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Determinants of anaemia in 3-59 months old children after a seasonal malaria chemoprevention campaign in rural area in Burkina Faso

Yves Daniel Compaoré[1*], Issaka Zongo[1], Bintou Soaré[1], Alassane Haro[1], Abdoul Aziz Siénou[1], R. Serge Yerbanga[1], Matthew Cairn[2], Daniel Chandramohan[2], Brian Greenwood[2] and Jean Bosco Ouédraogo[1]

[1]Biomedical and Public Health Department, Research Institute on Health Sciences, Bobo-Dioulasso, Burkina Faso.
[2]London School of Hygiene and Tropical Medicine, UK.

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Anaemia remains a major public health problem worldwide and malaria represents one of its main causes in malaria endemic areas. To determine the prevalence of anaemia and its associated factors after a campaign of seasonal malaria chemoprevention combined or not with azithromycin a secondary analysis was conducted on data from a cross-sectional survey at the end of the 2014 seasonal malaria chemoprevention campaign in the health district of Houndé, Burkina Faso. A complete clinical examination with measurements of anthropometric parameters, haemoglobin level was achieved alongside with malaria blood films. Malaria rapid diagnosis test was used in case of fever. Anaemia was defined as a haemoglobin level < 11 g/dl. A descriptive analysis followed by logistic regression was performed. The prevalence of anaemia was 45.71% globally. The addition of azithromycin to sulfadoxine-pyrimethamine plus amodiaquine, older age groups and weight gain reduced the risk of anaemia by 26, 52 and 19%, respectively. A history of one episode or more of malaria and being male increased this risk by 30 and 35%, respectively. At the end of the campaign, the prevalence of anaemia remains relatively high among recipients. However, the addition of azithromycin to sulfadoxine-pyrimethamine plus amodiaquine reduces the risk of anaemia.

Key words: Anaemia, children, cross-sectional study, malaria, seasonal malaria chemoprevention, epidemiology.

INTRODUCTION

Anaemia remains a major public health concern especially in developing countries. According to World Health Organization (WHO) anaemia is defined as a decrease in haemoglobin concentration below the lower limit of

*Corresponding author. E-mail: yvesdaniel.co@gmail.com. Tel: 0022670130213.

normal (LLN) values for individual's age (OMS, 2011). Thresholds defining anaemia generally take into consideration age, gender, gestational status, ethnicity, smoking and altitude (De Benoist et al., 2008; Stevens et al., 2013). According to WHO, pregnant women and under 5 years old children are mostly affected by anaemia. In 2019, all age anaemia prevalence was 22.8% globally (Gardner and Kassebaum, 2020), However, in the same year, 39.8% of children aged 6-59 months years and 36.5% of pregnant women worldwide suffered from anaemia worldwide. In the African region, the prevalence of anaemia was estimated at 60.2% among preschool children (WHO, 2021). Moreover, in sub-Saharan Africa, malaria plays an important role in the occurrence of new and severe anaemia cases and in maintaining the level of anaemia endemicity (Sanou and Ngnie-Teta, 2012). In Burkina Faso, as in many West African countries, data on malaria prevalence from 2010 to 2020 indicated a stagnation in the impact of implemented malaria control interventions in children under 5 (INSD et al., 2015; World Health Organization, 2016; WHO, 2020). In such a context, strengthening malaria control measures could improve malaria indicators in the affected countries. In Burkina Faso, seasonal malaria chemoprevention (SMC) was therefore adopted in 2013 by the National Malaria Control Program (NMCP) in order to strengthen the capacity for preventing malaria in 3-59 months old children. The scale-up of the program using sulfadoxine-pyrimethamine plus amodiaquine (SPAQ), as recommended by WHO in 2012, only began in 2014. Under clinical trial conditions, SMC was highly effective in reducing malaria incidence and its related deaths (Cissé et al., 2006; Dicko et al., 2008, 2011; Konaté et al., 2011; WHO, 2012). Previous studies also provided evidence of the impact of SMC on reducing the incidence of anaemia in under 5 children. In 2011, using the recommended SMC drugs authors reported a 47% reduction in the prevalence of moderate anaemia in the Kati region of Mali (Dicko et al., 2011) and 56% in Boussé, Burkina Faso (Konaté et al., 2011). In 2014 in Uganda, a 40% reduction in the prevalence of anaemia was recorded in a study using dihydroartémisinine-piperaquine (DHAPQ) (Nankabirwa et al., 2014). However, very few studies looked at the predictors of anaemia in children who have received SMC medications. Obviously, by preventing occurrence of malaria this new strategy eliminates an important cause of anaemia, and this could lead to a readjustment of the influence of other determinants of anaemia. Understanding these factors could help to better refine national and/or international programs against anaemia. Early in the scale-up of SMC in Burkina Faso, a pilot implementation study examined the additional benefit of combining azithromycin (AZ) with SPAQ (Chandramohan et al., 2019). This clinical trial, titled SMC+AZ and carried out from 2014 and 2016 in the health district of Houndé, offered an opportunity to evaluate the predictors of anaemia at the end of a SMC campaign with or without AZ. To our knowledge, no previous studies have explored these factors in the context of improved SMC effects with the combination of AZ. This study aimed to assess the prevalence of anaemia and its determinants at the end of a SMC campaign using SPAQ combined or not with AZ.

