

Immune responses after single-dose sulphadoxine–pyrimethamine indicate underestimation of protective efficacy of intermittent preventive treatment in infants

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Summary

OBJECTIVE To assess how intermittent preventive treatment in infants (IPTi) with sulphadoxine–pyrimethamine (SP) affects Immunoglobulin (IgG) immune responses against *Plasmodium falciparum* in infants from rural Ghana.

METHODS Randomized, placebo-controlled and double-blinded clinical trial with participants randomized in blocks of 10 to receive either 250 mg sulphadoxine/2.5 mg pyrimethamine or placebo at the age of 3 (IPTi-1), 9 (IPTi-2) and 15 (IPTi-3) months and followed-up for 21 months. (i) Anti-*P. falciparum* IgG levels were measured in 180 children at the age of 9 months. (ii) Longitudinal study of the relationship between IgG levels and *P. falciparum* infections and/or clinical malaria in 17 naive children until they reached the age of 2 years.

RESULTS IgG antibody levels against crude *P. falciparum* lysate were dependent on the frequency of preceding infections and significantly lower in children treated with SP.

CONCLUSION Placebo-treated children had an indifferentially higher incidence of *P. falciparum* infections than clinically observed, which implicates an underestimation of the protective efficacy of IPTi. IgG profiles in 17 children followed up until the age of 2 years provided no evidence for impaired immune responses after a single dose of SP within the framework of IPTi.

keywords sulphadoxine-pyrimethamine, intermittent preventive treatment in infants, IPTi, *Plasmodium falciparum* malaria, rebound

Introduction

The concept of intermittent preventive treatment of infants (IPTi) with sulphadoxine–pyrimethamine (SP) was developed as a control measure to reduce malaria morbidity and mortality in the most vulnerable population (Schellenberg *et al.* 2001) and evaluated in a number of clinical trials (Schellenberg *et al.* 2001; Massaga *et al.* 2003; Chandramohan *et al.* 2005; White 2005; Macete *et al.* 2006; Kobbe *et al.* 2007). The mechanism which mediates the protective effects of IPTi remains unclear. IPTi is thought to combine therapeutic and prophylactic effects of antimalarial drugs administered in intervals short enough to prevent malaria episodes, but long enough to allow the development of immunity against *Plasmodium falciparum*. A major concern of this approach is the potential of a clinical rebound effect: an increased risk of malaria after suspending the

intervention, as has been observed in highly endemic areas after long-term chemoprophylaxis (Menendez *et al.* 1997; Rosen & Breman 2004). Immunity against malaria is complex and develops after repeated infections, mainly mediated by antibodies (Bull *et al.* 1998). It is assumed that a clinical rebound effect of IPTi could be mirrored by impairment of antibody responses. Our aim was to shed some light on whether and how IPTi influences anti-plasmodial immunity.

Methods

Study group and area

Samples were collected from children enrolled in a randomized, placebo-controlled and double-blinded clinical trial on IPTi during the years 2003–2005 (Kobbe *et al.*

2007). The study was conducted in the rural Afigya Sekyere district, Ashanti Region, Ghana. The area is holoendemic for *P. falciparum* malaria with intense perennial transmission and seasonal peaks (up to 140 infective mosquito bites per individual per month, as measured in the peak season).

For all studies and analyses, ethical clearance was obtained through the Ethics Committee of the School of Medical Sciences, University of Science and Technology, Kumasi, Ghana, and written informed consent was obtained from the parent or guardian of each participant.

Study procedures

Briefly, 1070 infants 3 months of age (tolerance of 4 weeks accepted) were recruited at health centres of nine neighbouring villages in our study area. The investigational substances contained either 250 mg sulphadoxine/12.5 mg pyrimethamine or placebo (La Roche, Basel, Switzerland) and were randomized in blocks of 10. The tablets were crushed, mixed with water, and given, independently of body weight, to children at the age of 3 (IPTi-1), 9 (IPTi-2) and 15 (IPTi-3) months. After cessation of the trial the content and quality of the investigational product was verified by the manufacturer.

