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REVIEW

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# Proguanil as malaria chemoprophylaxis in sickle cell anaemia: the controversies, problems and the future: A narrative of literature

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**Abstract:** *Aim:* In Nigeria, proguanil is the recommended drug for malaria chemoprophylaxis in persons with sickle cell anaemia (SCA); however, over the years, studies have given controversial reports on the effectiveness of proguanil as chemoprophylaxis. This paper highlights the controversies and the problems of continuous chemoprophylaxis with proguanil; and the need to explore more effective malarial chemoprevention method: Intermittent Preventive Treatment (IPT). This is a narrative review of studies on the efficacy of malaria chemoprophylaxis in persons with SCA focusing on proguanil and IPT.
*Method:* A total of seven (7) studies on the efficacy of IPT and malaria chemoprophylaxis using proguanil in SCA were found using the following search engines: Google Scholar, Pub Med, MEDLINE, Med Scape and Cochrane review databases.
*Result:* Malaria chemoprophylaxis seems to be more useful in young children than in adults. Proguanil is less efficacious in reducing malaria induced morbidity and mortality in SCA, compared to IPT using sulphadoxine/pyrimethamine (SP) or mefloquine/artesunate (MQAS).
*Conclusion:* Age may bean important determinant of efficacyof malaria chemoprophylaxis in the reduction of malaria induced morbidity (parasite density, clinical malaria, severe anaemia, and vaso-occlusive crises) in persons with SCA; being more useful in young children than in adults. There may be a need to set separate policies on malaria chemoprevention for adults and children. It is paramount to consider a change of the current policy on malaria chemoprophylaxis in children with SCA from proguanil to IPT using SP, MQAS or other efficacious drugs for the present and the future.

**Keywords:** Intermittent preventive therapy, malaria, chemoprophylaxis, proguanil, Sickle cell anaemia, sulphadoxine/pyrimethamine.

## Introduction

Sickle Cell Anaemia (SCA) is the most common and severe form of sickle cell disease, accounting for about 70% of cases.[1] SCA is a genetic disorder characterized by mutation of the two β-globin gene of the haemoglobin molecule, resulting in homozygous haemoglobin S (HbSS), which polymerizes in the deoxygenated state and sickles the Red blood cells (RBCs).[1] Sickled RBCs cause vaso-occlusive crises and recurrent haemolysis leading to anaemia.[1]

Malaria is caused by plasmodium species and transmitted by the female anopheles mosquito.[2] In Nigeria, the most common species is the *Plasmodium falciparum*. Nigeria currently has the highest burden of malaria in the world, with 24% of global malaria deaths occurring in Nigeria.[3] Children aged under 5 years are the most vulnerable group affected by malaria.[3] Africa has the highest burden of SCA, with more than 200,000 cases each year. Nigeria has the highest burden of SCA globally, with more than 150,000 Nigerian children born each year with the disorder.[4]

The burden of malaria in children with SCA is reflected mainly by its impact on childhood morbidity and mortality.[5-6] A Kenyan study by McAuley *et al* in 2010, showed that although malaria is no more common in SCA children than in controls, the mortality of SCA children who had malaria was about 10 times higher than in children without SCA.[7] Following parasitaemia, accelerated sickling of red blood cells (RBCs) occurs, triggering vaso-occlusive, hemolytic and/or a sequestration crisis.[8-9] In addition to haemolysis of parasitized RBCs, malaria can also cause dyserythropoiesis, and splenic sequestration of unparasitized RBCs. Recurrent

haemolysis can produce folate-deficiency anaemia worsening the baseline anaemia, leading to severe anaemia.[9] Thus, malaria induces morbidity and mortality in SCA by triggering vaso-occlusive crisisand severe anaemia, leading to hospital admissions and sometimes deaths.[10] Long-term malaria prophylaxis has been shown to lower the incidence of malaria-induced severe anaemia, the number of hospital admissions and crises as well as mortality in SCA.[11-15] The efficacy of malarial chemoprophylaxis has been documented in SCA patients, especially in infants and young children living in moderate to high malaria transmission zone since 1956.[11-17]

*Malaria Continuous Chemoprophylaxis and SCA*

Malaria chemoprophylaxis can be defined as the use of anti-malaria medication to prevent the occurrence of the symptoms of malaria by inhibiting parasite growth at the pre-erythrocytic or erythrocytic stage of the parasite's life cycle, for the duration of the period at risk.[11-13] Drugs which act on the parasite in the liver tissue are termed "*causal prophylactics*", for example, doxycycline, atovaquone and proguanil, primaquine. "*Suppressive prophylactics*" or blood schizontocidal drugs act in the bloodstream when parasites invade the erythrocyctes. Most anti-malarial drugs fall into this category, for example, chloroquine, pyrimethamine, mefloquine.[11] In SCA, malaria presents with worsening of baseline anaemia and sickle cell crises; thus, based on the definition of malarial chemoprophylaxis, an efficacious drug will reduce the occurrence of malaria induced severe anaemia and sickle cell crises in children with SCA.[8-9]

A Cochrane review by Oniyangi and Omari in 2009 assessed the effects of malaria chemoprophylaxis in people with SCA;[14] and concluded that chemoprophylaxis is beneficial in people especially children with SCA, reducing morbidity and mortality with improved clinical outcome and reduction in hospitalization rate in them.[14] Thus, supporting policies recommending the practice of malarial chemoprophylaxis in people with SCA.