METHODOLOGY

Study design and population

A cross-sectional survey was carried out at the end of the 2014 malaria transmission season (between December 2014 and January 2015) as a sub-study of the SMC+AZ clinical trial (Chandramohan et al., 2019).

The SMC+AZ study was conducted in the health district of Houndé, specifically in the health facilities of Dougoumoto 2, Koumbia, Kari and Boni. In 2014, a total of 9600 children aged 3-59 months was enrolled in the SMC+AZ clinical trial. From this population, 2000 children were selected to participate in the end-of-malaria transmission season survey. The current secondary analysis used the existing dataset of this survey. The required sample size for this analysis was calculated for children aged 3-59 months who attended the survey using the following formula: $n = (Z\alpha/2)2 \times P (1 - P) \times D / E2$ (Hanga et al., 2014), where n is the sample size, $Z\alpha/2$ is the normal deviate for two-tailed alternative hypothesis at a level of significance ($Z\alpha/2 = 1.96$ for 95% confidence interval). P is the prevalence of anaemia estimated to 0.16 according to a previous study (Zongo et al., 2015), D is the design effect (1.5) and E is the margin of error (or precision, 0.02). The calculated sample size was adjusted for 15% of non-response and considering the already known population size N=9600. Therefore, the minimum required sample size was 1842 participants.

Study procedure

The protocol of the SMC+AZ trial has been fully described elsewhere (Chandramohan et al., 2019). Briefly, the survey consisted of a complete clinical examination with measurement of anthropometric parameters (height, weight) followed by haemoglobin level determination using an automatic photometer (HemoCue®); finally, a thick and thin blood smear was performed in all participants. A rapid diagnostic test for malaria detection (RDT) was undertaken only in case of fever (body temperature ≥ 37.5°C) or of history of fever within the 48 h preceding the survey. The results of the RDT were sent to the clinicians for timely care of the sick participants.

Statistical analysis

Data were extracted in Excel format, cleaned, and analysed using STATA version 15.1. A descriptive analysis was performed with proportions and means compared using a Pearson's or Fisher's Chi-square test and an independent Student's t test, respectively at a significance level $\alpha=0.05$. Then, an explanatory analysis was done using uni- and multivariate logistic regression in order to quantify the relationship between the dependent variable of interest and the explanatory variables. The dependent variable of interest was the presence of anaemia, a binomial variable taking the

modalities 0 (no anaemia) and 1 (presence of anaemia). Based on WHO age-specification, anaemia was defined as a haemoglobin (Hb) level < 11 g/dl in the study population. According to the severity grade, mild anaemia was defined as Hb ≥ 8 g/dl; Hb concentration between 5 and 8 g/dl defined moderate anaemia (8 g/dl< Hb ≥ 5 g/dl) and children with Hb less than 5 g/dl referred to severe anaemia (Hb < 5 g/dl) (OMS, 2011).