The observation period of 21 months started at recruitment (IPTi-1). Episodes of *P. falciparum* parasitaemia and clinical malaria were monitored monthly by active follow-up visits. A malaria episode was defined as every event of fever (rectal or tympanic temperature $>38.0^{\circ}\text{C}$ or fever during the preceding 48 h voluntarily reported by mothers) accompanied by asexual *P. falciparum* parasitaemia. Children were not rated at risk for malaria for 21 days after confirmed malaria episodes or after presumptive anti-malaria therapy. Blood films were taken at each scheduled contact (active visit) or when patients presented independently of regular visits (passive case detection). All episodes of clinical malaria were treated with artesunate (4 mg/kg/dose)/amodiaquine (10 mg/kg/dose) for 3 days.

Anti-*P. falciparum* IgG levels after single-dose SP or placebo

Anti-*P. falciparum* Immunoglobulin G (IgG) levels of children treated with a single dose of SP ($n = 90$) were compared with those of children who received a placebo ($n = 90$). Only children without clinical signs of malnutrition or human immunodeficiency virus (HIV) infection and without sickle cell trait (HbS and HbC carriers) were included in this analysis. Plasma samples of participants were taken during the treatment visit at the age of 9 months

(IPTi-2). The cohort of 1070 individuals was classified into three groups as follows: (i) those without observed parasitaemia or malaria between the ages of 3 and 9 months (designated as P-); (ii) those with at least one observed episode of parasitaemia but without clinical malaria between 3 and 9 months of age (P+); (iii) those with at least one observed episode of clinical malaria between 3 and 9 months of age (M+). From each of the three groups, 30 individuals of the SP arm and 30 of the placebo arm were randomly selected to participate in this study on the influence of a single-dose SP treatment on the IgG response.

For the second analysis, the 180 individuals selected were classified according to the cumulative number of preceding episodes of observed parasitaemia: (i) children without observed previous infections were designated as group '0' ($n = 30$ for both arms); (ii) children with one observed episode of parasitaemia were classified as group '1' ($n = 22$, placebo arm; $n = 34$, SP arm); (iii) children with more than one observed episode of parasitaemia were classified as group '2' ($n = 38$, placebo arm; $n = 26$, SP arm).

Longitudinal observation of anti-*P. falciparum* immune responses in children who received placebo

Children considered as immunologically naïve to *P. falciparum* were examined longitudinally to follow the development of anti-*P. falciparum* immune responses in comparison with plasmodial infections in the first 2 years of life. Children from the placebo arm ($n = 17$) were randomly selected who fulfilled the following criteria: (i) no observed *P. falciparum* infections between their month 3 and 9 of life, (ii) no detectable anti-*P. falciparum* IgG levels at month 9, and (iii) a complete set of six plasma samples collected every 3 months (at months 9, 12, 15, 18, 21, and 24).

Two analyses were carried out with these children. (i) Effect of *P. falciparum* infection on the IgG level: analyses were performed to assess IgG responses after an episode of parasitaemia or clinical malaria. The observation time was 1 month before IgG measurement in each of the 17 children (months 12, 15, 18, 21 and 24). Because of one missing follow-up value, 84 values were available for analysis. (ii) Effect of IgG level on *P. falciparum* infection: analyses were performed to estimate the effect of IgG levels on the risk of parasitaemia or clinical malaria. The observation time was the month following each IgG determination. In every child, this resulted in 5 months of observation (after months 9, 12, 15, 18 and 21) and, theoretically, in a number of 85 months of observation. Because of four missing follow-up values the total number was 81.

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Presence or absence of an episode of parasitaemia or clinical malaria during the observation time was associated with previous anti-*P. falciparum*-IgG levels. Both analyses were additionally performed with observation intervals of 2 and 3 months before or after IgG determinations.

