

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Gore-Langton, Georgia R; Cairns, Matthew; Compaoré, Yves Daniel; Sagara, Issaka; Kuepfer, Irene; Zongo, Issaka; de Wit, Mariken M; Barry, Amadou; Diarra, Modibo; Tapily, Amadou; +10 more... Coumare, Samba; Thera, Ismail; Nikiema, Frederic; Yerbanga, R Serge; Guissou, Rosemonde M; Tinto, Halidou; Dicko, Alassane; Chandramohan, Daniel; Greenwood, Brian; Ouedraogo, Jean Bosco; (2020) Effect of Adding Azithromycin to the Antimalarials used for Seasonal Malaria Chemoprevention on the Nutritional Status of African Children. *Tropical medicine & international health : TM & IH*. ISSN 1360-2276 DOI: <https://doi.org/10.1111/tmi.13390>

Downloaded from: <http://researchonline.lshtm.ac.uk/id/eprint/4656442/>

DOI: <https://doi.org/10.1111/tmi.13390>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>



Effect of Adding Azithromycin to the Antimalarials used for Seasonal Malaria Chemoprevention on the Nutritional Status of African Children

Georgia R. Gore-Langton¹, Matthew Cairns¹, Yves Daniel Compaoré², Issaka Sagara, Irene Kuepfer¹, Issaka Zongo², Mariken M. de Wit¹, Amadou Barry³, Modibo Diarra³, Amadou Tapily³, Samba Coumare³, Ismail Thera³, Frederic Nikiema², R. Serge Yerbanga², Rosemonde M. Guissou², Halidou Tinto², Alassane Dicko³, Daniel Chandramohan¹, Brian Greenwood¹, Jean Bosco Ouedraogo²

¹London School of Hygiene and Tropical Medicine, UK

²Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso

³Malaria Research and Training Center, University of Science, Techniques, and Technologies of Bamako, Mali

Abstract

Objectives: Mass administration of azithromycin has reduced mortality in children in sub-Saharan Africa but its mode of action is not well characterised. A recent trial found that azithromycin given alongside seasonal malaria chemoprevention was not associated with a reduction in mortality or hospital admissions in young children. We investigated the effect of azithromycin on the nutritional status of children enrolled in this study.

Methods: 19,578 children in Burkina Faso and Mali were randomised to receive either azithromycin or placebo alongside seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine monthly for three malaria transmission seasons (2014-2016). After each transmission season, anthropometric measurements were collected from approximately 4,000 randomly selected children (2,000 per country) at a cross-sectional survey and used to derive nutritional status indicators. Binary and continuous outcomes between treatment arms were compared by Poisson and linear regression.

Results: Nutritional status among children was poor in both countries with evidence of acute and chronic malnutrition (24.9-33.3% stunted, 15.8-32.0% underweight, 7.2-26.4% wasted). There was a suggestion of improvement in nutritional status in Burkina Faso and deterioration in Mali over the study period. At the end of each malaria transmission season, nutritional status of children did not differ between treatment arms (seasonal malaria chemoprevention plus azithromycin or placebo) in either the intention to treat or per protocol analyses (only children with at least three cycles of SMC in the current intervention year).

Conclusions: The addition of azithromycin to seasonal malaria chemoprevention did not result in an improvement of nutritional outcomes in children in Burkina Faso and Mali.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/TMI.13390](https://doi.org/10.1111/TMI.13390)

This article is protected by copyright. All rights reserved

Keywords: Malaria, seasonal malaria chemoprevention, azithromycin, nutrition, Mali, Burkina Faso

INTRODUCTION

Mass drug administration (MDA) with azithromycin (AZ) is a highly effective approach to the control of trachoma. Reductions in the incidence of skin, gastrointestinal, and respiratory infections have been recorded after mass distribution with AZ and reductions in childhood mortality have been found to varying degrees. Among Ethiopian children aged 1-9 years, a 49% reduction in all-cause mortality was found following a single dose of AZ administered yearly, biannually, or quarterly, a reduction sustained during the 26-month follow-up period (1, 2). The MORDOR (Mortality Reduction after Oral Azithromycin) trial conducted in Malawi, Niger, and Tanzania randomised children under 5 years of age to receive twice-yearly mass distributions of oral AZ for four years. Relative to children receiving placebo, an overall reduction in mortality of 13.5% (95% confidence interval (CI): 6.7, 19.8) was recorded. The impact on mortality was higher in Niger, an area with intense and seasonal malaria transmission (18.1% (95% Confidence Interval (CI): 10.0, 25.5)), than in Malawi or Tanzania (3).

The mechanism through which mass distribution of AZ reduces mortality is not understood (4). Improved nutritional status among children receiving AZ is a possible underlying mechanism through which mortality might be reduced. Azithromycin is an antibiotic widely used to treat bacterial infections. Diarrhoeal disease and lower respiratory tract infections are associated with growth faltering in many low-income countries (5-7). It is therefore plausible that mass distribution with AZ improves nutritional status by reducing these infections.

Previous research has shown improved nutritional status in livestock after the administration of AZ regardless of infection status (8). The administration of AZ to pregnant women improved birthweight outcomes of neonates in Malawi (9): mean child length and development scores were consistently higher and mortality lower in the group receiving AZ plus monthly sulfadoxine-pyrimethamine (SP) than in the group receiving monthly SP alone.

Similar beneficial results have been observed in children following antibiotic administration, but inconsistently. A meta-analysis of Randomised Controlled trials (RCTs) in low and middle income countries reported that antibiotic use increased height (0.04 cm/month) and weight (23.8 g/month). However, these trials all involved distribution of antibiotics other than AZ (8). Two trials in Niger found no difference in prevalence of wasting, stunting, being underweight, or mid-upper arm circumference (MUAC) between communities that received mass administration of AZ and those that did not (10, 11). Children of mothers in The Gambia who received AZ during labour were less likely to be malnourished or underweight at the

age of 11-13 months than children of mothers who received a placebo(12). Also in The Gambia, a comparison of height and weight in children who had been enrolled in a trachoma trial found no evidence that three annual rounds of MDA with AZ improved anthropometric indices compared to a single round of AZ, in spite of high treatment coverage(13).