Over the years, antimalaria drugs that have been used for continuous chemoprophylaxis in children with SCA include chloroquine, pyrimethamine, proguanil, malarone and mefloquine, either as a single drug or as combination drugs.[18-21] Some of these drugs – chloroquine, mefloquine and pyrimethamine, are currently less widely used for chemoprophylaxis either due to drug resistance, intolerable side effects, and unavailability or high cost of purchase.

*Proguanil as malaria continuous chemoprophylaxis in SCA*

Proguanil was recommended as the drug of choice for malaria chemoprophylaxis in Nigeria in 1990.[22] However, in 2011, the Federal Ministry of Health stated that: "Recent evidences have shown that proguanil no longer protects individuals with SCA against malaria; hence this drug can no longer be recommended."[23] Though the specific reasons why proguanil was no longer protective against malaria in individuals with SCA was not stated, efficacy studies involving proguanil as malaria chemoprophylaxis in SCA done between 1990 and 2011, showed controversial results. However, proguanil was re-introduced in 2014 as the drug of choice for chemoprophylaxis in persons with SCA.[24] The reason for the re-introduction was not stated.

*IPT as antimalarial chemoprevention in SCA*

IPT is a form of chemoprevention characterized by the administration of the therapeutic dose of an anti-malarial drug at defined intervals whether or not the individuals have malaria. They are provided with anti-malaria prophylactic protection for the duration the anti-malaria drug is present in the blood.[25-29] This strategy was first used among pregnant women in whom it was found to be very effective and drug compliance was adequate. It has been successfully used in Tanzania, Ghana and Mozambique among children.[28,30-31]
Sulphadoxine/pyrimethamine (SP) is an antifolate existing as a fixed drug combination. The mechanism of action of SP involves the synergistic action of pyrimethamine and sulphadoxine in inhibiting two enzymes important in the parasite's folate biosynthetic pathway - *Dihydrofolate reductase (dhfr), and 7,8-Dihydropteroate synthetase (dhps)*.[32-35]The mechanism of action of SP is to inhibit the multiplication of *P. falciparum* after infection.[30] Intermittent preventive treatment using SP (IPT-SP) offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.[30] The concept of IPT-SP is to combine both therapeutic and prophylactic effects of SP.[30]

The aim of this review is to highlight: the controversies arising from studies on the efficacy of proguanil as malaria chemoprophylaxis; the problems of continuous chemoprophylaxis; and the need to change from the use of continuous chemoprophylaxis(using proguanil) to more effective malaria chemoprevention method, such as IPT using antimalaria drugs with long half life in children with SCA to aid effective malaria chemoprophylaxis.

## Methods

Extensive literature search for studies on efficacy of proguanil as malaria continuous chemoprophylaxis in SCA, conducted up until 2014 was done using the following search engines: Google Scholar, Pub Med, MEDLINE, Med Scape, and Cochrane review databases. Keywords used for searching for publications include: proguanil, malaria chemoprophylaxis in SCA. All publications, including observational studies were included in the review. The same search engines were used to search

for studies on problems/factors affecting the effectiveness of proguanil as continuous chemoprophylaxis in SCA and studies comparing the efficacy of continuous malaria chemoprophylaxis using proguanil and IPT using drugs (such as SP and others) with long half life.
Studies not assessing the efficacy of proguanil or IPT based on the prevalence of parasitaemia/malaria or any other secondary outcome of malaria in sickle cell anaemia were excluded from the review.

## Results

*Proguanil as malaria chemoprophylaxis in SCA*

A total of three (3) studies on the efficacy of proguanil as malaria continuous chemoprophylaxis in persons with SCA, conducted between 1990 and 2014 were found; two were randomized controlled trials (Table 1),[20,36] while one was an observational study.[18]
The first study was a non-blind, prospective multicentre study in Nigeria, by Nwokolo *et al* in 1997; involving 113 adults and children older than five years with SCA. The efficacy of proguanil and mefloquine in malarial chemoprophylaxis was compared.[36] Efficacy was evaluated by the absence of parasitaemia during the course of the study (six months). They found a baseline parasite prevalence of 23.9% (which was cleared prior to study onset) in the study population, who were already on active proguanil prophylaxis. After the course of the study, there was no significant difference in the occurrence of parasite growth between the two groups.[36] (Table 1)
The second study was by Eke and Anochie in 2003. The authors conducted a 9-month randomized, placebo-controlled, open-label study comparing the effects of proguanil and pyrimethamine as malarial chemoprophylaxis in 101 children aged 1-16 years with sickle cell disease, at the University of Port Harcourt Teaching Hospital, Nigeria.[20] Prevalence of parasitaemia was similar in the proguanil, pyrimethamine and placebo groups. The use of proguanil was more efficacious than pyrimethamine and placebo in reducing parasite density and preventing clinical malaria, severe anaemia, bone crisis, blood transfusion and death in the presence of parasitaemia.[20] Table 1.

The third was an observational study by Awodu *et al* conducted in Benin City, Nigeria in 2008. Thirty seven (37) adults with SCA were involved; twelve (12) of them were on proguanil, seventeen on pyrimethamine and eight not any prophylaxis.[18] The prevalence of parasitaemia was similar in all study participants, there was no statistically significant difference in prevalence of parasitaemia in those on chemoprophylaxis and those not on chemoprophylaxis. The efficacy of chemoprophylaxis in reducing malaria induced morbidities in participants was not assessed.