Measurement of anti-*P. falciparum* IgG levels

Immunoglobulin G reactivity to crude *P. falciparum* lysate was determined by enzyme-linked immunosorbent assays (ELISA). The parasite lysate fraction was prepared from cultures of infected erythrocytes isolated from three children suffering from severe malaria and living in the same malaria-endemic region. The children were 1–6 years old and presented with prostration and severe anaemia (haemoglobin level <5 g/dl). The culture lysate was prepared from erythrocytes, which were infected with a minimum of two and a maximum of four parasite strains as determined by MSP1 band polymorphism (Smythe *et al.* 1990; Miller *et al.* 1993). Parasite culture handling and antigen preparation were carried out as described previously (Schreiber *et al.* 2006). For ELISA, the working dilution of plasma samples was 1:300. Each test sample was assessed in duplicate wells and in parallel in a blank well containing no antigen to consider unspecific plasma- and reagent-derived reactions (Schreiber *et al.* 2006). Inter-assay variation was controlled for by determining, on each plate, the reactivities of a positive and a negative pool of sera, which were taken from 13 malaria-exposed Ghanaian adults and 10 non-exposed European adults, respectively. The absorbance (OD₄₅₀) was measured and expressed as relative units (RU), calculated according to the following formula:

$$\frac{\text{mean OD}_{450}(\text{test sample}) - \text{blank}(\text{test sample})}{\text{mean OD}_{450}(\text{positive pool}) - \text{blank}(\text{positive pool})} \times 100 = \text{RU}$$

Statistical analyses

Statistical analyses were performed with STATA v9.2 (StataCorp, College Station, TX, USA). Differences between continuous non-normally distributed variables were assessed by two-sided Mann–Whitney tests and *P*-values <0.05 were considered significant.

Results

IgG level after *P. falciparum* infections and malaria episodes

In the first analysis, IgG levels of 180 9-month old children (90 of whom received SP and 90 placebo) were investigated

to assess the effect of a single-dose SP on the immune response. Children were grouped according to the occurrence of *P. falciparum* infections and malaria manifestations at age 3–9 months (Figure 1a). A first comparison of the three subgroups in placebo-treated individuals showed that IgG titres were, as expected, higher in children with observed previous malaria attacks (M+ subgroup) than after observed asymptomatic *P. falciparum* infections (P+ subgroup) (M+ *vs.* P+, *P* < 0.005) and lowest in those without any previous infections (P– subgroup) (M+/P+ *vs.* P–, *P* < 0.0001) (Figure 1a). A similar pattern was found when comparing the SP-treated children in the three subgroups: The IgG titres were highest in children with observed previous malaria attacks (M+ *vs.* P+, *P* < 0.002; M+ *vs.* P–, *P* < 0.0001) and lowest in those without any observed previous infections (P+ *vs.* P–, *P* < 0.002) (Figure 1a). Most notably, when the comparison was made between placebo-treated and SP-treated individuals for each of the subgroups, the IgG levels were always significantly higher in the placebo arm (*P* values as indicated in Figure 1a).

Three participants of the placebo P– group exhibited detectable IgG levels despite *P. falciparum* infection were not observed during the preceding 6 months. Additional plasma samples of these individuals taken at month 3 and 6 were analysed and the RU values at month 3–6–9 were as follows: child 1 RU: 58.9–24.5–30.2, child 2 RU: 18.4–29.9–95.8, child 3 RU: 22.4–11.7–34.9. The results show that increased IgG levels were already present at the age of 3 months. A considerable elevation of IgG levels between month 6 and 9 argues for unobserved infections during this period at least in children 2 and 3.

Association of IgG levels with the frequency of observed previous infections

To examine whether the differences in the comparison described above are a result of different frequencies of preceding infections, the children were also classified according to their cumulative number of infections. As expected, IgG levels increased significantly with the number of observed previous infections both in the placebo and the SP arm (Figure 1b). The lowest IgG levels were found in the group without any observed previous infection and IgG levels were higher in those with a single observed episode (placebo arm, *P* < 0.001; SP arm, *P* < 0.001). The highest IgG levels were detected in children with more than one plasmodial infection (placebo arm, *P* < 0.02; SP arm,