A manual forward stepwise procedure was used to select the explanatory variables to be included in the final regression model. A likelihood ratio (LR) test was used to compare models, at the significance threshold of α=0.05. To compare the distribution characteristics of the haemoglobin concentration by study arm, a kernel density plot and a cumulative distribution function were also performed.

Ethical consideration

The study protocol of the SMC+AZ trial was approved by the Ethics Committee for Health Research in Burkina Faso (DELIBERATION N° 2013-3-023) and by the ethics committee of the London School of Hygiene and Tropical Medicine. Participants' parents or legal guardians signed an informed consent form before their enrolment. Confidentiality of personal data was ensured through a constant use of identity numbers and restricted access to the database.

RESULTS

Characteristics of the study children

A total of 1844 participants aged 3-59 months were seen during the 2014 end-of-malaria transmission season survey (920 from the SPAQ + AZ group and 924 from the SPAQ + Placebo arm). Male accounted for approximately 52% (958/1844) of participants with a sex ratio of 1.08. The mean age of the participants was 33.58 ± 15.56 months; the age groups of 13-24 months and 25-36 months were predominant with proportions of 23.05% [95% CI (21.18 - 25.02)] and 22.99% [95%CI (21.12 - 24.97)], respectively. Participants had a mean weight of 11.93 ± 2.91 kg and a mean haemoglobin concentration of 11.06 ± 1.43 g/dl. No clinical malaria case was recorded during the survey. Table 1 provides a distribution of study children' general characteristics according to the study arms. Overall, general characteristics of the study children in the SPAQ + Placebo arm were similar to those from the SPAQ + AZ group suggesting an effective initial randomization and preselection of participants for the end-of-malaria transmission season survey.

The prevalence of anaemia in the study children

The prevalence of anaemia (Hb < 11g/dl) among the study population as a whole was 45.71% (843/1844). Figure 1 shows the distribution of anaemia among the study participants according to severity grades of anaemia. The prevalence of mild anaemia and that of moderate anaemia were 43.5 and 2.2%, respectively. None severe anaemia case was recorded during this survey.

Characteristics of study children according to their haemoglobin status

General characteristics of participants with respect to their haemoglobin concentration are shown in Table 2. The prevalence of anaemia in the SPAQ + placebo arm (48.81%) was significantly higher than that of the SPAQ +AZ arm (42.61%), p=0.008. More than half of the participants were anaemic in the following age groups 3-12, 13-24 and 25-36 months, p<0.001; a significantly lower prevalence of anaemia was observed in age groups 37-48 months (32.5%) and 49-59 months (16.71%). Participants with anaemia had a significantly lower mean body weight (10.68 ± 2.48 kg) compared to those without anaemia (12.99 ± 2.82 kg), p<0.001. Girls were significantly less affected by anaemia (42.33%) than boys (48.85%), p=0.005. Stunting, underweight and wasting were more common in children who were anaemic than in those who were not with the following prevalence, respectively 53.85% (p<0.001), 58.70% (p<0.001), 63.77% (p<0.001). In addition, participants with a history of one or more episodes of malaria and those with a history of one or more episode of gastroenteritis were more prevalent in children who were anaemic than in those who were not. The prevalence of anaemia was 51.57% (p=0.004) for those with a history of one or more episodes of malaria and 69.05% (p<0.001) for a history of one or more episodes of gastroenteritis.

Finally, participants with a recent episode of diarrhoea were also more prevalent in anaemic children (63.27%) than in those who were not, p=0.013.