In settings of seasonal malaria transmission, a highly effective approach to malaria control involves the administration of the antimalarials sulfadoxine-pyrimethamine and amodiaquine (SP-AQ) to children once a month for three or four months during the season of high malaria transmission, an intervention known as seasonal malaria chemoprevention (SMC). SMC prevents clinical malaria and severe malaria by about 70% -80% under trial conditions, and there is growing evidence of an impact on mortality from large-scale evaluations (14, 15). In 2017, 15.7 million children were included in SMC programmes in 12 countries (Burkina Faso, Cameroon, Chad, Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Nigeria, Senegal and Togo)(16).

To assess the effect of adding AZ to SMC, a randomised, double-blind, placebo-controlled trial was conducted in Houndé district of Burkina Faso and in the Bougouni district of Mali (17). The addition of AZ to SMC did not result in a lower incidence of the primary trial outcome - death or hospital admissions not due to trauma or surgery. However, gastrointestinal, upper respiratory tract and skin infections, and non-malarial febrile illnesses occurred less frequently among children who received AZ instead of placebo (17). Given the broad-spectrum activity of AZ, and its impact on these causes of morbidity, we investigated whether regular administration of AZ would lead to improvements in nutritional status.

MATERIALS AND METHODS

Study centres

The centres where this trial was conducted in Burkina Faso and Mali are predominantly rural with the majority of the population engaged in farming and/or petty trading(17). The rainy season lasts from July to October, followed by a long dry season (Figure S1 in the Supplementary Materials). The entire population of Burkina Faso (19.2 million) and 91% of the population of Mali (16.9 million) is classified as living in an area of high malaria transmission (>1 case per 1000 population per year)(16). Demographic Health Surveys (2010 Burkina Faso, 2012-13 Mali) estimate the prevalence of stunting in children at 34.6% in Burkina Faso and 38.3% in Mali, and the prevalence of wasting as 15.5% in Burkina Faso and 12.7% in Mali (18, 19).

Enrolment and randomisation

A household census was conducted in June 2014 and children of either sex who were 3 to 59 months of

age on 1st August 2014 were eligible for enrolment in the trial. Randomisation to the AZ or placebo groups was conducted at the household level (to avoid the potential effect of within-household transmission of infection). Drug combinations were administered in four cycles of three days, at monthly intervals, for three successive malaria transmission seasons (2014-16) (Figure S2 in the Supplementary Materials). Infants 3 to 11 months of age received 250 mg of sulfadoxine and 12.5 mg of pyrimethamine plus 75 mg of amodiaquine on day 1 and 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 AZ or matching placebo each month on days 1, 2, and 3. Children 1-4 years of age received double these doses.

Nutrition data

Clinical surveys were conducted approximately four to six weeks after the last dose of each SMC round had been given in 2014, 2015, and 2016 (i.e. between four-five months after the first course) (Figure S2 in Supplementary Materials). Two thousand children were randomly selected by an independent statistician from the randomisation list each year (stratified on randomisation by group and age) in each country for each survey. During these surveys weight, height, and MUAC were measured by trained nurses supervised by physicians, and a blood sample obtained for measurement of haemoglobin (Hb). Children were weighed using a weighing scale (Seca©), a tray was used for small children or the difference was calculated when weighing mother and baby relative to mother alone. Weight was recorded to the nearest 0.1 kg. Recumbent length measurements were taken for children under 2 years and standing height measurements for children above 2 years using a stadiometer (Seca©). Length/height measurements were taken twice and the average recorded. MUAC was measured on the left arm to the nearest 0.1 cm with a MUAC tape. Hb concentration was measured using a HemoCue®. In August 2015, anthropometric data were also collected prior to the first SMC distribution (MUAC obtained for all study participants) and prior to the second SMC distribution in August 2016, weight, height, and MUAC data were collected from the children selected for the full anthropometric at the end of the malaria transmission season survey that year (Figure S2 in Supplementary Materials).

Statistical analyses

Individual height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) Z-scores were calculated in Stata (Version 15, College Station, Texas), using the WHO 2007 reference populations (20). MUAC-for-age z-scores were calculated in Stata based on the WHO 2006 reference values.

Binary outcomes stunted, underweight, wasted, low MUAC-for-age were defined as individuals with corresponding Z-scores below -2 (HAZ, WAZ, WHZ, MUAC-for-age, respectively). Nutritional outcomes

were defined as severely stunted/underweight/wasted or very low MUAC-for-age when corresponding Z-scores were less than -3. Moderate anaemia was classified as Hb concentration below 10g/dL and severe anaemia as an Hb concentration less than 7g/dL(21).

Each binary outcome was compared between treatment arms (SMC + placebo or SMC + AZ) using Poisson regression to obtain prevalence ratios accounting for clustering at the household level. The primary analysis was an intention-to-treat analysis performed on the pooled data from both countries (controlling for country). Effect modification between country and study arm was investigated using the likelihood ratio test.

Country-specific analyses were also performed for Burkina Faso and Mali separately, along with a per-protocol analysis (including only children who had received at least three cycles of SMC in the current intervention year). Linear regression was used to compare the continuous outcomes (mean Z-scores and haemoglobin) between study arms.

In 2015 and 2016, when pre- and post- SMC anthropometric data were available, linear regression was used to compare difference in means over time between AZ and placebo groups.

Finally, to explore potential differences in the effect of AZ by age, pre-specified sub-group analyses were conducted including only children less than 12 months at administration of the first dose of SMC in each year and children 13-24 months at administration of the first dose of SMC in each year.

