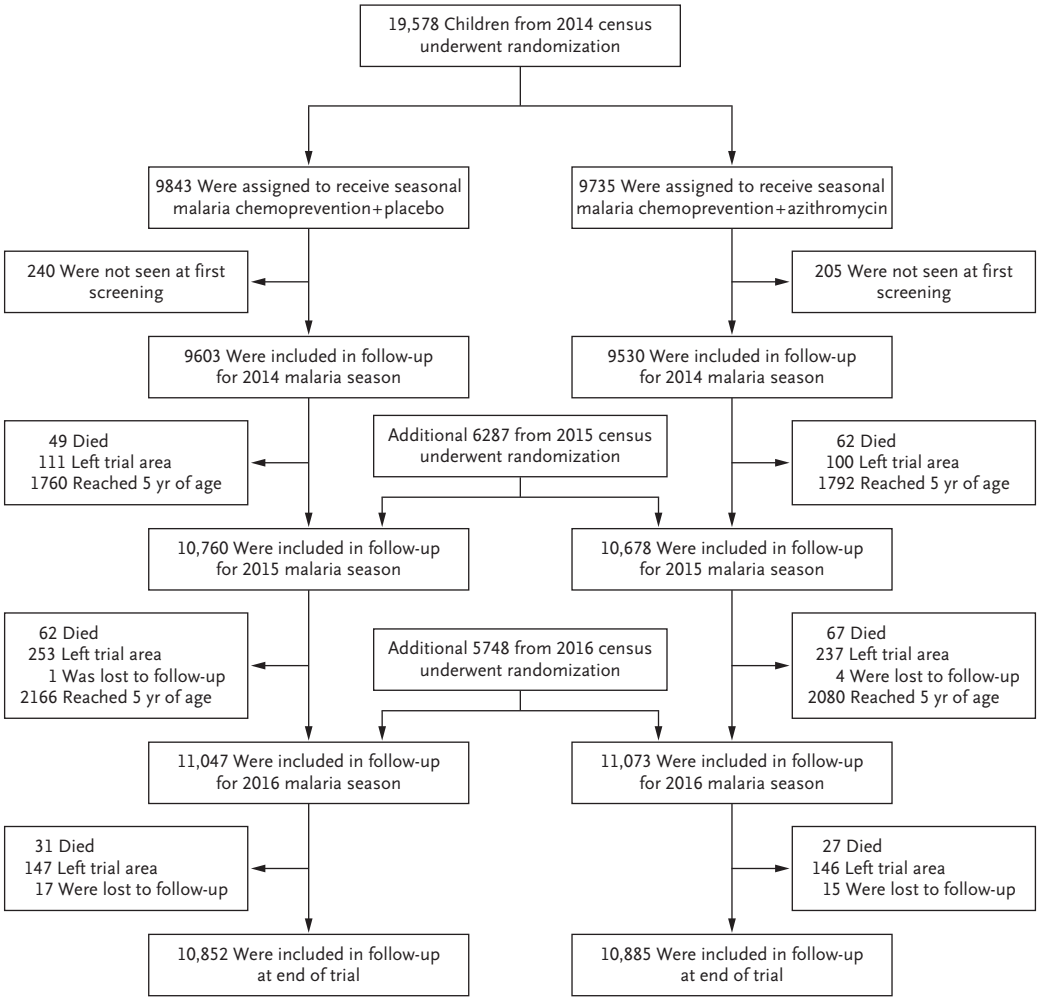

Figure 1. Screening, Randomization, and Follow-up.

overall number was 173 in the azithromycin group and 158 in the placebo group (events per 1000 child-years at risk, 19.8 vs. 18.2; incidence rate ratio, 1.1; 95% CI, 0.88 to 1.4) (Table S3 in the Supplementary Appendix).

