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Abstract This paper reviews the evidence for beneficial effects of malaria chemoprophylaxis on haematological responses, morbidity, mortality, health service utilization and rebound immunity in children. As anaemia may play an important role in childhood mortality, it is important to assess evidence from controlled trials of the potential of chemoprophylaxis to reduce childhood anaemia. An analysis of trials found good evidence that malaria chemoprophylaxis improves mean haemoglobin levels and reduces severe anaemia, clinical malaria attacks, parasite and spleen rates. Significant reductions in outpatient attendance and hospital admissions have been achieved, and substantial evidence from Gambian studies shows reductions in mortality. Chemoprophylaxis in children does not seem to produce any sustained impairment of immunity to malaria, although rebound effects may be greater in children who receive prophylaxis during infancy. Short periods of targeted prophylaxis are likely to be preferable to continuous drug administration. Evidence of the protective efficacy of malaria chemoprophylaxis in children shows that this strategy could be considered within integrated health programmes for specific time periods. Intermittent routine combination therapy early in childhood may be appropriate for those living under holoendemic conditions. Large-scale studies over a number of years are needed to address this issue and the impact of this approach on health service utilization, mortality, and the emergence of drug-resistant parasites.

Keywords Malaria/drug therapy/epidemiology; Malaria, Falciparum/drug therapy/epidemiology; Antimalarials/blood/therapeutic use; Anemia/drug therapy; Treatment outcome; Child; Infant mortality; Controlled clinical trials; Meta-analysis (*source: MeSH, NLM*).

Mots clés Paludisme/chimiothérapie/épidémiologie; Paludisme plasmodium falciparum/chimiothérapie/épidémiologie; Antipaludiques/sang/usage thérapeutique; Anémie/chimiothérapie; Evaluation résultats traitement; Enfant; Mortalité nourrisson; Essai clinique contrôlé; Méta-analyse (*source: MeSH, INSERM*).

Palabras clave Paludismo/quimioterapia/epidemiología; Paludismo falciparum/quimioterapia/epidemiología; Antimaláricos/sangre/uso terapéutico; Anemia/quimioterapia; Resultado del tratamiento; Niño; Mortalidad infantil; Ensayos clínicos controlados; Meta-análisis (*fuente: DeCS, BIREME*).

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Voir page 213 le résumé en français. En la página 213 figura un resumen en español.

Introduction

The literature that describes malaria prophylaxis in children from areas in which malaria is endemic spans 50 years of applied field research. The place of malaria chemoprophylaxis in the overall armamentarium for malaria control has been studied repeatedly during this time, but no general analysis of its role within an integrated malaria control programme has been presented.

The pharmacological approaches to malaria chemoprophylaxis have varied substantially over the years in terms of drugs and dosages. The term chemoprophylaxis implies that a drug is used before infection of tissue or blood, with the aim of preventing the infection or its clinical manifestations. In practice, however, many young children already will be parasitaemic when the antimalarial is taken and, in these circumstances, the use of the drug is a form of regular intermittent chemotherapy (although not necessarily with treatment doses). Short-acting drugs require more frequent use to achieve treatment and prophylactic effects than long-acting drugs. These therapeutic aspects are important considerations when assessing the place of chemoprophylaxis in strategies to control malaria.

Initial trials during the 1950s assessed the role of malaria chemoprophylaxis as a component of eradication efforts. In 1962, the WHO Expert Committee on Malaria reported that regular drug administration should be a priority for selected and particularly vulnerable groups (*1*). In highly endemic areas, such groups were considered to include pregnant women, nursing mothers, infants and small children, and groups of epidemiological and socioeconomic importance. In most countries in which malaria is endemic, chemoprophylaxis has subsequently largely been restricted to pregnant women. Greenwood recently showed that primary health care workers can give malaria chemoprophylaxis effectively to patients in at-risk groups; he concluded that this could have a major effect on the health of young children and women in their first

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pregnancy, despite potential disadvantages of drug resistance, safety, cost and the need for sustained drug delivery (*2*). Since this assessment, several randomized trials, some of which combined chemoprophylaxis with another partially effective malaria control measure, have provided new information. It is important to assess the evidence available from all of these trials.

We investigated the effects of malaria chemoprophylaxis on morbidity, haematological response and mortality in children by analysing controlled trials reported during the last 50 years. The focus was on studies in children, particularly those in the context of chemoprophylaxis as a strategy to reduce childhood anaemia, because malaria-related anaemia may play an important direct and indirect role in childhood mortality (*3*). Studies of adolescents, which span the childhood age range, were included. Reviewed were articles that reported the use of malaria chemoprophylaxis and intermittent treatment of children with reference to effects on haematological response, mortality, morbidity and immunity after the intervention was stopped. The overall aims were to assess the relevance of this approach within control programmes at country and international levels and to identify specific research needs.

Methods

We systematically searched the literature with a protocol that outlined methods and outcomes to identify trials of antimalarial chemoprophylaxis in children (Box 1). Trials were identified by searching MEDLINE up to June 2002 with the keywords "children and malaria", "children and anaemia and malaria" and "children and anaemia and prophylaxis or profylaxis", with no restrictions on fields, publication type, ages, entry or publication date, language (articles in all languages were searched), subsets, or sex.