Predictors of anaemia

Study factors individually associated with anaemia are shown in Table 3 as well as the results of the adjusted logistic regression analysis.

After adjustment, age group, gender, body weight, number of malaria episode during the SMC delivery period, and the SMC treatment arm to which children belonged remained significantly associated with anaemia at the end of the SMC campaign. Addition of AZ to SMC with SPAQ reduced the risk of anaemia by 26% at the end of the campaign. Participants aged 13-24 months were 91% more likely to develop anaemia compared with those aged 3-12 months. In contrast, participants from the 49-59 months age group had a 52% reduced risk of being anaemic compared to children aged 3-12 months. In addition, any 1 kg increase in participants' body weight was associated with a 19% reduction in the risk of

Table 1. General characteristics of study children according to SMC treatment arms.

Parameter	SPAQ + placebo, N=924	SPAQ + AZ, N= 920
	n (%)	n (%)
Gender		
Male	485 (52.49)	473 (51.41)
Mean age (months) ± SD	33.67 ± 15.61	33.48 ± 15.52
Age groups (months)		
03-12	94 (10.17)	94 (10.22)
13-24	211 (22.84)	214 (23.26)
25-36	213 (23.05)	211 (22.93)
37-48	206 (22.29)	194 (21.09)
49-59	200 (21.65)	207 (22.50)
Mean weight (kg) ± SD	11.91 ± 2.93	11.96 ± 2.89
Stunting	265 (28.68)	255 (27.72)
Underweight	156 (16.88)	137 (14.89)
Wasting	77 (8.33)	61 (6.63)
SMC rounds	265 (28.68)	255 (27.72)
Less than 3 rounds	42 (4.55)	37 (4.02)
3 rounds	149 (16.13)	153 (16.63)
4 rounds	733 (79.33)	730 (79.34)
1 or more malaria episodes during the season	222 (24.03)	224 (24.35)
1 or more episodes of gastroenteritis during the season	95 (10.28)	73 (7.93)
Fever at the time of survey	18 (1.95)	26 (2.83)
Cough at the time of survey	59 (6.39)	59 (6.41)
Diarrhoea at the time of survey	20 (2.16)	29 (3.15)
Clinical malaria	0 (0)	0 (0)
Positive parasitemia	24 (2.60)	22 (2.39)
Mean Hb ± SD (g/dl)	11.00 ± 1.43	11.12± 1.44

SMC: Seasonal malaria chemoprevention; AZ: azithromycin; SD: standard deviation; 95% CI: 95% confidence Interval; kg: kilogram; Hb: haemoglobin concentration; g/dl: gramme per deciliter.

anaemia. Compared to girls, male participants had a 35% increased risk of presenting with anaemia at the end of the campaign; surveyed participants who experienced one or more episodes of malaria were also at greater risk of anaemia (nearly 30% increased risk) compared to those who did not (Table 3).

Differences in the distribution of haemoglobin according to study group

The Figure 2 demonstrates that the observed prevalence of anaemia was largely explained by lower number of children with mild anaemia in the SMC+AZ group than that in the SMC+Placebo group.

DISCUSSION

This study showed that anaemia was common in children aged 3-59 months at the end of the malaria transmission season: approximately 46% of the children who received SMC with or without azithromycin were still anaemic, although SMC is known to be a very effective strategy in preventing clinical malaria (WHO, 2012). However, the prevalence of anaemia reported in this study is much lower than the 86% predicted by The World Bank estimates for children under 5 years of age living in