In the intention-to-treat population, there was evidence of an interaction between trial group and trial site (P=0.02 by the likelihood ratio test). The incidence of the primary end point was higher in the azithromycin group than in the placebo group in Burkina Faso (incidence rate ratio, 1.3; 95% CI, 1.0 to 1.7) but not in Mali (incidence rate ratio, 0.84; 95% CI, 0.64 to 1.1). The incidence of the primary end point according to year of age was similar in the two trial groups, both in the entire trial population (P=0.44 for interaction by the likelihood ratio test) and in each country individually (Fig. 2, and Figs. S2 and S3 in the Supplementary Appendix). The causes of deaths and hospital admissions that occurred during the intervention period and during the entire trial period are shown in Tables S4 through S9 in the Supplementary Appendix. Malaria was the most prominent cause of death and hospital admission in each trial group.

The incidence of clinic visits for the following events was lower with antimalarial agents plus azithromycin than with antimalarial agents plus placebo: gastrointestinal infections (incidence rate ratio, 0.85; 95% CI, 0.79 to 0.91), upper respiratory tract infections (incidence rate ratio, 0.85; 95% CI, 0.81 to 0.90), and nonmalarial fevers (incidence

Table 1. Incidence of Death or Hospital Admission That Was Not Due to Trauma or Elective Surgery during Three Successive Malaria-Transmission Seasons in the Intention-to-Treat Population.*

End Point	Seasonal Malaria Chemoprevention plus Placebo		Seasonal Malaria Chemoprevention plus Azithromycin		Incidence Rate Ratio (95% CI)	P Value	P Value for Interaction
	No. of Events	Events per 1000 Child-Yr at Risk (95% CI)	No. of Events	Events per 1000 Child-Yr at Risk (95% CI)			
Hospital admission or death							
Both sites	238	23.5 (20.7–26.6)	250	24.8 (21.9–28.0)	1.1 (0.88–1.3)	0.57	0.02
Burkina Faso	101	20.2 (16.6–24.6)	134	26.6 (22.4–31.5)	1.3 (1.0–1.7)	—	—
Mali	137	26.6 (22.5–31.5)	116	23.0 (19.2–27.6)	0.84 (0.64–1.1)	—	—
Hospital admission							
Both sites	188	18.5 (16.1–21.4)	184	18.2 (15.8–21.1)	0.98 (0.79–1.2)	—	0.13
Burkina Faso	86	17.2 (13.9–21.2)	100	19.8 (16.3–24.1)	1.2 (0.85–1.6)	—	—
Mali	102	19.8 (16.3–24.1)	84	16.6 (13.4–20.6)	0.83 (0.61–1.1)	—	—
Death							
Both sites	50	4.93 (3.73–6.50)	66	6.54 (5.14–8.32)	1.3 (0.92–1.9)	—	0.02
Burkina Faso	15	3.00 (1.81–4.98)	34	6.74 (4.81–9.43)	2.3 (1.2–4.1)	—	—
Mali	35	6.80 (4.88–9.47)	32	6.34 (4.48–8.96)	0.93 (0.58–1.5)	—	—

* Data were obtained during the intervention period of each malaria-transmission season, which was defined as the period from the administration of the first dose of the first cycle of the trial drugs until 30 days after the administration of the first dose of the last cycle. For all end points except the primary end point, confidence intervals for the rate ratios were not adjusted for multiple comparisons; inferences drawn from these intervals may not be reproducible. Rate ratios and the P value were estimated with the use of Poisson regression models with random effects. P values for interaction were estimated with the use of the likelihood ratio test.

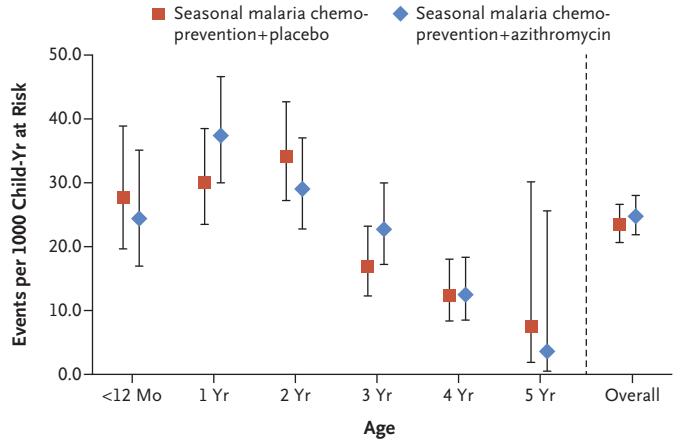

Figure 2. Incidence of Death or Hospital Admission That Was Not Due to Trauma or Elective Surgery during Three Successive Malaria-Transmission Seasons in Burkina Faso and Mali.