Reference lists of trial publications were examined, and malariologists provided advice on sources. All relevant major tropical medicine journals in English, French, and German from 1950 were searched by hand; these journals were not identified from the electronic search but were screened independently. Studies with different designs and randomization procedures were included as long as drugs were used to prevent the infection or its clinical manifestations within the first few weeks after treatment. Trials were included if participants were aged 0 months–19 years, a control group was present, and the minimum duration of follow-up was 10 weeks. All frequencies of drug use during follow-up were included. If interim analyses were available, only data for the end of the intervention period was used. We excluded studies that reported chemoprophylaxis for hyper-reactive malaria splenomegaly.

Box 1. **Outcomes selected for systematic literature search**

- Clinical malaria
- Febrile episodes
- Prevalence of parasites
- High-density parasitaemia
- Spleen rates (presence of palpable splenomegaly)
- Anaemia
- Prevalence of severe anaemia
- Mortality
- Weight gain
- Rebound malaria after chemoprophylaxis stopped (clinical malaria, prevalence of parasites or fever, and death)
- Health service attendance
- Antibody responses
- Facilitation of drug resistance

Results

Altogether, we identified 64 trials that reported results from Africa, Asia, Central America and the Pacific (*4–67*). Table A outlines the treatment groups, antimalarial schedules and duration of chemoprophylaxis (web version only, available at: http://www.who.int/bulletin/). Randomized procedures mostly were not stated. Most analyses were carried out on an intention-to-treat basis. The total number of children treated in the identified trials was approximately 15 000.

Morbidity effects

Estimates of percentage reductions in Table B (web version only available at: http://www.who.int/bulletin/) were calculated using the following formula.

$$\frac{\%\ \text{controls} - \%\ \text{treated}}{\%\ \text{controls}}$$

Reduction in parasitaemia refers to a reduction in the prevalence of infections caused by *Plasmodium falciparum*, or by all malaria species when *P. falciparum* was not reported separately. Significant reductions in parasitaemia in children who received chemoprophylaxis were observed in 42 studies and varied from 10.9% to 100% (*3, 5, 6, 9–11, 13–17, 22–33, 35, 37, 39, 40–43, 45, 46, 48, 49, 52, 54, 55–61, 67*). Three studies reported outcomes in relation to high-density parasitaemia (*14, 22, 52*); two from the Gambia found a beneficial effect (*14, 22*). Greenwood et al. reported no significant difference in prevalence of parasites between chemoprophylaxis and control groups from the same Gambian study population when parasite prevalence was determined in children aged 5 years who had received various durations of chemoprophylaxis (2–5 years) (*18*). These contrasting results may relate to differences in the age at which malaria immunity was acquired in the groups that received chemoprophylaxis.

In a study in Mali of children aged 0–9 years, although the parasite prevalence was lower in treated children, Delmont et al. observed no significant difference in parasite prevalence between treated and control groups (*38*). This study showed significant reductions in spleen rates in both groups on completion of the trial. A study from Senegal showed highly significant reductions in parasite prevalence and spleen rates in children under 5 years who received chloroquine weekly for 16 weeks during the rainy season (*57*). Twenty-five studies reported significant reductions in spleen rates with chemoprophylaxis (*3, 4, 11, 13, 14, 16, 22–25, 29, 32, 35, 37, 39–43, 48, 55–58, 61*). In the study of Delmont et al., reductions in spleen rates were found in treated and control groups (*38*).

Several morbidity-related parameters were reported. Fifteen studies reported a beneficial effect of malaria chemoprophylaxis on episodes of clinical malaria, although the definition of clinical malaria varied between studies (*8, 14, 16, 22, 23, 31, 34, 36, 45, 52, 54, 58, 61–63*). In Liberia, Hogh et al. reported no difference for "probable" clinical malaria but observed a significant effect for "possible" clinical malaria in children aged 6 months to 6 years (*36*). Another study

conducted at the same time in Liberia reported that 34% of parasite isolates were resistant to the chloroquine used for chemoprophylaxis (*74*). Hogh et al. observed significant reductions in clinical malaria (87.1%) and parasitaemia (>90%) in Mozambique (*45*). In Ethiopia (Awash Rift Valley), clinic visits for morbidity due to fever were not significantly reduced by chemoprophylaxis with chloroquine, but information on chloroquine resistance in the area was not available (*8*).

Nine studies showed reductions in febrile episodes (*5, 15, 16, 17, 22, 35, 49, 61, 63*); the differences were not significant for four of these (*15, 16, 22, 49*). The different findings have no obvious explanation because most of the studies used the same temperature definition for fever (>37.5 °C); however, temperatures may have been measured with different methods. Björkman et al. observed a beneficial effect for reported fevers only (*35*).

Four studies measured children's growth during chemoprophylaxis (*15, 23, 47, 75*). Only one did not show a significant improvement in weight gain (*23*). Variations in the age ranges of children measured in these studies (infant to school age) made estimates of mean effects on growth inappropriate.