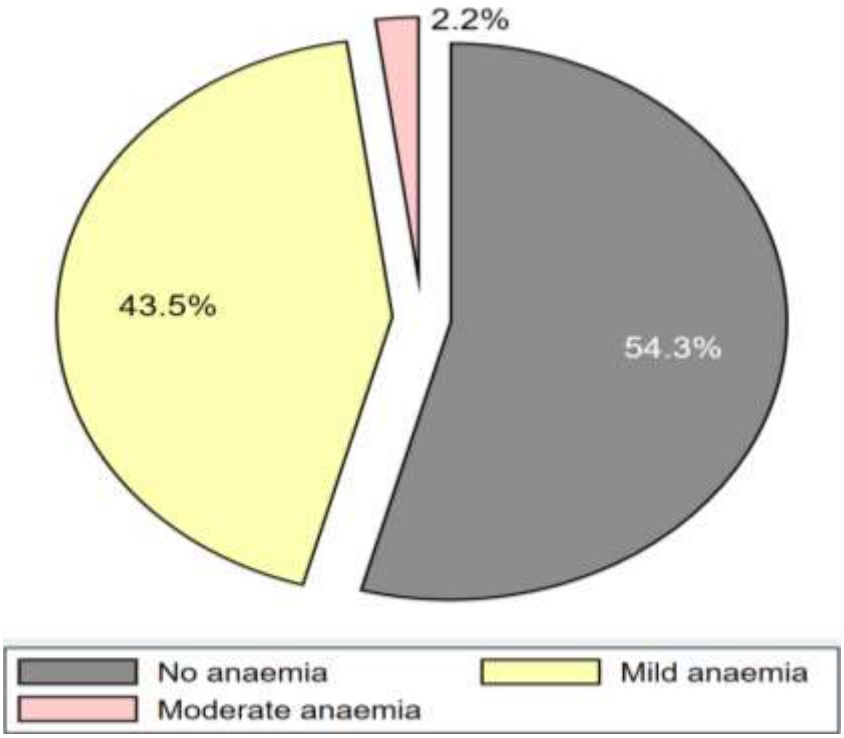

Figure 1. Distribution of study children according to their haemoglobin status.

Table 2. Distribution of study children according to anaemic status.

Parameter	Anaemic status (N=1844)				p
	No anaemia (N1=1001)		Anaemia (N2=843)		
	n	%	n	%	
Study groups					
SPAQ + Placebo	473	51.19	451	48.81	0.008
SPAQ + AZ	528	57.39	392	42.61	
Received SMC rounds					
Less than 3 rounds	40	50.63	39	49.37	
3 rounds	145	48.01	157	51.99	0.039
4 rounds	816	55.78	647	44.22	
Age groups (months)					
3-12	67	35.64	121	64.36	
13-24	123	28.94	302	71.06	
25-36	202	47.64	222	52.36	<0.001
37-48	270	67.50	130	32.50	
49-59	339	83.29	68	16.71	
Gender					
female	511	57.67	375	42.33	0.005
Male	490	51.15	468	48.85	
Mean weight ± SD (kg)	12.99 ± 2.82		10.68 ± 2.48		<0.001

Table 2. Contd.

Stunting					
No	761	57.48	563	42.52	<0.001
Yes	240	46.15	280	53.85	
Underweight					
No	880	56.74	671	43.26	<0.001
Yes	121	41.30	172	58.70	
Wasting					
No	951	55.74	755	44.26	<0.001
Yes	50	36.23	88	63.77	
Malaria episode during treatment season					
No episode	785	56.15	613	43.85	0.004
1 or more episodes	216	48.43	230	51.57	
Gastroenteritis during treatment season					
No episode	949	56.62	727	43.38	<0.001
1 or more episodes	52	30.95	116	69.05	
Fever					
No	981	54.50	819	45.50	0.234
Yes	20	45.45	24	54.55	
Parasitemia					
Negative	980	54.51	818	45.49	0.294
Positive	21	45.65	25	54.35	
Cough					
No	945	54.75	781	45.25	0.127
Yes	56	47.46	62	52.54	
Diarrhoea					
No	983	54.76	812	45.24	0.013
Yes	18	36.73	31	63.27	

AZ: Azithromycin; Hb: haemoglobin concentration; SD: standard deviation; SMC: seasonal malaria chemoprevention; p: Pearson's chi2 p value.