RESULTS

Study population

In July 2014, 19,578 children from 9,618 households were enrolled across both countries and randomly assigned to receive either SMC plus AZ (9,735 children) or SMC plus placebo (9,843 children) on up to four occasions each year for three years. The two study arms were well matched with regard to baseline characteristics such as age, sex, use of long lasting insecticidal net (LLIN), distance to the nearest health facility and hospital. Prevalence of rapid diagnostic (RDT) confirmed malaria at the first SMC cycle ranged between 5.1-6.4% over the three years and was similar between trial arms. The percentage of children who received all four monthly courses of the assigned regimen (SMC + placebo or SMC + AZ) was 75.0% in the first year, 66.3% in the second year, and 64.6% in the third year. The percentage of children who received at least three monthly courses was 92.8% in the first year, 86.8% in the second year, and 84.3% in the third year(17).

Surveys

At the end of the malaria transmission season survey in 2014, we measured the height, weight, MUAC and

Hb concentration of 4,009 children. After the transmission season in 2015 and 2016, measurements were taken from 3,976 and 3,975 children, respectively. Among children selected for the end of season surveys, MUAC of 3,837 children was also measured before the malaria transmission season in 2015, and pre-SMC MUAC, weight, and height data of 3,826 children were collected in 2016.

Nutrition status (regardless of trial arm)

The prevalence of stunting (HAZ<-2) remained consistently high in both countries over the study period, ranging from 24.9% (95% CI 23.1, 26.9) to 27.5% (95% CI: 25.8-29.8) in Burkina Faso and from 27.8% (95% CI 25.8-29.9) to 33.3% (95% CI 31.2-35.5) in Mali (Figure 1). In Burkina Faso, the prevalence of being underweight (WAZ<-2) or wasted (WHZ<-2) both increased over the study period, from 15.8% (95% CI 14.2-17.5) to 28.8% (95% CI 26.8-30.9) and from 7.2% (95% CI 6.1-8.4) to 23.8% (95% CI 21.9-25.8), respectively. In Mali the prevalence of being underweight or wasted decreased over the study period, from 32.0% (95% CI-29.8-34.3) to 16.8% (95% CI 15.2-18.5) and from 26.4 % (95% CI 24.3-28.5) to 7.7% (95% CI 6.6-9.0) respectively. Prevalence of low MUAC-for-age (MUAC-for-age<-2) increased in both study sites over the trial period, consistently slightly higher in Burkina Faso. Prevalence of moderate anaemia (Hb<10g/dL) increased over the study period in Burkina Faso, from 19.8% (95% CI 18.1-21.5) to 25.6% (95% CI 23.8-27.6). In Mali prevalence of anaemia was lowest in 2015, 18.2% (95% CI 16.5-19.9), and highest in 2016 at 25.7% (95% CI 23.8-27.7).

Effect of AZ on nutrition outcomes

In both study sites the prevalence of children with stunting, wasting, underweight or low MUAC was very similar between the two randomisation groups in all three years (Figures 2 and 3). The prevalence ratio (prevalence in SMC + AZ group relative to SMC + placebo group) for the primary comparison of pooled data from both countries at the 2016 post-SMC survey was 0.92 (95% CI 0.83, 1.02) for stunting, 1.01 (95% CI 0.90, 1.13) for being underweight, and 0.94 (95% CI 0.81, 1.08) for being wasted (Table 1). The low MUAC-for-age prevalence ratio in 2016 was 0.79 (95% CI 0.62, 1.01) and for anaemia, 0.97 (0.87, 1.07) (Table 1).

Country-specific analyses also show prevalence ratios fluctuating around one (no difference) for all indicators in all three years (Table 2 and Table 3). There is some evidence that the prevalence of stunting was lower in the SMC + AZ than SMC + placebo group in Burkina Faso in 2016 (PR 0.82 (95% CI 0.70, 0.95), $p=0.011$) (Table 2) and that the prevalence of being severely underweight was higher in the SMC + AZ group in Mali in 2016 (PR 1.78 (95% CI 1.10-2.88), $p=0.019$) (Table 3). No evidence was found for effect modification by country (Table S1 in the Supplementary Materials).

The difference in the mean of the continuous outcomes (Z-scores and Hb concentrations) between study arms was near zero in all years (Table 4). There was evidence of a slight increase in MUAC-for-age Z-score of 0.08 (95% CI: 0.02-0.14, $p=0.01$) and weight-for-age Z-score of 0.10 (95%CI: 0.01-0.18, $p=0.021$) among children allocated to receive SMC + AZ relative to the SMC + placebo group in 2014.

Comparison of pre- and post-SMC anthropometric data for Burkina Faso and Mali pooled in 2015 (MUAC-for-age only) and 2016 (HAZ, WAZ, WHZ, MUAC-for-age) did not provide evidence for a change in nutrition indicators between surveys (Tables S4 and S5 in the Supplementary Materials). Analysis of a subsample of data for children less than one year of age at the time of administration of the first yearly dose of SMC similarly revealed no difference between study arms (Figures S3-5 in the Supplementary Materials), as did analysis of children 13-24 months of age at the time of administration of the first yearly dose of SMC (Figures S6-8 in the Supplementary Materials).

Results of the per-protocol analysis were consistent with those from the intention to treat analysis; the addition of AZ to SMC did not improve nutrition outcomes when compared to SMC and placebo (Tables S2 and S3 in the Supplementary Materials).

DISCUSSION

Despite the fact that the addition of AZ to SMC significantly reduced the incidence of acute respiratory and gastrointestinal infections and non-malarial febrile illnesses (17), up to four monthly courses of directly-observed AZ did not improve the nutritional status of children in the study sites in Burkina Faso or Mali when distributed alongside the SMC regimen. A large majority of nutritional indicators did not differ significantly in prevalence between AZ and placebo groups in either country at any of the end of season surveys in the three-year trial. In the few instances where a difference in prevalence of a particular indicator was found in one of the study sites, the difference was not replicated on other occasions in either site, and is thus likely be a chance finding when considered in the context of the large number of comparisons undertaken.

The largest difference in mortality between AZ and placebo treatment groups in children in the MORDOR trial conducted in Malawi, Niger, and Tanzania, which administered AZ up to four times at six-month intervals, was found among children in the youngest age group (1 to 5 months of age) (24.9%, 95% CI 10.6-37.0) (3). Due to the lower age limit for SMC of three months, there were very few children in this age range at the end of the season, and consequently it was not possible to evaluate impact on nutrition in this age group. However, when restricting analysis to children less than 12 months of age we did not find an effect of AZ on nutritional status (Figures S3-S5 in the Supplementary Materials), nor among children 13-24 months, coinciding with the period post-weaning when nutritional status might be

expected to be especially poor (Figures S6-S8 in the Supplementary Materials).