In conclusion, evidence for reductions in the number of episodes of clinical malaria in most studies is good, despite differences in chemoprophylactic drugs and study designs. Reductions in parasite prevalence and spleen rates mostly confirm this conclusion. Disparities between studies may relate to confounding due to age effects.

Haematological effects

Of the 24 papers that reported haematological response (Table 1) (*11, 13, 14, 16–20, 22, 34, 35, 38, 46–48, 51, 53–55, 58, 61–63, 69*), six reported haemoglobin values (*11, 13, 47, 51, 55, 69*) and 18 packed cell volumes (PCV) (*11, 14, 16–20, 22, 34, 35, 38, 46, 48, 51, 54, 58, 61, 69*). Two of the studies that assessed haemoglobin in the Gambia (McGregor et al.) and Nigeria (Bradley-Moore et al.) reported significantly higher increases in haemoglobin concentrations in children who received malaria chemoprophylaxis than in controls (2.6 g/dl versus 1.1 g/dl, respectively) (*11, 51*). According to McGregor et al., this effect was significant after 18, but not 40, months of chemoprophylaxis. This difference could relate to smaller numbers of patients being assessed at 40 months or the acquisition of acquired malaria immunity in the control group. In the study by Archibald & Bruce-Chwatt in Nigeria, which reported no improvement in haemoglobin concentrations, recruited children were older than in most other studies and chemoprophylaxis was given only during school terms (*47*). Greater improvements in haemoglobin levels were reported in the Gambia for years when transmission of malaria was higher (*19*).

Twelve of the studies that reported PCV found a significant increase in the mean value from baseline in the chemoprophylaxis groups (1.4%–5.0%) (Table 1) (*11, 14, 16, 17, 19, 22, 24, 34, 35, 51, 58, 61, 69*). Two of these studies reported increases with monthly chemotherapy with chloroquine or proguanil but not with pyrimethamine (*34, 35*); this variation may relate to differences in patterns of drug resistance. Delmont et al. reported an increase in mean PCV in children who received chemoprophylaxis but did not determine the significance of this change (*38*).

A number of studies reported no significant change in mean PCV between study groups (*18, 20, 38, 46, 53, 54*), although all but one (*54*) showed increases in PCV. Two of these (*18, 20*) investigated the Gambian community for which a significant effect of chemoprophylaxis on PCV had been shown (*14, 16, 17*). This variation probably relates to differences in the age groups in these studies, because a positive effect was seen with younger children (3–59 months) but not with older children (5 years). The study that did not show an increase in PCV used a different prophylactic drug (proguanil) and involved a small sample of older children (*54*). A further study reported a significantly greater decrease in mean haemoglobin concentrations in the control group than in two intervention groups (*55*).

Of the studies that reported PCV values, four provided information on the prevalence of severe anaemia (PCV <25%) (*14, 53, 62, 63*) and three showed a significant decrease in severe anaemia in children who received malaria chemoprophylaxis (*14, 62, 63*). Two of these studies were in infants in an area of the United Republic of Tanzania with perennial malaria transmission and showed comparable protective efficacy, despite the use of different drugs (pyrimethamine–dapsone and pyrimethamine–sulfadoxine), frequencies of administration and doses (*62, 63*). In an area of the Gambia with seasonal malaria, PCV <20% was recorded in four children who received placebo, but in none of those who received pyrimethamine–dapsone ($P = 0.08$) (*14*). In northern Nigeria, Bradley-Moore et al. found no significant difference in the frequency of severe anaemia between study groups, although significant improvements in haemoglobin concentrations and PCV were observed (*51*). Anaemic children were not preselected in any of the studies in Table 1, although greater reductions in anaemia prevalence have been reported after treatment in anaemic children (*71*). In a study from Nigeria, Lucas et al. reported that significantly fewer participants (aged 8–17 years) who received malaria chemoprophylaxis showed a decrease in PCV than those who received placebo (*48*).

In summary, chemoprophylaxis over several months, with one of a variety of antimalarials, raised haemoglobin concentrations and reduced anaemia, especially in younger children or infants. The magnitude of the effect on mean haemoglobin concentrations generally was not greater than 1 g/dl. When intermittent therapeutic doses were used in infants, protective effects were greater (*63*). These haematological effects are consistent with the reductions in parasite prevalence and splenomegaly summarized in Table B.