Burkina Faso during the same period (The World Bank, 2018). In addition, the prevalence of moderate anaemia among children in the present study (2.2%) was much lower than the 24% recorded in the same region a year earlier during the malaria indicator survey (INSD et al., 2015). This result suggests that among severity grades of anaemia, moderate anaemia is the most sensitive to the effect of SMC. This finding supports the use of the moderate anaemia as an indicator of the performance of malaria control interventions as used in Demographic and Health Surveys (DHS) (Nambuusi et al., 2019; Letuka and Frade, 2020), malaria indicator surveys (Jima et al., 2010; Eyobo et al., 2014; INSD, 2015, 2018) as well as in clinical trials (Kweku et al., 2008; Cairns et al., 2010; Druetz, 2018). The prevalence of moderate anaemia recorded in the present study remains lower than the 15% reported by Zongo et al. (2015) but appears very close to the 2.7% found by Konaté et al. (2011) in Burkina Faso.

The results of this study also show the association of anaemia with a number of modifiable risk factors that can be addressed to improve the haemoglobin status of children at the end of malaria transmission season. First, implementation of SMC with the standard medications prevents nearly all treated children from experiencing malaria during the highest transmission season and that

Table 3. Crude and adjusted associations between study predictors and anaemia at the end of the SMC campaign.

Parameter	Anaemic status				
	COR	95% CI	p (LR test)	aOR	95% CI
Study groups					
SPAQ + Placebo	1	-	-	1	-
SPAQ + AZ	0.78**	0.65 - 0.93	0.007	0.74**	0.61 - 0.91
Received SMC rounds					
Less than 3 rounds	1	-	-	-	-
3 rounds	1.11	0.67 - 1.82	0.038	-	-
4 rounds	0.81	0.51 - 1.28		-	-
Age groups (months)					
3-12	1	-		1	-
13-24	1.35	0.94 - 1.95		1.91**	1.29 - 2.81
25-36	0.60**	0.42 - 0.86	< 0.001	1.26	0.81 - 1.97
37-48	0.26***	0.18 - 0.38		0.80	0.48 - 1.35
49-59	0.11***	0.07 - 0.16		0.48*	0.26 - 0.90
Gender					
Female	1	-	-	1	-
Male	1.30**	1.08 - 1.56	0.004	1.35	1.100 - 1.66
Weight (kg)	0.72***	0.70 - 0.75	< 0.001	0.81***	0.76 - 0.87
Stunting					
No	1	-	-	-	-
Yes	1.57***	1.28 - 1.93	< 0.001	-	-
Underweight					
No	1	-	-	-	-
Yes	1.86***	1.44 - 2.40	< 0.001	-	-
Wasting					
No	1	-	-	-	-
Yes	2.21***	1.54 - 3.17	< 0.001	-	-
Malaria during treatment season					
No episode	1	-	-	1	-
1 or more episodes	1.36 **	1.10 - 1.68	0.004	1.29*	1.02 - 1.64
Gastroenteritis during treatment season					
No episode	1	-	-	-	-
1 or more episodes	2.91 ***	2.07 - 4.09	< 0.001	-	-
Fever					
No	-	-	-	-	-
Yes	1.43	0.78 - 2.62	0.235	-	-
Parasite carriage					
Negative	1	-	-	-	-
Positive	1.42	0.79 - 2.56	0.235	-	-

Table 3. Contd.

Cough					
No	1	-	-	-	-
Yes	1.33	0.92 - 1.94	0.124	-	-
Diarrhoea					
No	1	-	-	-	-
Yes	2.08 *	1.15 - 3.75	0.012	-	-

COR: Crude Odds Ratio; aOR: adjusted Odds Ratio; 95% CI: 95% Confident Interval; *: p<0.05; **: p<0.005; ***: p<0.0005 .