*Intermittent preventive treatment (IPT) in malarial chemoprevention in SCA*

A total of four studies on the efficacy of IPT for malaria chemoprevention in SCA werefound.[37-40] Two (2)of the studies comparedthe efficacy of continuous chemoprophylaxis using proguanil and Intermittent Preventive Therapy (Table 2);[39-40] both studies concluded that IPT was more efficacious in reducing clinical malaria compared to proguanil.[39-40]

In Uganda, Nakibuuka *et al*, in2009 conducted a double-blinded randomized controlled trial comparing the efficacy of monthly sulphadoxine/pyrimethamine (SP) preventive treatment, versus weekly chloroquine (CQ) for malaria prophylaxis in children.[37](Table 2). The prevalence of malaria related admissions, and bone crises were higher in the CQ group compared to the SP group. The effect on anaemia (haemoglobin concentration) was not measured.

Diop *et al*, in a double-blind randomized controlled trial conducted in 2011, compared the impact of monthly sulphadoxine-pyrimethamine (SP) during the high-transmission season (September-February) versus placebo on malaria incidence and morbidity of SCA in Senegal.[38] Overall prevalence of parasitaemia was 6.6% and all cases were found in the placebo group; none in the SP group had parasitaemia.[38] The need for blood transfusion and patients' complaints was significantly reduced ($p = 0.001$ and $p = 0.002$ respectively) in the SP group; whereas, no impact was observed on vaso-occlusive crisis and hospitalization (Table 2).

In Nigeria, a Randomized trial was done in Ilorin by Olaosebikan *et al* in 2015, comparing the safety, effectiveness and tolerability of daily proguanil, bimonthly Mefloquine/Artesunate (MQAS), and bimonthly Sulphadoxine/pyrimethamine/Amodiaquine (SPAQ) in children and adults with SCD.[49] (Table 2). Clinical malaria was lower in the MQAS group, with a relative protective efficacy of 61% compared with the proguanil group; while the relative efficacy of SPAQ versus that of proguanil was 36%.[39] There was no significant difference in the mean haemoglobin concentration seen in all groups. The rate of occurrence of severe illnesses (including vaso-occlusive crises) requiring hospital admission was the same in all groups.

In a randomised study done in Jos, involving 154 patients (including adults) with SCA, the prevalence of malaria parasitaemia was significantly reduced in the SP group compared to the proguanil group ($p = 0.01$).[40] The prevalence of malaria attacks in the SP group was significantly lower than that in the group on prophylaxis with proguanil ($p< 0.0003$) Table 2. The prevalence of bone crises was significantly higher in the group receiving proguanil compared to those receiving SP ($p<0.0001$).[40]

**Table 1:** Summary of Randomized Controlled Trials involving efficacy of proguanil as malaria chemoprophylaxis in Sickle Cell Anaemia between 1990 and 2014

| Author | Study Duration | Location | Sample Size/Age | Study Design | Parasitaemia | Secondary Outcome | Limitation of Study |
|---|---|---|---|---|---|---|---|
| Nwokoloet *al*, 1997 | 6 months | Eastern Nigeria | 113 participants included children > 5 years and adults. Participants had baseline parasites prevalence of 23.9% | Non prospective randomized comparative study between weekly mefloquine and daily proguanil | Mefloquine: 10.8%<br>Proguanil: 18.2%<br>p>0.05 | None | -No secondary outcome measured<br>-Involved both adult and children > 5 years, thus result cannot be applied in children under 5 years |
| Eke and Anochie, 2003 | 9 months | South - South, Nigeria | 97 participants aged 1-16 years | Randomized placebo-controlled, open-label study comparing efficacy of proguanil, pyrimethamine and placebo. Participants had baseline parasitamia | P = 19.4%<br>PR = 15.6%<br>PL = !7.2% | MPD<br>P= 909.4/µl<br>PR= 22.1/µl<br>PL=1538.6/µl<br>p<0.05<br>Proguanil versus placebo<br>p=0.045<br>Pyrimethamine versus placebo<br><br>Bone crisis:<br>P= 5.6%<br>PR 0.0%<br>PL = 17.2%<br>p>0.05<br><br>Haemolytic crisis:<br>P = 0.0%<br>PR = 9.4%<br>PL = 24.1%<br>p>0.05<br><br>Blood transfusion:<br>P = 0.0%<br>PR = 9.4%<br>PL = 27.6%<br>p<0.05<br><br>Clinical malaria:<br>P = 38.9%<br>PR = 15.6%<br>PL = 31.0%<br>p>0.05<br><br>Hospital admission:<br>P = 5.6%<br>PR = 15.6%<br>PL = 37.9%<br>p>0.05 | -Parasite clearance was not ensured at the beginning of the study<br>-Proguanil is not a drug for the treatment of malaria but for prophylaxis |