Mortality effect

We identified nine articles that reported information on child mortality from five study populations (*5, 11, 14–16, 18, 52, 53, 62*); four of these described the same Gambian population (*14–16, 18*). One of these Gambian studies in children aged 1–4 years showed significant reductions in mortality in children who received chemoprophylaxis with pyrimethamine–dapsone 9 months after starting chemoprophylaxis (64%; 95% confidence interval (CI), 37–117 mortality reduction compared with baseline) (*14*). The mortality actually increased in those who received placebo (143%; 95% CI 91–225). Children with less than average compliance with chemoprophylaxis had a significantly increased risk of death (relative risk, 5.4; 95% CI, 3.2–14.6). Beneficial effects were most apparent during the rainy season. After 3–4 years of malaria

Table 1. **Effect of malaria chemoprophylaxis on haematological responses**

Year of publication	Reference	Antimalarial	Response		
			Mean packed cell volume (%)	Mean haemoglobin (g/dl)	Packed cell volume <25% (%)[a]
1956	(*47*)	Pyrimethamine	NR[b]	0.12[c]	NR
	(*11*)	Chloroquine	2.41[d]	After 18 months: 2.6[e] After 40 months: 0.4	NR
1970	(*13*)	Pyrimethamine–sulfadoxine	NR	0.2 (6–10 years)	NR
		Pyrimethamine		3.4 (6 months–4 years) 0.1 (6–10 years)	
1980	(*34*)	Chlorproguanil	3.21[d]	NR	NR
		Pyrimethamine	0.74		
1981	(*38*)	Chloroquine	0.9	NR	NR
1985	(*54*)	Proguanil	–1.2	NR	NR
		Pyrimethamine–sulfalene			
	(*51,69*)	Chloroquine	2.7[e]	1.1[e]	NS
		Pyrimethamine (weekly)	1.4	1.0[f]	NR
		Pyrimethamine (monthly)	2.0	0.9[f]	NR
1986	(*35*)	Chloroquine	2.0[f]	NR	NR
		Proguanil	1.4[f]		
		Pyrimethamine	0.0		
1988	(*19*)	Pyrimethamine–dapsone	5.0[e]	NR	NR
		Chlorproguanil	2.5[f]		
	(*14*)	Pyrimethamine–dapsone	2.7[d]	NR	–15.0[g]
	(*17*)	Pyrimethamine–dapsone	3.1[c]	NR	NR
1989	(*20*)	Pyrimethamine–dapsone + chlorproguanil	1.40	NR	NR
1990	(*16*)	Pyrimethamine–dapsone	1.6[d]	NR	NR
1992	(*46*)	Pyrimethamine–dapsone	0.5	NR	NR
	(*55*)	Amodiaquine	NR	0.84	NR
		Pyrimethamine–dapsone	NR	0.45	NR
1993	(*21,22*)	Pyrimethamine–dapsone	1.32[f]	NR	NR
	(*53*)	Chloroquine	NR	NR	0.42 (NS)[h i]
		Pyrimethamine	NR	NR	0.52 (NS)
1995	(*18*)	Pyrimethamine–dapsone	0.3	NR	NR
1997	(*61*)	Pyrimethamine–dapsone			
		1–4 years	0.1	NR	NR
		5–9 years	1.9[e]		
	(*62*)	Pyrimethamine–dapsone	NR	NR	–57.3[e]
1998	(*58*)	Pyrimethamine–dapsone	3.25[d]	NR	NR
2001	(*63*)	Pyrimethamine–sulfadoxine	NR	NR	–50.3[f]

[a] In the study by Lucas (*48*), 26.3% had no change in PCV ($P<0.01$).
[b] NR, not recorded.
[c] Estimated from percentage haemoglobin (standard 12.8 g/dl).
[d] $P<0.01$.
[e] $P<0.001$.
[f] $P<0.05$.
[g] Packed cell volume <30%.
[h] Packed cell volume <20%.
[i] NS, not significant.

chemoprophylaxis in this population, Menon et al. reported a 70.8% reduction in mortality compared with baseline in children aged 3 months to 5 years (*16*). In the placebo group a 42.4% reduction occurred. This difference was however not statistically significant ($P = 0.06$). Children from a narrower age band (12 months to 5 years) showed a greater reduction in mortality compared with baseline (chemoprophylaxis, 76.5%, placebo 38.5%, $P<0.03$) (*16*). The inclusion of infants in the larger analysis may have reduced the mortality effect, because young infants are less susceptible to severe malaria than older children (*72*). After 5 years of continued prophylaxis in the same population, mortality in children aged under 5 years in the treated prophylaxis group was 15% lower than in the placebo group (282 vs 339 deaths) (*18*). It is not possible to determine whether this reduction was significant from the data provided, and there was considerable loss to follow-up.

The Gambian studies are the only ones that examined long-term effects on mortality and showed that gains were maintained (Greenwood B, personal communication, 2002). In a further Gambian study that used chlorproguanil or pyrimethamine–dapsone, more deaths were reported in the chlorproguanil group; differences in deaths between the treatments and placebo were not significant (*15*). In neighbouring Senegal, morbidity and mortality were reduced after the first 3 years of a chloroquine chemoprophylaxis programme between 1963 and 1966 (*7, 73*).

In the United Republic of Tanzania, Menendez et al. used the same antimalarial chemoprophylaxis that was used in the Gambia (pyrimethamine–dapsone) but in infants; they reported no difference in mortality between the infants who received chemoprophylaxis or placebo (*62*). Studies with chloroquine prophylaxis in the Gambia and Nigeria found no significant differences in mortality (*11, 52*). Small study numbers and loss to follow-up were important confounders in these studies, which were not powered to detect a mortality effect, and chloroquine resistance may have been a factor in one of them (*53*). A further study in Nigeria reported that 3.5% of children who received pyrimethamine died, compared with 8.5% of children who received placebo ($P = 0.026$) and 7.7% of those who received chloroquine ($P = 0.7$), (*54*). Among Namibian refugees in Angola, two children died in the placebo group and one in the intervention group (*5*).