Differences were seen in the direction of change of nutrition status over the study period between Burkina Faso and Mali. All five key nutritional indicators (stunted, underweight, wasted, low MUAC-for-age, anaemic) increased in prevalence over the study period in Burkina Faso while they decreased in prevalence in Mali, with the exception of the prevalence of low MUAC-for-age which also increased in Mali. These patterns are difficult to explain, especially changes in the prevalence of wasting in both countries in 2014 and 2016, and do not correlate with differential rainfall between the countries (Figure S1 in the Supplementary Materials) nor with differences in the incidence of gastro-intestinal illness (Fig S9-10 in the Supplementary Materials). The prevalence of stunting was lower in both study sites than reported in the national DHS; possibly due to “healthy participant effect” and/or the shorter hunger season in these districts than in many other parts of Burkina Faso or Mali.

Administration of AZ with SMC reduced the incidence of acute respiratory and gastrointestinal infections and so it might have been expected to have a beneficial impact on nutrition. However, a large majority of the episodes of diarrhoea detected in this study were acute episodes which are likely to have had only a transitory effect and are not likely to have led to a detectable effect in a single survey conducted at the end of rainy season up to four months after an acute episode had been noted. In addition, poor nutrition rather than infection is the predominant cause of malnutrition, including stunting, in young children in both Burkina Faso and Mali.

A possible explanation for the absence of a benefit on nutritional status from administration of AZ is that antibiotics alter the ecology of the intestinal microbiome which may hinder nutrient supply and allow overgrowth of species with potential pathogenicity, possibly counter balancing any beneficial effects (22-24). Although the delivery of four monthly courses of AZ provides a period of sustained protection, it is possible that the timeframe was too short to observe major improvements in nutritional status.

The high level of coverage achieved with SMC, involving frequent contacts between young children and care givers, provides an opportunity for additional interventions aimed at improving nutrition. Which additional interventions might prove effective is uncertain. In our study community workers administering SMC were instructed on the importance of referring children with severe malnutrition to a local nutritional rehabilitation centre and this may have saved some lives. However, it did not have any impact on the prevalence of clinical malnutrition at the population level (17). In Nigeria, overall nutritional status among children aged 6-24 months did not improve in children who received nutritional supplementation alongside SMC compared to children receiving SMC alone, although the study was small and not randomised (25).

An important characteristic of this study was its large sample size, allowing small differences in

Accepted Article

nutritional status between randomisation groups to be detected. However, it had a number of weaknesses including the infrequent measurement of nutritional status and the lack of a control group not receiving SMC. Exploration of the role of potential confounders such as socio-economic status would also have been valuable but was not possible in a trial of this size. A further limitation is the generalisability of results beyond the setting of the study and SMC distribution regimen. Through partaking in the study, the children in the placebo arm are likely to have received a higher level of care than the standard in each of the study sites, thus potentially diluting effects the intervention may have had. However, given the large number of indicators measured and a lack of any consistent differences between AZ and placebo, the overall interpretation is likely to be robust.

In conclusion, in these two areas of intense seasonal malaria transmission in Burkina Faso and Mali, where nutritional status is poor and fluctuates seasonally, the addition of AZ to the antimalarials used for SMC did not result in improved nutritional status.

References

1. Keenan JD, Ayele B, Gebre T, Zerihun M, Zhou Z, House JI, et al. Childhood Mortality in a Cohort Treated With Mass Azithromycin for Trachoma. *Clinical Infectious Diseases*. 2011;52(7):883-8.
2. Porco TC, Gebre T, Ayele B, House J, Keenan J, Zhou Z, et al. Effect of Mass Distribution of Azithromycin for Trachoma Control on Overall Mortality in Ethiopian Children: A Randomized Trial. *JAMA*. 2009;302(9):962-8.
3. Keenan JD, Bailey RL, West SK, Arzika AM, Hart J, Weaver J, et al. Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa. 2018;378(17):1583-92.
4. Bar-Zeev N, Moss WJ. Hope and Humility for Azithromycin. 2019;380(23):2264-5.
5. Weisz A, Meuli G, Thakwalakwa C, Trehan I, Maleta K, Manary M. The duration of diarrhea and fever is associated with growth faltering in rural Malawian children aged 6-18 months. *Nutr J*. 2011;10(1):25-.
6. Eccles MP, Cole TJ, Whitehead RG. Identification of factors affecting infant growth in developing countries. *Archives of disease in childhood*. 1989;64(11):1559-65.
7. Rowland MG, Rowland SG, Cole TJ. Impact of infection on the growth of children from 0 to 2 years in an urban West African community. *The American journal of clinical nutrition*. 1988;47(1):134-8.
8. Gough EK, Moodie EEM, Prendergast AJ, Johnson SMA, Humphrey JH, Stoltzfus RJ, et al. The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials. 2014;348:g2267.
9. Hallamaa L, Cheung YB, Maleta K, Luntamo M, Ashorn U, Gladstone M, et al. *Child Health Outcomes*

After Presumptive Infection Treatment in Pregnant Women: A Randomized Trial.

2018;141(3):e20172459.