P=Pyrimethamine, PR=Proguanil, PL=Placebo, MPD=Mean Parasite Density

**Table 2:** Summary of Randomized controlled trials on the efficacy of Intermitted Preventive Therapy for malaria chemoprevention in Sickle Cell Anaemia

| Author | Duration | Location | Sample Size/ Age | Study Design | Parasitaemia/ Parasite density | Secondary Outcome | Limitation of Study |
|---|---|---|---|---|---|---|---|
| Nakibuuka *et al* (2009) | 4 months | Uganda | 242 children. 6 months – 12 years | Double-blind randomized controlled trial comparing efficacy of SP and CQ | SP: 14%<br>CQ: 26% | Hospital admissions<br>SP: 2.5%<br>CQ: 5.7%<br><br>Bone crises<br>SP: 0.0%<br>CQ: 2.5% | -Short study duration |
| Diop *et al* (2011) | 6 months | Senegal | 60 participants with mean age 24 months | Open randomized controlled trial. Compared the impact of monthly SP and placebo. | SP: 0.0%<br>PL: 13.3% | Bone crises<br>SP: 16.7%<br>PL: 16.7%<br><br>Hospital admission<br>SP: 16.7%<br>PL: 16.7%<br><br>Blood transfusion<br>SP: 0.3%<br>PL: 13.3% | -Small sample size<br>-Short study duration/follow up period<br>-Parasite clearance of study participant prior to study not stated. |
| Olasebikan *et al* (2015) | 8 months | Western Nigeria | 270 ≥6months and ≥5kg of age. | Open randomized trial comparing the safety, effectiveness and tolerability of daily proguanil bimonthly MQAS and bimonthly SPAQ in children and adults with SCD. | P: 5.9%<br>SPAQ: 6.6%<br>MQAS: 2.9% | Clinical malaria:<br>P: 21.1%<br>SPAQ:23.3%<br>MQAS:7.7%<br><br>Mortality<br>P:0.0%<br>SPAQ:3.3%<br>MQAS:4.4%<br><br>Hospital admission<br>P:65.6%<br>SPAQ:66.7%<br>MQAS: 62.2% | -Parasite clearance of study participant prior to study not stated<br>-The interval between doses of SPAQ was too long considering the half-life of SP |
| Dawam*et al* (2016) | 3 months | North-Central Nigeria | 154 participants (114 children and 40 adults). | Randomized control comparing monthly sulphadoxine/ Pyrimetha-mine versus daily proguanil. | P: 30%<br>SP: 14% | Clinical malaria<br>P: 57%<br>SP: 16%<br>p<0.0003<br><br>Bone crises<br>P: 69%<br>SP: 33%<br>p<0.0001 | -Short study duration/follow up period. |

SP=Sulphadoxine/Pyrimethamine, P=Proguanil, CQ=Chloroquine, PL=Placebo, SPAQ=Sulphadoxine/Pyrimethamine/Amodiaquine, MQAS=Mefloquine/Artesunate SCD=Sickle Cell Disease

## Discussion

*Proguanil as malaria chemoprophylaxis in SCA: The Controversy*

In the study by Nwokolo *et al*, due to the occurrence of parasitaemia in the study group that received proguanil, the authors noted that there was a high failure rate with proguanil as malaria chemoprophylaxis in persons with SCA. This high failure rate with proguanil may be due to drug resistance or non compliance with the daily dose of proguanil. This study did not assess the effect of proguanil on clinical outcomes such as: severe anaemia, VOC, the need for blood transfusion and hospitalization; this is important because malaria chemoprophylactic effect involves the prevention of malaria and its sequel and not only the prevention of parasitaemia.[11-13] Also, it involved adults and children older than 5 years, thus the results from this study may not be applicable to infants and young children. This study was non-blinded, thus bias may not have been eliminated from the outcome.

In the study by Eke *et al* in 2003, persistence of parasitaemia was seen in both the proguanil and

pyrimethamine groups. This could be due to the fact that parasite clearance was not ensured prior to commencement of the study. Thus, the study design used was that for antimalaria therapeutic efficacy (in which one of the study outcomes is parasite clearance) and not prophylactic efficacy. Proguanil and pyrimethamine are drugs used for chemoprophylaxis and not treatment of malaria. Despite this limitation in this study, the use of proguanil was more efficacious than pyrimethamine in reducing parasite density and preventing clinical malaria, severe anaemia, bone crisis, blood transfusion and death in the presence of parasitaemia.[20]

The study byAwodu *et al* concluded that antimalaria chemoprophylaxis was not necessary in SCA.[18] This study was underpowered to evaluate the efficacy of proguanil as chemoprophylaxis, due to small sample size and the study design, which was an observational study instead of a randomized case control study. Also, the only outcome of the study was the presence of parasitaemia; the effect of proguanil on other outcome of malaria was not evaluated.

Based on the effect of proguanil on preventing occurrence and persistence of parasitaemia, all threestudies (Nwokolo *et al*, Awodu *et al*, and Eke and Anochie), concluded that proguanil had ahigh failure rate in preventing parasitaemia. This may explain why proguanil was discontinued as malaria chemoprophylaxis in persons with SCA. However, Eke*et al* went further to show that proguanil was efficacious in reducing malaria induced anaemia and sickle cell crises, such as VOC, even in the presence of parasitaemia. This may explain why proguanil was re-introduced as malaria chemoprophylaxis in 2014.