In conclusion, substantial evidence from studies in the Gambia shows that mortality is reduced in children who receive prophylaxis with pyrimethamine–dapsone over 2–5 years. Other studies that did not show significant effects on mortality used shorter periods of chemoprophylaxis and included small numbers of participants that may not have been large enough to detect an effect, even if one was present.

Health service effects

Reductions in parasite prevalence would be expected to reduce the risk of serious malaria before clinical presentation and, as a result, to reduce health service attendance. Studies that reported the effect of malaria prophylaxis on health service attendance are summarized in Table 2. Significant reductions were observed for outpatient visits and hospital admissions (*5, 52, 62, 63, 69*), except in the study by Schellenberg et al., which reported no reduction in outpatient visits (*63*). The difference could be due to the less frequent use of intermittent antimalarials in the last-mentioned study (treatment doses over a seven-month period in infants aged two, three and nine months). Differences between the studies in the frequencies of child follow-up by research staff also may have influenced health attendance frequency.

A short-term chemoprophylaxis study (10 weeks) in a seasonal transmission area of Ethiopia reported no significant reduction in study referrals for febrile illness associated with parasitaemia (relative risk 0.93, 95% CI 0.78–1.12) (*8*). Prescription of antimalarial drugs also was less frequent in children who were receiving chemoprophylaxis in Burkina Faso (*6*). Among Namibian refugees in Angola, the number of hospital admissions of children who received proguanil was 47% lower than of those who received placebo ($P<0.01$) and blood transfusions were less frequent with proguanil ($P = 0.05$) (*5*).

Two early studies reported on school attendance after malaria prophylaxis. Absenteeism (more than four absences per term) was reduced significantly in a study in Ghana among those aged 12–20 years (relative risk, 0.50; 95% CI, 0.37–0.68) (*23*), but it was not affected in a Nigerian study among younger children aged 5–10 years (relative risk, 1.03; 95% CI, 0.93–1.15) (*47*).

In conclusion, outpatient visits and hospital admissions were reduced in the limited number of studies that reported these important outcomes.

Rebound effects

Table 3 summarizes data on malaria-related indices from assessments after malaria chemoprophylaxis was discontinued; the duration of assessments varied from three months to one year. The duration of prophylaxis also varied from three intermittent treatments in infants aged under one year up to five years of continuous prophylaxis in children recruited after six months of age. Despite differences in study design with respect to chemoprophylactic antimalarial drug and malaria transmission rates, only three studies showed a significant rebound effect for clinical malaria (*5, 53, 62*). In one study from the United Republic of Tanzania, first and multiple episodes of malaria were

Table 2. **Effect of malaria prophylaxis on health service attendance**

Year of publication	Reference	Relative risk	
		Outpatient visit	Hospital admission
1985	(*52*)[a]		
	Proven malaria	0.26 (0.14–0.48)[b]	NR[c]
	Suspected malaria	0.32 (0.18–0.55)	NR
	(*69*)[a,d]	0.07 (0.01–0.46)	NR
1988	(*5*)[e]	NR	0.53 (0.36–0.78)
1997	(*62*)[f]	0.90 (0.83–0.97)	0.61 (0.51–0.71)
2001	(*63*)[g]	1.03 (0.95–1.13)	0.70 (0.53–0.92)

[a] Chloroquine.
[b] Figures in parentheses are 95% confidence intervals.
[c] NR, not reported.
[d] Pyrimethamine.
[e] Proguanil.
[f] Pyrimethamine–dapsone.
[g] Pyrimethamine–sulfadoxine.

Table 3. **Relative risk estimates for rebound malaria during period following chemoprophylaxis**