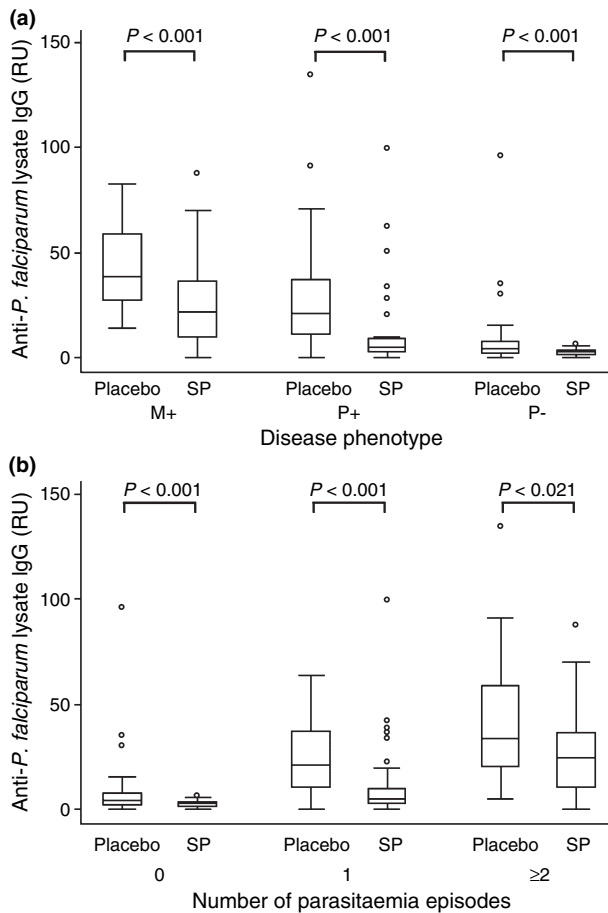


Figure 1 IgG antibody responses to *P. falciparum* lysate antigens were determined in 180 9-month-old children by ELISA, with 30 participants in each subgroup. (a) M+, at least one observed preceding malaria episode between 3 and 9 months of age; P+, at least one observed preceding asymptomatic *P. falciparum* infection between 3 and 9 months of age; P-, no observed preceding *P. falciparum* infection between 3 and 9 months of age. (b) Children were stratified by the number of episodes (0, 1 or ≥2) of *P. falciparum* infections (as measured by the observed presence of parasitaemia) between 3 and 9 months of age.

$P < 0.002$). IgG levels were again significantly higher in individuals who received placebo than those administered a single-dose SP (P -values as indicated in Figure 1b).

Impact of the anti-*P. falciparum* IgG level on infection and malaria

In order to assess whether the lower IgG levels in the SP group reflect a higher risk for subsequent infections, anti-*P. falciparum* IgG levels of 17 children from the placebo arm at months 9, 12, 15, 18 and 21 of life were

analysed in relation to *P. falciparum* infections and clinical malaria episodes that followed 1 month after IgG determination (Table 1). In total, information on 81 observations of the total 85 was available (since information on four active follow-up visits were missing). The analysis showed that the anti-*P. falciparum* IgG levels were not significantly associated with the occurrence of parasitaemia or clinical malaria in the following month ($P_{\text{Mann-Whitney}}$ not significant). Comparable results were obtained when the occurrence of parasitaemia or malaria events was assessed 2 or 3 months after IgG level measurements (data not shown).

Under the assumption that the true probability to observe different IgG levels between children with and without parasitaemia or malaria in the following month is higher than 0.78, the power to detect this difference with the Mann-Whitney test was higher than 80%.

Anti-*P. falciparum* immune responses after infection and malaria

In order to measure anti-*P. falciparum* immune responses after an episode of parasitaemia or malaria, IgG levels were determined at months 12, 15, 18, 21, 24 of life and analysed in relation to the presence or absence of a preceding episode of parasitaemia or malaria. As a result of one missing active follow-up visit, 84 observations were available for this analysis. Anti-*P. falciparum* lysate IgG responses increased significantly following an episode of parasitaemia within a month ($P_{\text{Mann-Whitney}} < 0.03$) or

Table 1 Anti-*Plasmodium falciparum* lysate IgG responses before and after asymptomatic infection (parasitaemia) or symptomatic infection (malaria)

Determination of presence or absence of parasitaemia or malaria	IgG level before infection		IgG level after infection	
	$n = 81$	RU, median	$n = 84$	RU, median
Parasitaemia				
Yes†	26	39.0	19	38.6
No‡	55	24.0	65	20.7*
Malaria				
Yes	10	27.0	9	26.8
No	71	16.0	75	13.3**

A total of 85 plasma samples were available for analysis (five visits in 17 children), numbers (n) were accordingly reduced if preceding or subsequent visits were missing.