Due to the fact that Nwokolo *et al*, and Awodu *et al* studies involved adults and children older than 5 years, and showed high failure rate of proguanil in preventing or reducing parasitaemia; while Eke and Anochie involved young children and infants with SCA, and concluded that proguanil was effective in reducing malaria induced morbidity in children with SCA, can it be inferred that proguanil is of little or no benefit in adults with SCA compared to children with SCA? Should separate policies on use of malarial chemoprophylaxis for infants/young children, and for adults with SCA be made in the country? Age has some meaningful impact on the effectiveness of malaria chemoprophylaxis in preventing malaria induced morbidity in children with SCA. This can be explained by the fact that the level of antibodies (IgM and IgG) against parasite antigens is low in infants and young children, but antibody production increases with age.[10] Thus, development of acquired immunity against malaria in children generally is immature, especially in children less than five years, compared to older children and adults. Also children with SCA, have less antigenic stimulation and also autosplenectomy, which further impairs and slows down the development of acquired malaria immunity in them.[10] Therefore, young children with SCA benefit more from protection against malaria than adults with SCA.

Despite the re-introduction of proguanil as chemoprophylaxis in persons with SCA, its use has been associated with some problems that have continually questioned its effectiveness in the population at risk. These include:

*Problems associated with proguanil as chemoprophylaxis*

Poor drug compliance: Geerligs *et al*, in 2003 stated that "compliance is poor when drugs are administered as daily or weekly doses, without an established workable and effective delivery system such as routine immunization clinics".[41] In a study by Olasebikan *et al*, in 2015, adherence to daily proguanil doses, by patients attending sickle cell clinic was poor, with 57% of patients using <75% of daily doses. Thus, due to problems of delivery and compliance to the daily regimen, the effectiveness of continuous chemoprophylaxis using proguanil was reduced.[39]

Cost-effectiveness: Goodmann *et al* in 1999, showed that childhood continuous chemoprophylaxis with a drug that costs approximately 0.1 US dollars, per administration is highly cost effective.[42] This may not be the case in poor resource settings, like Nigeria, if the drug is administered daily (like proguanil). Also, in Nigeria, 50% of the population live below the poverty line of 1.90 US dollars.[43] Dawaam *et al* in 2016, estimated that in Nigeria, the average cost of daily proguanil for a month is approximately N450 (approximately 1.0 US dollars), compared to the average cost of N58 (0.1 US dollars) for monthly SP.[40]

Drug resistance: In Kenya, the deployment of pyrimethamine for mass drug administration (MDA) for chemoprophylaxis lead to the development of pyrimethamine resistance.[44] This is due to the fact that development of drug resistance occurs due to drug pressure, which facilitates the propagation of resistant parasite strains that have escaped the drug.[45] Cross resistance between proguanil and pyrimethamine has been established.[46] This may explain the inefficacy of proguanil in significantly reducing parasitaemia.[18,36] Resistance to pyrimethamine and proguanil is mediated by the presence of mutations on the *dihydrofolate reductase(dhfr)* gene at codons 51, 59, and 108.[47-48] The prevalence of these mutations in isolates from Africa, has been shown to be high, upto 51%.[49]Additional mutation at codons 16 and 164 leads to significant resistance to proguanil.[45]

*Advantages of Intermittent preventive therapy*

Ensuring drug compliance with the weekly or daily regimen of continuous chemoprophylaxis such as proguanil and establishing an acceptable delivery system at a cheap and affordable cost, are major challenges to the protective effectiveness of continuous chemoprophylaxis such as proguanil. The use of Intermittent Preventive Treatment (IPT) is a method that has been used to

overcome these challenges.

**Drug compliance and Good delivery system:** IPT involves the administrationof effective antimalaria drug monthly or bimonthly through an efficient delivery system, such as immunization schedule, or during monthly or bimonthly follow up visits in sickle cell clinics.[31,39,40] Thereby encouraging drug compliance, unlike daily administration of daily proguanil, which is associated with high rate of poor compliance.[39]

**Cost-effectiveness:** IPT using SP is cheap and readily available. Thus it is highly cost-effective when delivered via an established and good delivery system, such as during routine SCA clinic; the cost per dose for purchase of SP (including wastage) is 0.0136 US dollars, which is more cost effective than continuous chemoprophylaxis, even at a cost of 0.1 US dollars per dose of chemoprophylaxis.[42] SP is about 8 times cheaper than proguanil.[40] In addition, in a study in Nigeria, IPT was found to reduce health system costs and showed significant savings to households from malaria cases averted.[39]

**Drug resistance:** Another advantage of IPT-SP is that it remains efficacious in the presence of SP resistance, unlike other drugs used for continuous chemoprophylaxis such as pyrimethamine and chloroquine.[27] SP resistance is mediated by the presence ofthe quintuple mutant haplotype (*dhfr* N51I+C59R+S108N and *dhps* A437G+K540E). However, Gosling *et al*, reported that with a high prevalence of the quintuple molecular mutation, IPT-SP in infants and young children is unlikely to be efficacious, but where the prevalence of the quintuple mutation is less than 56%, IPT-SP remains efficacious.[50]

**Effect of IPT on the development of naturally-acquired immunity to malaria:** Unlike continuous chemoprophylaxis, IPT involves the administration of a drug at intervals short enough (usually monthly or bimonthly) to produce drug concentrations preventing the onset of disease, but long enough to enable the development of protective immunity. Thus, IPT is less likely to interfere with development of acquired immunity and cause rebound effect.[27,28,31] It is hypothesized that IPT using SP, which has long serum half-life could result in the generation of low dose blood stage inoculate and attenuated infections that may contribute to acquisition of protective immunity by the induction of higher IgG responses.[27,28] Thus, the use of IPT in children with SCA may enhance and not delay their acquisition of protective immunity, which is naturally delayed in them.