Year of publication	Reference	Period of prophylaxis	Period following prophylaxis (months)	Antimalarial	Prevalence (95% CI)			
					Clinical malaria	Parasitaemia	Fever	Probability of death
1953	(*25*)	7.5 months	3	Chloroquine	NR[a]	0.41 (0.26–0.64)[b]	NR	NR
				Chlorguanide	NR	0.85 (0.63–1.15)	NR	NR
1956	(*47*)	2 years	3	Pyrimethamine	NR	0.77 (0.53–1.11)	NR	NR
1986	(*35*)	2 years	12	Chloroquine–proguanil–pyrimethamine	NR	NI[c]	I[d]	NR
1988	(*17*)	2 years	6	Pyrimethamine–dapsone	0.78 (0.22–2.74)	0.73 (0.55–0.97)	1.54 (0.65–3.63)	NR
	(*14*)	9 months	12	Pyrimethamine–dapsone	0.56 (0.11–2.88)	NR	NR	NR
	(*5*)	4 months	4	Proguanil	1.30 (1.07–1.57)[e]	NR	1.22 (0.98–1.52)	NR
1991	(*60*)	13 weeks	1	Proguanil	NI	0.96 (0.75–1.25)	NI	NR
				Chlorproguanil	NI	0.84 (0.60–1.18)	NI	NR
1993	(*53*)	1–5 years	5	Pyrimethamine	1.77 (0.54–5.79)	NR	NR	NR
				Chloroquine	3.50 (1.17–10.48)	NR	NR	NR
1994	(*45*)	1 year	6	Pyrimethamine–dapsone	NR	NI	NR	NR
1995	(*18*)	2–5 years	12–24	Pyrimethamine–dapsone	NR	1.14 (0.83–1.56)	NR	0.80 (0.22–2.95)[h] 2.43 (0.77–7.68)[i]
1997	(*62*)	10 months	1–11	Pyrimethamine–dapsone	1.8 (1.3–2.5)[f]	NR	NR	NR
					1.4 (1.1–1.7)[g]	NR	NR	NR
1998	(*39*)	12 weeks	1	Pyrimethamine–proguanil	NR	0.24 (0.07–0.84)	NR	NR
2001	(*63*)	3 intermittent treatments	9	Sulfadoxine–pyrimethamine	NI	NR	NR	NR

[a] NR, not recorded.
[b] Figures in parentheses are 95% confidence intervals.
[c] NI, prevalence not increased after chemoprophylaxis.
[d] I, prevalence significantly increased for chloroquine group only ($P<0.05$).
[e] Presumptive treatments.
[f] Excluding withdrawals during follow-up.
[g] All children.
[h] Two years after prophylaxis.
[i] One year after chemoprophylaxis.

significantly higher during the second year of life — irrespective of whether children who received treatment during the follow-up period were included in the estimate (*62*). Prevalence of severe anaemia was also increased after chemoprophylaxis.

The impact of malaria episodes on immunity might be very different depending on whether the episode is experienced by an infant or older child, although the overall effect of chemoprophylaxis is still beneficial. This difference in impact relates to the physiological state of the child and their level of age-dependent malaria immunity. Research in some parts of Africa in the 1950s suggested that regular drug administration for up to two years in schoolchildren did not interfere with pre-existing immunity and that termination of treatment did not create additional risks (*1*). Infants may be at higher risk of rebound effects after chemoprophylaxis, as observed in the Tanzanian study (*62*). In Nigerian children, significant rebound effects followed prophylaxis with chloroquine but not pyrimethamine (*52*); the reason for this difference was not clear. A third study reported rebound clinical malaria among Namibian refugees in Angola who might also have had low pre-existing immunity to malaria (*5*). In Guatemala, a low transmission area, there was no evidence of an increase in spleen rate after treatment (*25*). Björkman et al. reported a "tendency" for increased reporting of fever ($P<0.05$) in the chloroquine chemoprophylactic group (*35*); this result may have been spurious, however, because the incidence of fever was high in the internal control group.

Two studies reported the risk of rebound mortality (*18, 52*). The probability of death among Gambian children aged 5–10 years after malaria chemoprophylaxis was stopped at age 5 years was similar for children who had received pyrimethamine–dapsone for some period during their first five years of life and those who had received placebo. The probability of death between 5–6 years of age — that is, during the first year after chemoprophylaxis was stopped — was a little higher among children who received chemoprophylaxis, but this difference was not significant (*18*). In the Nigerian study, only one unexplained death occurred among 94 children followed for six months after chemoprophylaxis was stopped at 1–2 years of age (*52*).

All but one of nine studies that reported indirect fluorescent antibody measurements to *P. falciparum* parasites after chemoprophylaxis showed significant reductions in antibody measurements (Table 4). Gamma immunoglobulin and total immunoglobulin G antibody levels were also reduced. One study from Gabon showed recovery of fluorescent

Table 4. **Serum antibody concentration changes following chemoprophylaxis**

Year of publication	Reference	Period of prophylaxis is (years)	Antimalarial	Percentage reduction		
				Serum IgG	Total IgG	Immunofluorescent malaria antibody
1956	(*11*)	3	Chloroquine	–24.2[a]	NR[b]	NR
1964	(*12*)	<1	Pyrimethamine	NR	NR	–85.7[c]
1975	(*66*)	1.5–2.5	Pyrimethamine	NR	NR	Reduced[c]
1985	(*52*)	1–2	Chloroquine	NR	–22.2[c]	–76.8[b]
1986	(*35*)	2	Chloroquine Proguanil Pyrimethamine	NR NR NR	–24.7[c] –30.8[c] –17.7	NS[d] NS NS
1987	(*70*)	1–1.8	Chloroquine	NR	NR	–9.2 to –13.1[c]
1988	(*17*)	2	Pyrimethamine–dapsone	NR	NR	–11.2[c]
1989	(*20*)	3	Pyrimethamine–dapsone–chlorproguanil	NR	NR	–10.2[c]
1994	(*45*)	1	Pyrimethamine–dapsone	NR	NR	–10.3[c]
1995	(*18*)	2–5	Pyrimethamine–dapsone	NR	NR	Reduced[c]

[a] Statistical significance not determined.
[b] NR, not reported.
[c] Significant percentage reduction in seropositivity to total anti-*P. falciparum* antibody ($P<0.05$).
[d] NS, not significant.

antibody titres by age 5–9 years in children who received early chemoprophylaxis (*76*). The role these antibodies play in the development of natural clinical immunity is uncertain, because fluorescent antibody measurements reflect exposure and provide little or no information on protective immunity. The difference in immunological parameters between drugs acting on the blood stages, such as chloroquine, and causal chemoprophylactic drugs, such as pyrimethamine, proguanil, and primaquine, is unclear.