10. Amza A, Kadri B, Nassirou B, Stoller NE, Yu SN, Zhou Z, et al. A cluster-randomized controlled trial evaluating the effects of mass azithromycin treatment on growth and nutrition in Niger. *The American journal of tropical medicine and hygiene*. 2013;88(1):138-43.
11. Amza A, Yu SN, Kadri B, Nassirou B, Stoller NE, Zhou Z, et al. Does mass azithromycin distribution impact child growth and nutrition in Niger? A cluster-randomized trial. *PLoS neglected tropical diseases*. 2014;8(9):e3128-e.
12. Roca A, Camara B, Oluwalana C, Lette K, Bottomley C, D'Alessandro U. Long-lasting effect of oral azithromycin taken by women during labour on infant nutrition: Follow-up cohort of a randomized clinical trial in western Gambia. *PLOS ONE*. 2018;13(10):e0206348.
13. Burr SE, Hart J, Edwards T, Harding-Esch EM, Holland MJ, Mabey DCW, et al. Anthropometric indices of Gambian children after one or three annual rounds of mass drug administration with azithromycin for trachoma control. *BMC public health*. 2014;14:1176-.
14. Meremikwu MM, Donegan S, Sinclair D, Esu E, Oringanje C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. *Cochrane Database of Systematic Reviews*. 2012(2).
15. Wilson AL. A systematic review and meta-analysis of the efficacy and safety of intermittent preventive treatment of malaria in children (IPTc). *PLoS One*. 2011;6(2):e16976.
16. World Health Organization. *World Malaria Report 2018*. 2018.
17. Chandramohan D, Dicko A, Zongo I, Sagara I, Cairns M, Kuepfer I, et al. Effect of Adding Azithromycin to Seasonal Malaria Chemoprevention. *New England Journal of Medicine*. 2019;380(23):2197-206.
18. The Demographic and Health Surveys Program. Nutrition Indicator Data: Mali 2013 [Available from: <https://dhsprogram.com/Topics/Nutrition/index.cfm>].
19. World Health Organization. World Health Statistics data visualization dashboard 2017 [Available from: <http://apps.who.int/gho/data/view.sdg.3-2-data-ctry>].
20. World Health Organization. *WHO Child Growth Standards*. 2007.
21. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. *Vitamin and Mineral Nutrition Information System*. 2011.
22. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med*. 2016;8(1):39-.
23. Guarner F, Malagelada J-R. Gut flora in health and disease. *The Lancet*. 2003;361(9356):512-9.
24. Doan T, Hinterwirth A, Arzika AM, Cotter SY, Ray KJ, O'Brien KS, et al. Mass Azithromycin Distribution

and Community Microbiome: A Cluster-Randomized Trial. *Open forum infectious diseases*. 2018;5(8):ofy182.

25. Ward A, Guillot A, Nepomnyashchiy LE, Graves JC, Maloney K, Omoniwa OF, et al. Seasonal malaria chemoprevention packaged with malnutrition prevention in northern Nigeria: A pragmatic trial (SMAMP study) with nested case-control. *PLOS ONE*. 2019;14(1):e0210692.

Correspondence: Georgia R. Gore-Langton, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. Email Georgia.Gore-Langton@lshtm.ac.uk

Figure 1: Prevalence of key nutritional measures in children aged 3-59 months in Burkina Faso and Mali over the study period 2014-2016

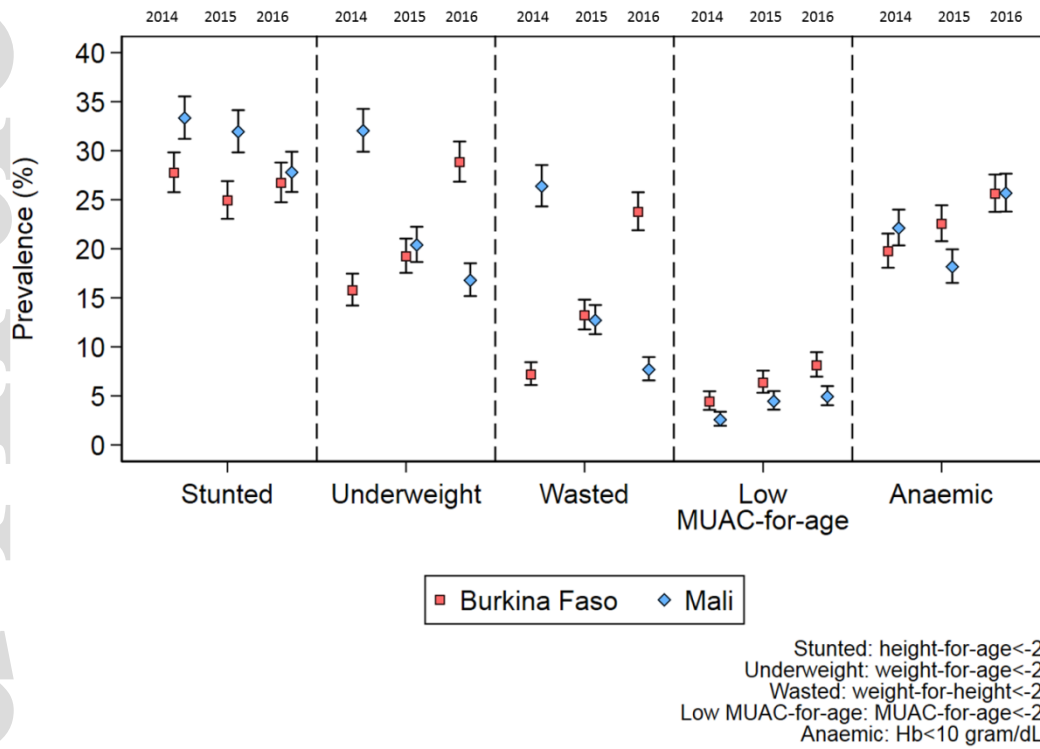


Figure 2: Prevalence of key nutritional measures in children aged 3-59 months between study arms (SMC+ placebo and SMC + AZ) in Burkina Faso over the study period 2014-2016