*The efficacy of IPT compared to continuous chemoprophylaxis: proguanil*

In the study by Nakibuuka *et al*, in 2009, SP was more efficacious than CQ as malaria chemoprevention.[37] This can be explained by the presence of higher prevalence of chloroquine resistance compared to SP resistance. Although the effect on anaemia (haemoglobin concentration) was not measured, the authors concluded that: malaria chemoprevention by monthly intake of SP during the high transmission period of the parasite reduced the prevalence of malaria and painful crises, hospital admission; and also was safe in SCA patients living in malaria endemic area.

Diop *et al*, in 2011, concluded that: malaria chemoprevention by monthly intake of SP reduced the prevalence of parasitaemia and was safe in patients with SCA living in malaria endemic area.[38] This study had some limitations: the study had a small sample size and the study was not done during the peak transmission period of malaria. This may explain the low prevalence of parasitaemia in the study. Unlike that found in the study by Nakibuuka *et al*, there was no impact on VOC and hospitalization. This difference may be due to the different study design: while the Senegal study involved adults, the study in Uganda included only children. Like proguanil, can it be inferred that IPT may indeed be more beneficial in children compared to adults?

The study by Olaosebikan *et al* showed that the incidence of clinical malaria was lower in the MQAS group, compared with the proguanil and the SPAQ groups. This lower efficacy in the SPAQ group compared to the MQAS group may be due to the long interval (2 months) between doses, as SP offers a personal protection against clinical malaria for a period of approximately 35 days following administration.[30,32] There was no significant difference in the mean haemoglobin concentration seen in all groups. The rate of occurrence of severe illnesses (including vaso-occlusive crises) requiring hospital admission was the same in all groups. This may be because hospitalization was due to sepsis and not malaria, as the prevalence of malaria was low in the study population.[40] Although this study could not include a placebo group, the similar effect of all 3 drugs on hospitalization due to vaso-occlusive crises; and on the haemoglobin concentration may mean that all 3 drugs have equal efficacy in reducing severe anaemia and vaso-occlusive crises in children with SCA. However, based on the higher relative efficacy and effectiveness (safer and increased drug compliance) of MQAS and SPAQ compared to proguanil in reducing clinical malaria, the authors concluded that there is need to explore the use of other regimens that are more effective than daily proguanil.

Similarly, in the study done in Jos, the authors concluded that monthly chemoprophylaxis with SP was more efficacious than daily proguanil in reducing the prevalence of asymptomatic malaria parasitaemia, clinical malaria attack and sickle cell crises in patients (adult and children) with sickle cell disease.[40]

## Conclusion

Although, proguanil has a high failure rate in significantly preventing or reducing parasitaemia in persons (including children) with SCA, proguanil is efficacious in reducing parasite density, sickle cell crises and clini-

cal malaria in young children. Proguanil seems to be more efficacious in children than adults. Continuous chemoprophylaxis using proguanil is less efficacious and less effective in preventing or reducing parasitaemia, compared to monthly IPT using SP, or MQAS. The higher efficacy of IPT in reducing clinical malaria, sickle cell crises and hospitalization compared to proguanil may be dose dependent, being more efficacious when doses are given monthly instead of bimonthly. In addition, based on the higher relative efficacy and effectiveness (safer, more cost effective and increased drug compliance) of SP, MQAS and SPAQ compared to proguanil in reducing clinical malaria, changing the current policy on malaria chemoprevention in children with SCA from proguanil to IPT using SP, or other efficacious drugs needs to be explored and adopted for the present and the future.

**Recommendation**

Future studies on efficacy of proguanil in SCA, should study children and adults as separate study groups.
Future studies involving efficacy and safety of malaria chemoprophylaxis, such as proguanil should use a study design focused not only on prophylactic efficacy of proguanil in preventing parasitaemia, but also on preventing or reducing specific study outcomes (secondary outcomes), such as clinical malaria, parasitaemia, VOC, blood transfusion or severe anaemia, hospital admissions and mortality.
There may be a need to set separate policies on malaria chemoprevention for adults and children; considering the increased vulnerability of young children with SCA to malaria and the fact that chemoprevention is more beneficial in them.

**Limitation of study**

This review involved an observational study, and only few studies were involved in the review as randomized controlled trials on efficacy of malaria chemoprophylaxis in SCA are few.