†Children who had at least one observed episode 1 month before or after blood sampling.

‡Children who did not have any observed episodes 1 month before or after blood sampling.

* $P = 0.02$, ** $P = 0.03$, by Mann-Whitney test.

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malaria ($P_{\text{Mann-Whitney}} < 0.02$) (Table 1). Similar results were obtained when parasitaemia or malaria infections were assessed 2 or 3 months before IgG levels were measured (data not shown).

Discussion

The association between anti-*P. falciparum* antibody titres and the number of preceding infections detected in our study group confirms the well-known observation that anti-parasite IgG levels are a marker of the frequency of former infections (Marsh *et al.* 1989). However, in our study this proxy measure could not completely distinguish between groups of children with different numbers of observed previous infections because of methodological reasons, individual variations of immune responses, and false information on the true number of infections during the observation time. Indeed, it can be assumed that a number of infection episodes between our monthly follow-up visits may not have been detected, the consequence of which was an underestimation of the number of *P. falciparum* infections and malaria attacks counted by clinical observations. The finding that three individuals from the placebo arm without observed infections (10%) had significant levels of anti-*P. falciparum* antibodies, most likely as a result of unrecognized infections, supports this assumption.

Interestingly, when we analysed IgG levels of children with comparable manifestations or a similar frequency of preceding infections, we found consistently higher antibody titres in the placebo than the SP arm. A similar observation was reported in primigravid women after treatment with SP who had reduced IgG levels against pregnancy-associated malaria-variant surface antigens in comparison with untreated women (Staalsoe *et al.* 2004). As expected, a general difference in anti-plasmodial immune responses was not observed in this study.

Several explanations are conceivable for the decreased anti-*P. falciparum* IgG responses in the SP arm. Firstly, SP therapy could exhibit immune suppressive effects. Although a potential influence of SP on specific antigen responses is conceivable, an effect on *P. falciparum* lysate responses is very unlikely and has not been reported so far. Furthermore, studies reviewed in Rosen & Breman (2004), which assessed the immune responses after vaccination in combination with SP therapy reported no evidence of a difference. Secondly, assuming that IgG levels reflect the number of previous parasitaemia episodes, decreased anti-*P. falciparum* IgG responses in the SP arm could indicate a higher number of undetected infections in the placebo group. If so, it would follow that the protective efficacy was underestimated in the trial when only considering infection episodes and malaria attacks observed during

study visits. A differential error in the proportion of undetected infections in the two study arms is very unlikely since our data were derived from a randomized, double-blinded clinical trial. Other factors, such as duration of infections or timing of the last episodes, may be affected by the SP dose, implying changes in the development of the IgG levels.

In SP-based IPTi trials published so far, reported protective efficacies ranged between 20% and 59% (Menendez *et al.* 1997; Schellenberg *et al.* 2001; Chandramohan *et al.* 2005). In our trial, we calculated a protective efficacy of IPTi of about 20% with regard to observed malaria episodes (Kobbe *et al.* 2007). From the data presented here it can be assumed that this efficacy measure is underestimated even though it is impossible to quantify the difference. Theoretically, the number of undetected malaria attacks should be highest in trials with long periods between active visits or in those restricted to passive case detection, with the consequence of even greater underestimation of malaria protection by IPTi.

A possible clinical rebound is one of the concerns of IPTi. However, our longitudinal analysis provided no evidence that the anti-*P. falciparum* immune response is an indicator for an impaired protection from subsequent episodes. It cannot be excluded that, according to the study design, children were selected in the sub-groups with a generally higher (M+) or lower (P-) risk for malaria for environmental or genetic reasons. Obviously, the probability for malaria in the subsequent month is dependent on an overall risk of individuals and this could confound the immune response measured by IgG.