I bars indicate 95% confidence intervals.

rate ratio, 0.79; 95% CI, 0.73 to 0.87) (Table 2). An exploratory analysis showed that, among children who had a clinic visit for nonmalarial fever, 269 children in the azithromycin group and 442 children in the placebo group had a skin condition (events per 1000 child-years at risk, 26.6 vs. 43.6; incidence rate ratio, 0.61; 95% CI, 0.53 to 0.73). Among children who had a clinic visit for nonfebrile illness, 428 children in the azithromycin group and 556 children in the placebo group had a skin condition (events per 1000 child-years at risk, 42.4 vs. 54.8; incidence rate ratio, 0.77; 95% CI, 0.67 to 0.89). The number of children with a skin condition that most likely had a bacterial cause was substantially lower in the azithromycin group than in the placebo group, especially among those with nonmalarial fever (66 vs. 145; events per 1000 child-years at risk, 6.54 vs. 14.3; incidence rate ratio, 0.46; 95% CI, 0.33 to 0.62).

Table 2. Incidence of Clinical Events Treated at Health Centers or by Community Health Workers during Three Successive Malaria-Transmission Seasons in Burkina Faso and Mali in the Intention-to-Treat Population.*

Event	Seasonal Malaria Chemoprevention plus Placebo		Seasonal Malaria Chemoprevention plus Azithromycin		Incidence Rate Ratio (95% CI)
	No. of Events	Events per 1000 Child-Yr at Risk (95% CI)	No. of Events	Events per 1000 Child-Yr at Risk (95% CI)	
Parasitologically confirmed malaria	10,845	1068.7 (1048.8–1089.0)	10,394	1029.5 (1009.9–1049.4)	0.97 (0.93–1.0)
Radiographically confirmed pneumonia	13	1.3 (0.74–2.2)	14	1.4 (0.82–2.3)	1.1 (0.49–2.4)
Clinical pneumonia or lower respiratory tract infection	339	33.4 (30.0–37.2)	285	28.2 (25.1–31.7)	0.84 (0.70–1.0)
Gastrointestinal infection	1,985	195.6 (187.2–204.4)	1,647	163.1 (155.4–171.2)	0.85 (0.79–0.91)
Upper respiratory tract infection†	5,763	567.9 (553.4–582.8)	4,893	484.6 (471.2–498.4)	0.85 (0.81–0.90)
Nonmalarial fever‡	1,424	140.3 (133.2–147.8)	1,122	111.1 (104.8–117.8)	0.79 (0.73–0.87)
Trauma†	128	12.6 (10.6–15.0)	135	13.4 (11.3–15.8)	1.1 (0.85–1.4)
Clinical malnutrition†	9	0.89 (0.46–1.7)	5	0.50 (0.21–1.19)	0.56 (0.19–1.7)
Other outpatient visit†	1,377	135.7 (128.7–143.1)	1,132	112.1 (105.8–118.8)	0.83 (0.76–0.91)

* Data were obtained during the intervention period of each malaria-transmission season, which was defined as the period from the administration of the first dose of the first cycle of the trial drugs until 30 days after the administration of the first dose of the last cycle. Confidence intervals for the rate ratios were not adjusted for multiple comparisons; inferences drawn from these intervals may not be reproducible.
† This event was not a prespecified secondary end point.
‡ Nonmalarial fever was defined as a temperature of at least 37.5°C or a history of fever within 24 hours that was not due to malaria, lower or upper respiratory tract infection, or gastrointestinal infection.