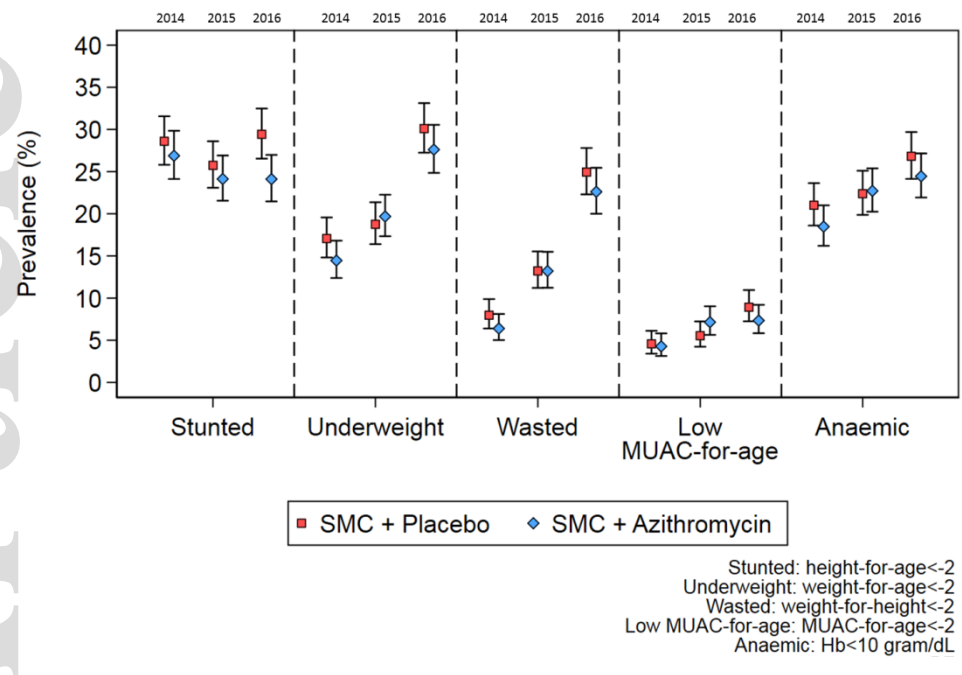


Figure 3: Prevalence of key nutritional measures in children aged 3-59 months between study arms (SMC+ placebo and SMC + AZ) in Mali over the study period 2014-2016

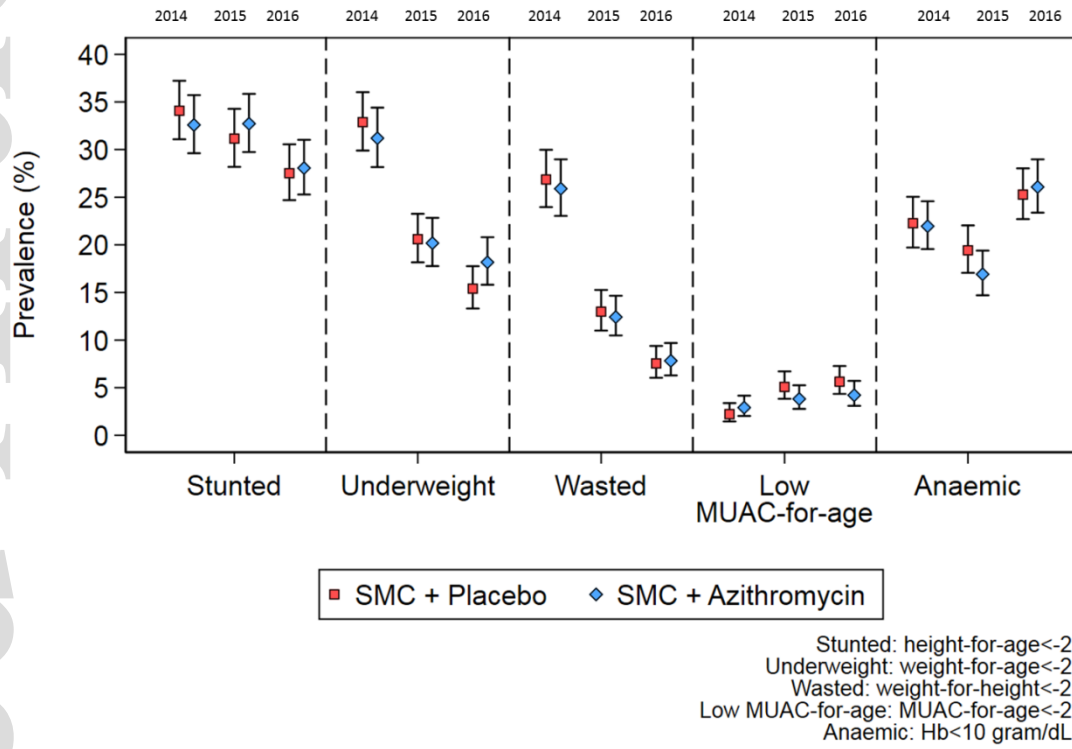


Table 1. Prevalence and prevalence ratios of key nutritional measures in children aged 3-59 months between study arms (SMC+ placebo and SMC + AZ) in Burkina Faso and Mali over the study period 2014-2016