Nevertheless, the possibility of a clinical rebound through antibodies against specific parasite antigens cannot be excluded. Studies of SP-based IPTi published so far do not report an extensive rebound of malaria episodes (Menendez *et al.* 1997; Schellenberg *et al.* 2001; Verhoef *et al.* 2002; Desai *et al.* 2003; Macete *et al.* 2006; Kobbe *et al.* 2007). On the other hand, there is some evidence in support of a rebound of episodes with high-density parasitaemia and mild anaemia in children in their second year of life (Chandramohan *et al.* 2005; Kobbe *et al.* 2007). Evidence for a parasitological rebound has been found after a single-dose of SP applied in the frame of IPTi with a selection of parasite strains carrying resistance-associated mutations (Marks *et al.* 2005). However, it is not yet clear whether the inherent risk of IPTi to provoke the development of drug resistance is outweighed by its protective effects (Breman & O'Meara 2005). Our results suggest that there are more episodes of *P. falciparum* infections and mild malaria than assessed by observational surveys and that protection against mild malaria by IPTi is higher than that estimated so far.

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References

- Breman JG & O'Meara WP (2005) Intermittent preventive treatment for malaria in infants: moving forward, cautiously. *Journal of Infectious Diseases* **192**, 1869–1871.
- Bull PC, Lowe BS, Kortok M, Molyneux CS, Newbold CI & Marsh K (1998) Parasite antigens on the infected red cell surface are targets for naturally acquired immunity to malaria. *Nature Medicine* **4**, 358–360.
- Chandramohan D, Owusu-Agyei S, Carneiro I *et al.* (2005) Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in Ghana. *British Medical Journal* **331**, 727–733.
- Desai MR, Mei JV, Kariuki SK *et al.* (2003) Randomized, controlled trial of daily iron supplementation and intermittent sulfadoxine-pyrimethamine for the treatment of mild childhood anemia in western Kenya. *Journal of Infectious Diseases* **187**, 658–666.
- Kobbe R, May J, Kreuzberg C *et al.* (2007) A randomized controlled trial on extended intermittent preventive anti-malarial treatment in infants. *Clinical Infectious Diseases* **45**, 16–26.
- Macete E, Aide P & Aponte JJ *et al.* (2006) Intermittent preventive treatment for malaria control administered at the time of routine vaccinations in Mozambican infants: a randomized, placebo-controlled trial. *Journal of Infectious Diseases* **194**, 276–285.
- Marks F, Von Kalckreuth V, Kobbe R *et al.* (2005) Parasitological rebound effect and emergence of pyrimethamine resistance in *Plasmodium falciparum* after single-dose sulfadoxine-pyrimethamine. *Journal of Infectious Diseases* **192**, 1962–1965. Erratum in: *Journal of Infectious Diseases* (2006) **193**, 1340.
- Marsh K, Otoo L, Hayes RJ, Carson DC & Greenwood BM (1989) Antibodies to blood stage antigens of *Plasmodium falciparum* in rural Gambians and their relation to protection against infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **83**, 293–303.
- Massaga JJ, Kitua AY, Lemnge MM *et al.* (2003) Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. *Lancet* **361**, 1853–1860.
- Menendez C, Kahigwa E, Hirt R *et al.* (1997) Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* **350**, 844–850.
- Miller LH, Roberts T, Shahabuddin M & McCutchan TF (1993) Analysis of sequence diversity in the *Plasmodium falciparum* merozoite surface protein-1 (MSP-1). *Molecular and Biochemical Parasitology* **59**, 1–14.
- Rosen JB & Breman JG (2004) Review. Malaria intermittent preventive treatment in infants, chemoprophylaxis, and childhood vaccinations. *Lancet* **363**, 1386–1388.
- Schellenberg D, Menendez C, Kahigwa E *et al.* (2001) Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo-controlled trial. *Lancet* **357**, 1471–1477.
- Schreiber N, Brattig N, Evans J *et al.* (2006) Cerebral malaria is associated with IgG2 and IgG4 antibody responses to recombinant *Plasmodium falciparum* RIFIN antigen. *Microbes and Infection* **8**, 1269–1276.
- Smythe JA, Peterson MG, Coppel RL, Saul AJ, Kemp DJ & Anders RF (1990) Structural diversity in the 45-kilodalton merozoite surface antigen of *Plasmodium falciparum*. *Molecular and Biochemical Parasitology* **39**, 227–234.
- Staalsoe T, Shulman CE, Dorman EK, Kawuondo K, Marsh K & Hviid L (2004) Intermittent preventive sulfadoxine-pyrimethamine treatment of primigravidae reduces levels of plasma immunoglobulin G, which protects against pregnancy-associated *Plasmodium falciparum* malaria. *Infection and Immunity* **72**, 5027–5030.
- Verhoef H, West CE, Nzyuko SM *et al.* (2002) Intermittent administration of iron and sulfadoxine/pyrimethamine to control anaemia in Kenyan children: a randomised controlled trial. *Lancet* **360**, 908–914.
- White NJ. (2005) Review. Intermittent presumptive treatment for malaria. *Public Library of Science Medicine* **2**, e3.