Among children who were randomly selected for weekly follow-up visits during the intervention period, the prevalence of malaria parasitemia ranged from 3 to 7% and was similar in the two groups. At the end of the malaria-transmission season, the prevalence of malaria parasitemia ranged from 4 to 10% and the prevalence of anemia ranged from 20 to 26%. For both variables, results were similar in the two trial groups (Table 3). Among primary school children who lived in the trial areas and did not receive seasonal malaria chemoprevention, the prevalence of malaria parasitemia at the end of the malaria-transmission season ranged from 50 to 65% (Table 3).

SAFETY

No severe adverse events that were judged by investigators to be related to the trial drugs were recorded. Diarrhea was the most frequent adverse event reported after administration of the trial drugs. The incidences of diarrhea and of other adverse events that occurred during the week after administration of the trial drugs were similar in the two trial groups (Table S10 in the Supplementary Appendix).

DISCUSSION

In this trial, the incidence of death or hospital admission that was not due to trauma or elective surgery did not differ significantly between children who received seasonal malaria chemoprevention plus azithromycin and children who received seasonal malaria chemoprevention plus placebo when data from Burkina Faso and Mali were combined for the primary analysis. However, the incidence of death or hospital admission was higher with azithromycin than with placebo in Burkina Faso but not in Mali. No plausible mechanism to explain this difference was found, and given the borderline increased incidence in Burkina Faso, it may be a chance finding. The incidences of gastrointestinal infections, upper respiratory tract infections, and nonmalarial fevers were lower with azithromycin than with placebo (by 15%, 15%, and 21%, respectively), and in an exploratory analysis,

Table 3. Prevalence of Malaria Parasitemia and Anemia among Children in the Trial and Prevalence of Malaria Parasitemia among Primary School Children.*

Variable	Seasonal Malaria Chemoprevention plus Placebo	Seasonal Malaria Chemoprevention plus Azithromycin	Prevalence Rate Ratio (95% CI)
	no./total no. (%)		
Among children in the trial			
Malaria parasitemia, according to data from weekly visits during the malaria-transmission season			
2014	49/1507 (3.25)	44/1483 (2.97)	0.92 (0.62–1.4)
2015	107/1563 (6.85)	103/1539 (6.69)	0.98 (0.75–1.3)
2016	81/1598 (5.07)	90/1589 (5.66)	1.1 (0.84–1.5)
Malaria parasitemia, according to data from cross-sectional surveys at the end of the malaria-transmission season			
2014	84/1997 (4.21)	67/2012 (3.33)	0.79 (0.57–1.1)
2015	187/1966 (9.51)	171/2010 (8.51)	0.89 (0.73–1.1)
2016	173/1982 (8.73)	212/1999 (10.6)	1.2 (1.0–1.5)
Anemia, according to data from cross-sectional surveys at the end of the malaria-transmission season			
2014			
Hemoglobin, <10 g/dl	432/1997 (21.6)	407/2012 (20.2)	0.93 (0.83–1.1)
Hemoglobin, <7 g/dl	16/1997 (0.80)	10 /2012 (0.50)	0.62 (0.28–1.4)
2015			
Hemoglobin, <10 g/dl	411/1966 (20.9)	399/2010 (19.9)	0.95 (0.84–1.1)
Hemoglobin, <7 g/dl	20/1966 (1.02)	17/2010 (0.85)	0.83 (0.44–1.6)
2016			
Hemoglobin, <10 g/dl	516/1982 (26.0)	505/1999 (25.3)	0.97 (0.87–1.1)
Hemoglobin, <7 g/dl	20/1982 (1.01)	18/1999 (0.90)	0.89 (0.47–1.7)
	Burkina Faso	**Mali**	**Both Sites**
	no./total no. (%)		*no./total. no.*
Among primary school children			
Malaria parasitemia, according to data from blood samples at the end of the malaria-transmission season			
2014			
Any parasitemia	308/497 (62.0)	294/496 (59.3)	602/993
Density, >5000/mm^3	23/497 (4.6)	31/496 (6.3)	54/993
2015			
Any parasitemia	324/529 (61.2)	326/500 (65.2)	650/1029
Density, >5000/mm^3	29/529 (5.5)	47/500 (9.4)	76/1029
2016			
Any parasitemia	251/500 (50.2)	268/500 (53.6)	519/1000
Density, >5000/mm^3	28/500 (5.6)	26/500 (5.2)	54/1000