Indicator	Post 2014 (N=4009)			Post 2015 (N=3976)			Post 2016 (N=3981)		
	SMC+P	SMC+AZ		SMC+P	SMC+AZ		SMC+P	SMC+AZ	
Total children, n (%)	1997 (49.8)	2012 (50.2)		1966 (49.5)	2010 (50.6)		1982 (49.8)	1999 (50.2)	
	N (%)	N (%)	PR (95% CI); p-value	N (%)	N (%)	PR (95% CI); p-value	N (%)	N (%)	PR (95% CI); p-value
Stunted (HAZ<-2)*	618 (31.3)	590 (29.7)	0.95 (0.86, 1.05); 0.29	555 (28.4)	564 (28.4)	1.00 (0.90, 1.11); 0.98	538 (28.5)	502 (26.1)	0.92 (0.83, 1.02); 0.11
Severely stunted (HAZ<-3)*	222 (11.2)	207 (10.4)	0.92 (0.77, 1.11); 0.41	214 (11.0)	223 (11.2)	1.03 (0.85, 1.24); 0.77	166 (8.8)	163 (8.5)	0.97 (0.78, 1.19); 0.75
Underweight (WAZ<-2)**	493 (24.8)	456 (22.8)	0.91 (0.82, 1.02); 0.12	385 (19.7)	398 (19.9)	1.01 (0.89, 1.15); 0.84	447 (22.6)	456 (22.9)	1.01 (0.90, 1.13); 0.91
Severely underweight (WAZ<-3)**	189 (9.5)	160 (8.0)	0.83 (0.68, 1.02); 0.078	127 (6.5)	133 (6.7)	1.03 (0.81, 1.30); 0.82	152 (7.7)	148 (7.4)	0.96 (0.77, 1.19); 0.69
Wasted (WHZ<-2)***	335 (17.2)	316 (16.1)	0.93 (0.80, 1.07); 0.30	253 (13.1)	252 (12.8)	0.98 (0.83, 1.15); 0.80	313 (16.1)	297 (15.2)	0.94 (0.81, 1.08); 0.38
Severely wasted (WHZ<-3)***	149 (7.7)	144 (7.3)	0.95 (0.76, 1.18); 0.63	112 (5.8)	117 (6.0)	1.03 (0.80, 1.33); 0.84	141 (7.2)	139 (7.1)	0.97 (0.78, 1.22); 0.80
Low MUAC-for-age (MUAC-for-age<-2)****	64 (3.4)	68 (3.6)	1.06 (0.76, 1.48); 0.74	97 (5.3)	102 (5.5)	1.03 (0.79, 1.35); 0.83	134 (7.2)	108 (5.8)	0.79 (0.62, 1.01); 0.06
Very low MUAC-for-age (MUAC-for-age<-3)****	9 (0.5)	12 (0.6)	1.32 (0.56, 3.11); 0.53	18 (1.0)	11 (0.6)	0.60 (0.28, 1.26); 0.18	16 (0.9)	12 (0.6)	0.74 (0.35, 1.55); 0.42
Anaemic (Hb <10g/dL)	432 (21.6)	407 (20.2)	0.93 (0.83, 1.05); 0.27	411 (20.9)	399 (19.9)	0.95 (0.84, 1.07); 0.40	516 (26.0)	505 (25.26)	0.97 (0.87, 1.07); 0.58
Severely anaemic (Hb <7 g/dL)	16 (0.8)	10 (0.5)	0.62 (0.28, 1.36); 0.23	20 (1.0)	17 (0.8)	0.83 (0.43, 1.61); 0.58	20 (1.0)	18 (0.9)	0.89 (0.47, 1.67); 0.71

*HAZ data missing for 51 children in 2014, 37 in 2015, 166 in 2016

**WAZ data missing for 29 children in 2014, 22 in 2015, 13 in 2016

***WHZ data missing for 102 children in 2014, 80 in 2015, 76 in 2016

****MUAC data missing for 230 children in 2014, 286 in 2015, 252 in 2016

Table 2. Prevalence and prevalence ratios of key nutritional measures in children aged 3-59 months between study arms (SMC+ placebo and SMC + AZ) in Burkina Faso over the study period 2014-2016

Indicator	Post 2014 (N=2010)			Post 2015 (N=3976)			Post 2016 (N=1975)		
	SMC+P	SMC+AZ		SMC+P	SMC+AZ		SMC+P	SMC+AZ	
Total children (n)	1009 (50.2)	1001 (49.8)		983 (49.2)	1017 (50.9)		973 (49.3)	1002 (50.7)	
	N (%)	N (%)	PR (95% CI); p-value	N (%)	N (%)	PR (95% CI); p-value	N (%)	N (%)	PR (95% CI); p-value
Stunted (HAZ<-2)*	286 (28.6)	267 (26.9)	0.94 (0.81; 1.09), 0.41	251 (25.7)	243 (24.1)	0.94 (0.80; 1.09), 0.41	271 (29.4)	232 (24.1)	0.82 (0.70; 0.95), 0.011
Severely stunted (HAZ<-3)*	87 (8.7)	70 (7.0)	0.81 (0.59; 1.10), 0.18	68 (7.0)	73 (7.2)	1.04 (0.76; 1.43), 0.81	84 (9.1)	70 (7.3)	0.80 (0.59; 1.08), 0.15
Underweight (WAZ<-2)**	172 (17.1)	144 (14.5)	0.85 (0.69; 1.04), 0.12	184 (18.8)	199 (19.7)	1.05 (0.87; 1.26), 0.60	292 (30.1)	275 (27.6)	0.92 (0.80; 1.06), 0.23
Severely underweight (WAZ<-3)**	41 (4.1)	25 (2.5)	0.62 (0.38; 1.01), 0.053	55 (5.6)	59 (5.8)	1.04 (0.73; 1.49), 0.83	127 (13.1)	104 (10.4)	0.80 (0.62; 1.02), 0.075
Wasted (WHZ<-2)***	79 (8.0)	63 (6.4)	0.80 (0.58; 1.11), 0.18	128 (13.2)	132 (13.2)	1.00 (0.79; 1.26), 0.99	238 (24.9)	220 (22.6)	0.91 (0.77; 1.07), 0.24
Severely wasted (WHZ<-3)***	19 (1.9)	14 (1.4)	0.74 (0.37; 1.47), 0.39	52 (5.4)	62 (6.2)	1.16 (0.80; 1.66), 0.43	122 (12.8)	114 (11.7)	0.92 (0.72; 1.17), 0.48
Low MUAC-for-age (MUAC-for-age<-2)****	43 (4.6)	40 (4.3)	0.93 (0.61; 1.43), 0.75	50 (5.5)	66 (7.2)	1.29 (0.90; 1.84), 0.16	80 (8.9)	68 (7.3)	0.82 (0.60; 1.12), 0.21
Very low MUAC-for-age (MUAC-for-age<-3)****	4 (0.4)	2 (0.2)	0.50 (0.09; 2.73), 0.43	9 (1.0)	8 (0.9)	0.87 (0.34; 2.24), 0.77	11 (1.2)	8 (0.9)	0.70 (0.28; 1.74), 0.45
Anaemic (Hb <10g/dL)	212 (21.0)	185 (18.5)	0.88 (0.73; 1.05), 0.15	220 (19.4)	231 (22.7)	1.01 (0.86; 1.19), 0.86	261 (26.8)	245 (24.5)	0.91 (0.79; 1.06), 0.22
Severely anaemic (Hb <7 g/dL)	5 (0.5)	6 (0.6)	1.21 (0.37; 3.95), 0.75	11 (1.1)	10 (1.0)	0.88 (0.38; 2.06), 0.77	13 (1.3)	10 (1.0)	0.75 (0.33; 1.69), 0.48