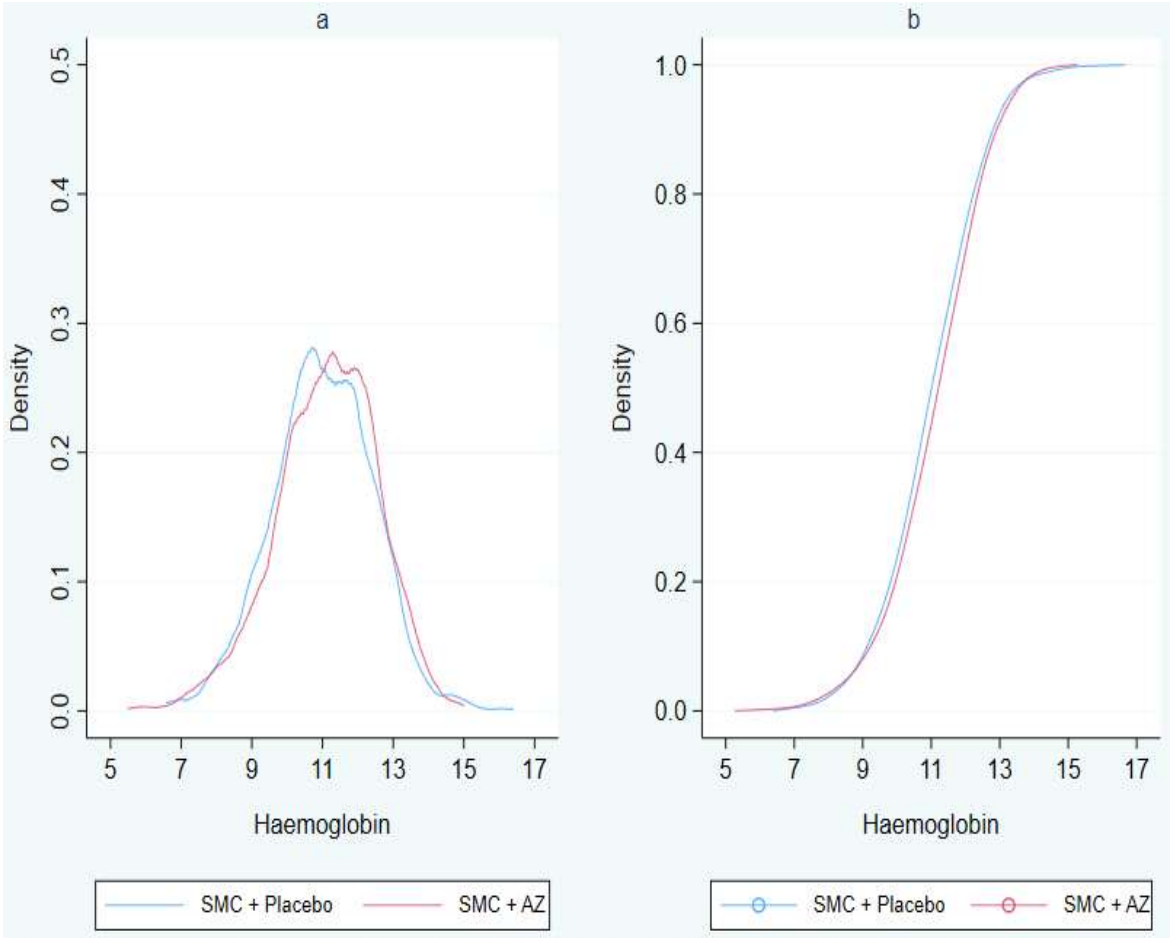

Figure 2. Kernel density plot (a) and cumulative distribution function (b) of the haemoglobin concentration in study children according to the treatment group.