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N. Schreiber *et al.* **Immune response after single dose sulphadoxine-pyrimethamine**

Les réponses immunitaires après une dose unique de sulfadoxine-pyriméthamine indiquent la sous-estimation de l'efficacité protectrice du traitement préventif intermittent chez les enfants en bas âge

OBJECTIF Evaluer comment le traitement préventif intermittent (TPI) chez les enfants en bas âge avec du sulfadoxine-pyriméthamine (SP) affecte le développement de l'immunité acquise contre *Plasmodium falciparum* chez les enfants en bas âge en zone rurale au Ghana.

MÉTHODE (i) Etude clinique randomisée, placebo-contrôlée et en double-aveuglée mesurant les taux d'IgG chez 180 enfants âgés de 8 à 16 semaines qui ont été randomisés dans des groupes de 10 pour recevoir 250 mg de sulfadoxine +12,5 mg de pyriméthamine ou du placebo à l'âge de trois (TPI-1), neuf (TPI-2) et quinze mois (TPI-3). Les enfants ont été suivis durant 21 mois. (ii) Etude longitudinale de la relation entre les taux d'IgG et les infections à *P. falciparum* et/ou la malaria clinique chez 17 enfants jusqu'à ce qu'ils aient atteint l'âge de deux ans.

RÉSULTATS Les taux d'anticorps IgG produits contre un lysate brut de *P. falciparum* dépendaient de la fréquence des infections précédentes et étaient significativement plus bas chez les enfants traités au SP.

CONCLUSION Les enfants ayant reçu du placebo avaient une incidence indifféremment plus élevée des infections à *P. falciparum*, ce qui implique une sous-estimation de l'efficacité protectrice du TPI. Les profils d'IgG chez 17 enfants suivis jusqu'à l'âge de deux ans n'ont fourni aucune évidence pour des réponses immunitaires altérées après une dose unique de SP dans le cadre du TPI chez les enfants en bas âge.

mots clés sulfadoxine-pyriméthamine, traitement préventif intermittent, malaria à *Plasmodium falciparum*, rebond

La respuesta inmune tras una dosis de sulfadoxina-pirimetamina sugiere una subestimación de la eficacia protectora del tratamiento intermitente preventivo en niños

El tratamiento preventivo intermitente en niños (IPTi) con sulfadoxina-pirimetamina (SP) está considerado como una medida prometedora para la reducción de la morbilidad y la mortalidad por malaria en áreas endémicas. Sin embargo no se conoce como el tratamiento con SP afecta el desarrollo de la inmunidad adquirida a *Plasmodium falciparum*. En este estudio se ha evaluado el efecto de una sola dosis de SP sobre la respuesta inmune anti-*P. falciparum* en 180 niños. Los niveles de anticuerpos IgG contra el lisado crudo de *P. falciparum* eran independientes de la frecuencia de infecciones anteriores, y significativamente menores en niños tratados con SP. Los resultados sugieren una mayor incidencia de infecciones por *P. falciparum* en niños tratados con placebo según observación clínica, e implican una subestimación de la eficacia protectora del IPTi. Los perfiles de IgG en 17 niños seguidos hasta los dos años de edad no proveían evidencia de una respuesta inmune afectada después de la administración de una dosis única de SP dentro del marco del IPTi.

palabras clave sulfadoxina-pirimetamina, IPTi, malaria por *Plasmodium falciparum*, efecto rebote