*HAZ data missing for 17 children in 2014, 18 in 2015, 92 in 2016

**WAZ data missing for 6 children in 2014, 8 in 2015, 9 in 2016

***WHZ data missing for 33 children in 2014, 33 in 2015, 48 in 2016

****MUAC data missing for 136 children in 2014, 175 in 2015, 153 in 2016

Table 3. Prevalence and prevalence ratios of key nutritional measures in children aged 3-59 months between study arms (SMC+ placebo and SMC + AZ) in Mali over the study period 2014-2016

Indicator	Post 2014 (N=1999)			Post 2015 (N=1976)			Post 2016 (N=2006)		
	SMC+P	SMC+AZ		SMC+P	SMC+AZ		SMC+P	SMC+AZ	
Total children (n)	988 (49.4)	1011 (50.6)		983 (49.8)	993 (50.3)		1009 (50.3)	997 (49.7)	
	N (%)	N (%)	PR (95% CI); p-value	N (%)	N (%)	PR (95% CI); p-value	N (%)	N (%)	PR (95% CI); p-value
Stunted (HAZ<-2)*	332 (34.1)	323 (32.6)	0.96 (0.84, 1.09); 0.50	304 (31.1)	321 (32.7)	1.05 (0.92, 1.20); 0.47	267 (27.5)	270 (28.1)	1.02 (0.88, 1.18); 0.80
Severely stunted (HAZ<-3)*	135 (13.9)	137 (13.8)	1.00 (0.79, 1.26); 0.98	146 (15.0)	150 (15.3)	1.02 (0.82, 1.28); 0.85	82 (8.5)	93 (9.7)	1.14 (0.86, 1.52); 0.36
Underweight (WAZ<-2)**	321 (32.9)	312 (31.2)	0.95 (0.83, 1.09); 0.45	201 (20.6)	199 (20.2)	0.98 (0.82, 1.17); 0.82	155 (15.4)	181 (18.2)	1.18 (0.97, 1.44); 0.10
Severely underweight (WAZ<-3)**	148 (15.2)	135 (13.5)	0.89 (0.71, 1.12); 0.31	72 (7.4)	74 (7.5)	1.02 (0.74, 1.39); 0.91	25 (2.5)	44 (4.4)	1.78 (1.10, 2.88); 0.019
Wasted (WHZ<-2)***	256 (26.9)	253 (25.9)	0.96 (0.82, 1.13); 0.65	125 (13.0)	120 (12.4)	0.96 (0.76, 1.21); 0.71	75 (7.5)	77 (7.8)	1.04 (0.76, 1.41); 0.82
Severely wasted (WHZ<-3)***	130 (13.6)	130 (13.3)	0.98 (0.77, 1.23); 0.84	60 (6.2)	55 (5.7)	0.91 (0.64, 1.31); 0.63	19 (1.9)	25 (2.5)	1.33 (0.73, 2.42); 0.35
Low MUAC-for-age (MUAC-for-age<-2)****	21 (2.2)	28 (2.9)	1.31 (0.75, 2.28); 0.34	47 (5.1)	36 (3.8)	0.75 (0.49, 1.15); 0.19	54 (5.6)	40 (4.2)	0.75 (0.50, 1.12); 0.16
Very low MUAC-for-age (MUAC-for-age<-3)****	5 (0.5)	10 (1.0)	1.96 (0.68, 5.71); 0.21	9 (1.0)	3 (0.3)	0.33 (0.09, 1.20); 0.093	5 (0.5)	4 (0.4)	0.81 (0.22, 2.98); 0.75
Anaemic (Hb <10g/dL)	220 (22.3)	222 (22.0)	0.98 (0.84, 1.16); 0.87	191 (19.4)	168 (16.9)	0.87 (0.72, 1.05); 0.15	255 (25.3)	260 (26.1)	1.03 (0.89, 1.20); 0.68
Severely anaemic (Hb <7 g/dL)	11 (1.1)	4 (0.4)	0.36 (0.11, 1.11); 0.074	9 (0.9)	7 (0.7)	0.77 (0.27, 2.22); 0.63	7 (0.7)	8 (0.8)	1.16 (0.42, 3.17); 0.78

*HAZ data missing for 34 children in 2014, 19 in 2015, 74 in 2016

**WAZ data missing for 23 children in 2014, 14 in 2015, 4 in 2016

***WHZ data missing for 69 children in 2014, 47 in 2015, 28 in 2016

****MUAC data missing for 94 children in 2014, 111 in 2015, 99 in 2016

Table 4. Difference in mean continuous outcomes Z-scores and haemoglobin in children aged 3-59 months between study arms (SMC+ placebo and SMC + AZ) in Burkina Faso and Mali over the study period 2014-2016

Indicator	2014		2015		2016	
	Difference in mean between study arms (95% CI)	p-value	Difference in mean between study arms (95% CI)	p-value	Difference in mean between study arms (95% CI)	p-value

Height-for-age (Z-score)	0.49 (-0.04, 0.14)	0.30	0.00 (-0.09, 0.09)	0.99	0.05 (-0.03, 0.14)	0.23
Weight-for-age (Z-score)	0.10 (0.01-0.18)	0.021	-0.01 (-0.08, 0.07)	0.87	0.01 (-0.08, 0.09)	0.89
Weight-for-height (Z-score)	0.07 (-0.03, 0.17)	0.15	-0.01 (-0.10, 0.09)	0.88	-0.01 (-0.11, 0.09)	0.85
MUAC-for-age (Z-score)	0.08 (0.02, 0.14)	0.01	-0.01 (-0.08, 0.05)	0.68	0.01 (-0.05, 0.07)	0.75
Haemoglobin (g/dL)	0.07 (-0.02, 0.16)	0.12	0.08 (-0.01, 0.17)	0.068	0.06 (-0.04, 0.15)	0.23