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**References**

1. Stuart MJ, Nigel RL. Sickle-Cell Disease. *Lancet*. *2004;364:1343–60.*
2. World Health Organization. malaria, International travel and health. Available at:https://www.who.int/ith/diseases/malaria/en/.cited August 21, 2020.
3. World Health Organization. The "World malaria report 2019" at a glance. Regional and global trends in burden of malaria cases and deaths. Available at: https://www.who.int/news-room/feature-stories/detail/world-malaria-report-2019. Assessed on May 20, 2020.
4. World Health Organization. Sickle cell anaemia. Report by the Secretariat of the Fifty-ninth World Health Assembly A59/9 2006
5. World Health Organization. The global burden of disease: 2004 update. Health statistics and Information Centre. Available at:http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/. Assessed on December 2013.
6. Weighing Nigeria's sickle cell burden: is it the world's highest? Africa check 2020. Available at: African health comfact from fiction. Https://africacheck.org/reports/weighing-nigerias-sickle-cell-burden-is-it-the-worlds-highest/. Assessed on March 2020.
7. McAuley CF, Webb C, Makani J, Macharia A, Uyoga S, Opi DH *et al.* High mortality from *Plasmodium falciparum* malaria in children living with sickle cell anaemia on the coast of Kenya. *Blood 2010;116:1663–68.*
8. Luzzatto L. Sickle Cell Anaemia and Malaria. *Mediterr J Hematol Infect Dis 2012;4:e2012065.*
9. Juwah AI, Nlemadim EU, Kaine W. Types of anaemic crisis in paediatric patients with sickle cell anaemia seen in Enugu. *Nigeria. Arch Dis Child*. *2004;89:572–76*
10. Makani J, Komba AN, Williams TN. Malaria in patients with sickle cell anaemia:burden, risk factors, and outcome at the outpatient clinic and during hospitalization. *Blood 2010;115:215–20*
11. Molineaux L, Fleming AF, Cornille-Brøgger R, Kagan I, Storey J. Abnormal haemoglobins in the Sudan Savanna of Nigeria. III. Malaria, immunoglobulins and antimalarial antibodies in sickle cell disease. *Ann Trop Med Parasitol. 1979;73:301-10.*
12. Colbourne MJ, Edington GM. Sickling and malaria in the Gold Coast. *British Medical Journal 1956;4970:784-86*
13. Pearson HA, Gallagher D, Chilcote R. Developmental pattern of splenic dysfunction in sickle cell disorders. *Pediatrics.1985;76:392–97.*

14. Oniyangi O, Omari AAA. In areas where malaria is common, malaria drug prophylaxis benefits people with sickle cell disease. The Cochrane Data base of Systematic Reviews 2006;4:CD003489. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0012. Assessed May 20, 2015.
15. Warley MA, Hamilton PJ, Marsden PD, Brown RE, Merselis JG, Wilks N. Chemoprophylaxis of homozygous sicklers with antimalarials and long-acting penicillin. *British Medical J 1965;2(5453):86–88. DOI: 10.1136/bmj.2.5453.86*
16. Lewthwaite CJ. A trial of chemoprophylaxis in sickle cell anaemia. Preliminary communication. *East Afr Med J. 1962;39:196-99.*
17. Storey J, Fleming AF, Cornille-Brøgger R, Molineaux L, Matsushima T, Kagan I. Abnormal haemoglobins in the Sudan savanna of Nigeria IV. Malaria, immunoglobulins and antimalarial antibodies in haemoglobin AG individuals. *Ann Trop Med Parasitol. 1979;73:311-15.*
18. Awodu OA, Wagbatsoma VA, Enosolease ME.Malaria parasitaemia and antimalaria chemoprophylaxis in sickle cell anaemia patients in steady state. *Turk J Haematol 2008;25:8-12*
19. Greenwood B. Review: Intermittent preventive treatment—A new approach to the prevention of malaria in children in areas with seasonal malaria transmission. *Trop Med Int Health.2006;11:983-91*
20. Eke FU and Anochie I. Effects of pyrimethamine versus proguanil in malarial chemoprophylaxis in children with sickle cell disease: a randomized, placebo-controlled, open-label study. *Current Therapeutic Research 2003;64(8):616-25. doi: 10.1016/j.curtheres.2003.09.003.*
21. Nhabomba AJ, Guinovart C, Jimenez A, Manaca MN, Quinto L, Cistero P *et al.*Impact of age of first exposure to *Plasmodium falciparum* on antibody responses to malaria in children: a randomized, controlled trial in Mozambique. *Malaria J 2014;**13**:121. https://doi.org/10.1186/1475-2875-13-121*
22. Federal Republic of Nigeria. Guidelines for malaria control for physicians in Nigeria. Federal Ministry of Health 1990. Published 1990.
23. Federal Republic of Nigeria. National Policy on Malaria Diagnosis and Treatment. Federal Ministry of Health. National Malaria and Vector Control Division. Reviewed June, 2011.
24. Federal Republic of Nigeria. National Guideline for the Control and Management of Sickle Cell Disease. Federal Ministry of Health. Published 2014.
25. World Health Organization. Intermittent preventive treatment for infants using sulphadoxine-pyrimethamine (SP-IPTi) for malaria control in Africa: Implementation Field Guide. September 2011.
26. IPTi decision-support tool. Intermittent preventive treatment in infants. IPTi consortium. London school of tropical medicine and hygiene. Available at: http://ipti.lshtm.ac.uk/data/ Accessed: June 23, 2012.
27. IPTi consortium. Intermittent preventive treatment in infants. Available at: web.archive.org/web/20141119203909/http://ipti-malaria.org/Theprojectandresults/tabid/265/Default.aspx. Assessed on January 8, 2020.
28. Quelhas D, Puyol L, Quintó L, Casas ES, Nhampossa T, Macete E, *et al*. Impact of intermittent preventive treatment with sulphadoxine-pyrimethamine on antibody responses to erythrocytic-stage *Plasmodium falciparum* antigens in infants in Mozambique. *Clin Vaccine Immunol 2008;15:1282-91.*
29. WHO Advisory Committee on serological responses to Expanded Programme on Immunization vaccines in infants receiving Intermittent Preventive Treatment for malaria (IPTi) final report.WHO 2009.
30. O'Meara WP, Breman JG, McKenzie FE: The promise and potential challenges of intermittent preventive treatment for malaria in infants (IPTi). *Malar J. 2005;4:33.* Available at https://doi.org/10.1186/1475-2875-4-33. Assessed on January 18, 2020
31. Aponte JJ, Schellenberg D, Egan A, Breckenridge A, Carneiro I, Critchley J*et al*. Efficacy and safety of intermittent preventive treatment with sulphadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. *The Lancet 2009;374:1533-42.*
32. Schellenberg KA and Coatney GR. The influence of antimalarial drugs on nucleic acid synthesis in *Plasmodium gallinaceum and Plasmodium berghei*. *BiochemPharmacol1961;6:143–52.*
33. Gutteridge WE and Trigg PI. Action of pyrimethamine and related drugs against *Plasmodium knowlesi* in vitro. *Parasitology 1971;62:431–44.*
34. Newbold CI, Boyle DB, Smith CC, and Brown KN. Stage specific protein and nucleic acid synthesis during the asexual cycle of the rodent malaria *Plasmodium chabaudi*. *Mol BiochemParasitol1982;5:33–44.*
35. Gritzmacher CA and Reese RT. Protein and nucleic acid synthesis during synchronized growth of *Plasmodium falciparum*. *J Bacteriol1984;160:1165–67.*