In conclusion, despite reductions in humoral immunity, clinical immunity seemed not to be reduced significantly after chemoprophylaxis; this may be due to enhanced cell-mediated immune responses to malaria in protected children (*20*). Prophylaxis may lead to a higher incidence of rebound attacks of clinical malaria after prophylaxis during infancy (*62*). The period of prophylaxis may need to be extended beyond the first year of life or, alternatively, only intermittent prophylaxis or treatment might be provided for infants.

Facilitation of drug resistance

Not many studies have assessed the potential problem of drug resistance after the use of chemoprophylactics in children. Resistance to pyrimethamine after mass prophylaxis and short periods of prophylaxis is well described for children (*26, 68, 77, 78*). The prolonged use of chloroquine on a large scale in Ghana, Madagascar and former Tanganyika did not result in the appearance of resistance (*79*). This was particularly relevant in Madagascar, where once-weekly chloroquine had been distributed for 12 years as an effective suppressant to 1.25 million children (*80*).

One study investigated drug sensitivity during implementation of chemoprophylaxis and documented a decreased sensitivity to pyrimethamine–dapsone, although these findings may also have related to increased malaria transmission (*61*). Other studies in Liberia and the Gambia have not shown selection of resistant strains to chloroquine or chlorproguanil (*81–83*).

Discussion

Our analysis found substantial evidence that malaria chemoprophylaxis can improve mean haemoglobin concentrations and can reduce the prevalence of severe anaemia, the number of attacks of clinical malaria, parasite and spleen rates, and child mortality. Three studies showed significant reductions in outpatient visits (*52, 62, 69*) and three showed significant reductions in hospital admissions (*5, 62, 63*). Only one study showed a significant increase in clinical malaria prevalence after prophylaxis in infants (*62*). Of studies that reported malaria fluorescent antibody titres, all but one (*35*) showed significant reductions with chemotherapy. These studies are not strictly comparable as malaria transmission rates undoubtedly were substantially different between the areas concerned. Nevertheless, the consistency of these findings should be emphasized in relation to the broad therapeutic differences between the various antimalarial agents, pharmacological properties, dosage schedules, and levels of transmission and drug resistance.

Clarifications

Certain clarifications must be considered in relation to these conclusions. First, haematological improvement tends to be greater in younger children — an observation that also is supported by data from vector control studies and bed net interventions (*14, 84*). Second, few studies have reported mortality as a rebound effect after chemoprophylaxis, and, as sample sizes in these were small, the power to detect such an effect was low. No clear indication for a rebound effect on mortality was reported after vector control and chemoprophylactic measures in Garki, Nigeria (*85*). Third, evidence on the influence of sustained chemoprophylaxis on the spread of drug-resistant parasites — considered to be one of the main factors holding back its more widespread introduction — is limited (*86*). Fourth, to avoid the risks of drug resistance

developing, shorter periods of targeted prophylaxis with treatment doses are likely to be preferable to low drug concentrations with less well targeted therapy. Drugs that provide long-term suppression, probably due to slow elimination (for example, sulfadoxine–pyrimethamine), would be less likely to induce resistance in combination therapy. The long duration of protection with tafenoquine is due to its long half-life and its efficacy against hepatic stages of the disease (*10*).

Fifth, little evidence supports the view that chemoprophylaxis substantially impairs development of protective immunity beyond infancy. It seems likely that malaria chemoprophylaxis of children does not impair protective immunity to malaria, such that immunological differences are sustained over time. An enhanced immune response to vaccination with polysaccharide antigens has been reported with chloroquine prophylaxis (*87*), but reduced antibody responses to primary immunization with intradermal human diploid-cell rabies vaccine have also been reported (*88*). Sixth, drugs that have gametocidal activity could also disrupt transmission during the rainy season. Reductions in gametocyte prevalence have been reported with chloroquine chemoprophylaxis in children in Burkina Faso (63% reduction) (*89*), Senegal (85% reduction) (*57*) and Nigeria (76.8% reduction) (*69*). Other chemoprophylaxis studies in children have not shown this effect (*9, 25*), and higher gametocyte prevalence is reported to follow failure of treatment of *P. falciparum* malaria with sulfadoxine–pyrimethamine and the combination of chloroquine, sulfadoxine and pyrimethamine (*90*). Differences between drugs may relate to interference with gametocyte production, drug resistance or differences in study design.