* The primary school children lived in the trial areas and did not receive seasonal malaria chemoprevention. Confidence intervals for the rate ratios were not adjusted for multiple comparisons; inferences drawn from these intervals may not be reproducible.

the incidence of skin diseases, especially those that most likely had a bacterial cause, was also lower with azithromycin; these results are consistent with findings of previous studies in which azithromycin was used in trachoma control programs.[4-8]

The findings of our trial contrast with those of the MORDOR (Mortality Reduction after Oral Azithromycin) trial conducted in Malawi, Niger, and Tanzania, in which azithromycin was given to children younger than 5 years of age twice a year for 2 years and then was associated with a 13.5% (95% CI, 6.7 to 19.8) lower overall all-cause mortality than placebo, with the effect being most marked in Niger.[14] Children who were assigned to the azithromycin group in our trial had greater exposure to azithromycin than those in the MORDOR trial (four courses each year for up to 3 years in our trial, as compared with two courses each year for 2 years in the MORDOR trial); such enhanced exposure might have been expected to have an effect on mortality that was at least equal to the effect seen in the MORDOR trial, but this was not the case.

There are several possible explanations for the different outcomes of these two trials. One possible explanation is that azithromycin, which has antimalarial activity,[15] contributed to decreased mortality in the MORDOR trial partly through its effect on malaria, and this benefit was lost when an additional, effective antimalarial combination was given at the same time as azithromycin. However, the effect of azithromycin on malaria has been inconsistent when azithromycin has been given in mass drug administration programs.[16-18] In addition, all the children in our trial received sulfadoxine–pyrimethamine, which has weak antimicrobial properties, and this may have reduced the potential benefit of adding another antimicrobial to the regimen. Finally, coverage with a pneumococcal conjugate vaccine was high among the children in our trial, and this may have reduced the potential benefit of azithromycin in lowering mortality from pneumonia.

In the MORDOR trial, the greatest effect of azithromycin on all-cause mortality was seen in the first year of life.[14] This finding suggests that, despite the results of this trial, the addition of azithromycin to the sulfadoxine–pyrimethamine used for intermittent prevention of malaria in infants[19] is an option worth investigating in countries with a high malaria burden in the first year of life.

The prevalence of malaria at the end of the malaria-transmission season was substantially lower among children who were enrolled in our trial than among primary school children who were living in the same areas and were not receiving seasonal malaria chemoprevention, a finding that indicates that seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine was having a major protective effect against malaria in these populations. Nevertheless, the proportion of deaths and hospital admissions that were attributable to malaria was still large in both trial groups, despite good access to treatment and high coverage with long-lasting insecticide-treated bed nets. Effective control of malaria in these and other, similar areas necessitates additional control measures.

A limitation of the trial is that randomization was performed according to household rather than village; randomization according to household reduced the potential for bias but precluded the potential for a herd effect that might have occurred had randomization according to village been performed. Only limited safety data were obtained because seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine and mass administration of azithromycin have now been given to millions of children with no major safety concerns.

In conclusion, among children in Burkina Faso and Mali, the addition of azithromycin to the antimalarial agents used for seasonal malaria chemoprevention did not result in a lower incidence of death or hospital admission that was not due to trauma or surgery than antimalarial agents plus placebo. We also noted that the incidences of clinic visits for gastrointestinal infections, upper respiratory tract infections, and nonmalarial febrile illnesses, without adjustment for multiple comparisons, were lower among children who received antimalarial agents plus azithromycin than among those who received antimalarial agents plus placebo.

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APPENDIX

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