36. Nwokolo C, Wambebe C, Akinyanju O, Raji A.A, Audu B.S. Mefloquine versus Proguanil in Short-Term Malaria Chemoprophylaxis in Sickle Cell Anaemia. *Clinical Drug Investigation2001;21:537 -44*
37. Nakibuuka V, Ndeezi G, Nakiboneka D, Ndugwa CM, Tumwine JK. Presumptive treatment with sulphadoxine-pyrimethamine versus weekly chloroquine for malaria prophylaxis in children with sickle cell anaemia in Uganda: a randomized controlled trial. Malaria Journal 2009;8:237. doi:10.1186/1475-2875-8-237. Available at: http:// www.malaria journal.com/ content/8/1/237. Assessed on October 2013.
38. Diop S, Soudré F, Seck M, Guèye YB, Diéye TN, Fall AO. Sickle-cell disease and malaria: evaluation of seasonal intermittent preventive treatment with sulphadoxine-pyrimethamine in Senegalese patients-a randomized placebo-controlled trial. *Ann Haematol.* 2011;90:23-27.
39. Olaosebikan R, Ernest K, Bojang K, *et al*. A Randomized Trial to Compare the Safety, Tolerability, and effectiveness of 3 Antimalarial Regimens for the Prevention of Malaria in Nigerian Patients With Sickle Cell Disease. *The J Infectious Diseases 2015;212:617-25.*
40. Dawam JA, Madaki JKA, Gambazai AA, Okpe ES, Larndam N, Onu A *et al*. Monthly sulphadoxine-pyrimethamine combination versus daily proguanil for malaria chemoprophylaxis in sickle cell disease: a randomized controlled study at the Jos University Teaching Hospital. *Nigerian J Medicine. 2016;25(2):119-27*
41. Geerligs P.D, Brabin B.J, Eggelte T.A. Analysis of the effects of malaria chemoprophylaxis in children on haematological responses, morbidity and mortality. *Bulletin WHO 2003;81:205-16*
42. Goodman CA, Coleman PG, Mills AJ. Cost-effectiveness of malaria in sub-Saharan Africa. *The Lancet 1999;354:378-85*
43. The World Bank. Poverty and equity data portal. Available at: http:// povertydata.worldbank.org/ poverty/region/SSF. Cited September 2020.
44. Clyde DF, Shute GT. Resistance of *P.falciparum* in Tanganiyika to pyrimethamine administered at weekly intervals. *Trans.R.Soc.Trop.Med. Hyg. 1954;51:505-13.*
45. Drug Resistance. Malaria Site. Available at www.malariasite.com/tag/a. Assessed: February 26, 2015
46. Peterson DS, Milhous WK, Wellems TE. Molecular basis of differential resistance to cycloguanil and pyrimethamine in Plasmodium falciparum malaria. *Proc Natl Acad Sci. 1990:8:3018-22.doi: 10.1073/pnas.87.8.3018.*
47. Staines HM, Burrow R, Teo BH, Ster IC, Kremsner PG, Krishna S. Clinical implications of *Plasmodium* resistance to atovaquone/ proguanil: a systematic review and meta-analysis. *J Antimicrobial Chemotherapy, 2018;73:581–95.*
48. D Parzy 1 , C Doerig, B Pradines, A Rico, T Fusai, J C Doury. Proguanil resistance in Plasmodium falciparum African isolates: assessment by mutation-specific polymerase chain reaction and in vitro susceptibility testing. *Am J Trop Med Hyg1997;6:646-50.doi: 10.4269/ ajtmh.1997.57.646*
49. Muehlen M, Schreiber J, Ehrhardt S, Otchwemah R, Jelinek T, Bienzle U*et al.* Short communication: Prevalence of mutations associated with resistance to atovaquone and to the antifolate effect of proguanil in Plasmodium falciparum isolates from northern Ghana . *Trop Med Int Health 2004;3:361-3.doi: 10.1111/j.1365-3156.2004.01201.*
50. Gosling RD, Gesase S, Mosha JF. Protective efficacy and safety of three antimalarial regimens for Intermittent Preventive Treatment for malaria in infants: a randomised placebo controlled trial. *Lancet 2009; 9:609971*