improves their anaemic status. In children who experienced one or more episodes of malaria despite the implementation of SMC, a 30% increase in the risk of anaemia was observed in this study. Findings of the present study are consistent with previous studies that had already shown that when SMC based on SPAQ is optimally administered, it has a significant protective effect against the occurrence of clinical malaria and anaemia estimated to 73 to 92% and 15 to 67%, respectively (Dicko et al., 2011; Konaté et al., 2011;

Zongo et al., 2015; NDiaye et al., 2016). The addition of azithromycin to SPAQ was associated with a supplementary reduction in the prevalence of anaemia estimated to 26% in the present study; and that reduction is mostly related to the number of children with mild anaemia. We hypothesize that the addition of AZ to SPAQ optimizes the effect of conventional SMC drugs, probably due to the broad spectrum of anti-parasitic and antibacterial activity of AZ (Andersen et al., 1998; Heppner et al., 2005). This result also shows that SMC offers a valuable opportunity
to combine different curative and/or preventive public health therapeutic strategies that can target children and their parents individually or simultaneously (Coldiron et al., 2017). Children in the current trial who were malnourished were more likely to be anemic than those who were not. Previous studies have already demonstrated a reciprocal relationship between iron deficiency anaemia and growth in children. In a double-blind clinical trial, Sazawal et al. (2010) reported that a balanced nutritional intake improves not only the growth of children aged 1-4 years, but also their iron stores reducing the prevalence of anaemia. In India, Bhatia and Seshadri (1993) found that anaemic children had significantly lower body weights, shorter heights and lower weight-for-age scores than non anaemic children.

The results of this study also show the association of anaemia with several non-modifiable factors. Firstly, the risk of anaemia was higher in children under 36 months of age and significantly lower in children aged 36 months and older. This finding could be explained by a better nutrition in children aged 36 months and older after a difficult and critical post-weaning period between 13 and 24 months in general. Results of the present study are consistent with those of Magalhães and Clements (2011) who reported a high frequency of anaemia in children under 24 months of age and an increase in haemoglobin concentration in older children in three West African countries including Burkina Faso, Ghana and Mali. In Kenya, Ngesa and Mwambi (2014), stated that children under 12 months of age are most susceptible to anaemia. Secondarily, in the present study, boys were at greater risk of anaemia than girls. Similar observations have been reported in previous studies conducted in Kenya (Akhwale et al., 2004; Ngesa and Mwambi, 2014) and in Ghana (Owusu-Agye et al., 2002). However, the reasons why boys appear to be at greater risk for anaemia remain unclear.

This study has a number of limitations. Because of the secondary nature of the analysis, data presented were restricted to the variables collected and available in the 2014 end-of-malaria transmission season survey database of the SMC+AZ clinical trial. The survey did not take into account variables that are often associated with anaemia in the literature, such as socioeconomic factors (household wealth index, level of education and occupation of parents, household food habits, etc). At the clinical level, no thorough investigation was done to determine the causes of anaemia other than malaria; the use of a device that only measures the haemoglobin concentration did not allow for a biological characterization of anaemic cases. Finally, the lack of data on participants' anaemic status at the beginning of the SMC campaign could have introduced a misclassification bias in the results of this study.

Nevertheless, the results of this study are valuable, with strong scientific findings related to the large population size and detailed information on morbidity. A final strength of this study is that it is one of the few studies to examine risk factors for anaemia in a population receiving SMC and to reveal that SMC does not significantly alter important risk factors for anaemia, other than malaria, observed in previous studies.

Conclusion

In malaria endemic areas, the impact of seasonal malaria chemoprevention (SMC) on the reduction of anaemic cases is significant but remains insufficient; factors that increase the risk of anaemia at the end of a SMC campaign among beneficiaries are age less than 36 months, male gender and experience of one or more episodes of malaria during the SMC delivery period. The addition of azithromycin to SPAQ, age over 36 months, and good nutrition are in contrast protective factors. The negative impact of anaemia on the psychomotor and socio-economic development of children makes it urgent to find further strategies to reduce the burden of anaemia in this population.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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