Targeted prophylaxis

Where a small proportion of the population is at high risk from severe or fatal malaria and where relatively safe drugs are still effective, a strong case for targeted prophylaxis can be made (*2*). A workshop on chemoprophylaxis in endemic regions also broadly supported targeted use (*91*), except for the use of mass chemoprophylactic programmes (*92*). Concerns related to sustainability, cost-effectiveness, appropriate delivery systems and development of drug resistance have restricted further consideration of this control measure except in pregnant women (*93*). Particularly effective drugs may reduce malaria parasite load, which could reduce the frequency of malaria symptoms. This effect could be analogous to that obtained through use of bednets, which may reduce the symptoms of malaria (by lowering parasite densities) without lowering the incidence of positive smears. Integrated programmes that used bednets and chemoprophylaxis of children were more effective than the use of chemoprophylaxis alone in reducing morbidity in Sierra Leone and the Gambia (*22, 58*). In the Gambia, the addition of chemoprophylaxis had no additional effect on mortality reduction (*22*).

Intermittent treatment

In view of recent evidence that indicates the protective effect of intermittent routine malaria treatment during infancy (*63*) and the substantial heterogeneous evidence for major benefits from regular chemoprophylaxis in children, a higher priority should be given to the implementation of this control measure within integrated malaria control strategies. The case for intermittent routine combination treatment in early childhood for those living under holoendemic conditions should be assessed further. Advantages of intermittent treatment are that concerns about compliance are reduced when drugs are provided on a regular basis and that delivery is facilitated by combining it with immunization or other routine health contacts. Regular chemoprophylaxis by rural village health workers has also proved an effective method of controlling malaria in children under 5 years in the Gambia (*14*), and a reasonable level of compliance was achieved with a single-dose prophylactic (pyrimethamine–dapsone) (*94*). The establishment of a workable and effective system is of paramount importance for securing optimal benefits using malaria chemoprophylaxis.

Conclusion

The eighteenth report of the WHO Expert Committee on Malaria recommended various tactical variants for malaria control (*95*). These included the regular distribution of prophylactic antimalarial drugs to special population groups, such as infants and young children, as well as schoolchildren. Mass prophylaxis in children aged under 5 years was not recommended because of difficulties in achieving continuous suppression and concerns about interference with protective immunity, development of drug resistance and misdirection of scarce resources (*95*). The evidence from this review suggests that the administration of chemoprophylaxis to young children within integrated health programmes may be appropriate, as long as delivery problems can be overcome, a suitable drug is available (because there is no ideal drug for prophylaxis (*96*)), and the effect on immunity is containable. The cost-effectiveness of chemoprophylaxis has also been shown (*97*).

Further research is required to assess intermittent schedules of appropriate drug combinations for young children that provide effective suppression, are safe, easy to deliver and acceptable for recipients, and have few side-effects, especially haemolytic potential (failure of children to participate in one chloroquine chemosuppression programme was related to minor side-effects) (*98*). Large-scale studies over a number of years are needed to establish the place of chemoprophylaxis in the overall antimalarial armamentarium and the influence of this approach on health service utilization in young children, mortality and emergence of multi-drug resistant parasites. Although the benefits of malaria chemoprophylaxis for pregnant women have been well established (*99*), evaluation of its use by adolescent girls before pregnancy should also be considered — as long as it can be safely delivered.

At a certain level of drug resistance, prophylaxis must become ineffective and appropriate strategies will have to be found to protect the drugs now available and those being developed against the emergence and selection of drug resistance. Without this research, we will be unable to determine whether resistance to malaria chemoprophylaxis (or intermittent treatment) develops among children who receive such drugs in a scheduled manner. Through these endeavours, we can support the rights of children to protect themselves against malaria. ■

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Résumé

Analyse des effets de la chimioprophylaxie du paludisme chez l'enfant sur la réponse hématologique, la morbidité et la mortalité

Le présent article examine les données montrant les effets bénéfiques de la chimioprophylaxie du paludisme sur la réponse hématologique, la morbidité, la mortalité, l'utilisation des services de santé, les phénomènes de rebond et l'état immunitaire chez l'enfant. Comme l'anémie peut jouer un grand rôle dans la mortalité chez l'enfant, il importe d'évaluer les données d'essais contrôlés sur la capacité de la chimioprophylaxie à réduire l'anémie chez l'enfant. Une analyse des résultats de tels essais a montré que la chimioprophylaxie du paludisme améliore les taux moyens d'hémoglobine et réduit l'anémie sévère, les accès de paludisme, l'indice plasmodique et l'indice splénique. Une baisse significative des consultations ambulatoires et des hospitalisations a été observée, et de nombreuses données d'études réalisées en Gambie font apparaître une réduction de la mortalité. La chimioprophylaxie chez l'enfant ne semble pas affecter durablement l'immunité antipaludique bien que l'effet rebond puisse être plus marqué chez les sujets ayant reçu une chimioprophylaxie pendant la première enfance. De brèves périodes de prophylaxie bien ciblée sont probablement préférables à un traitement continu. Les preuves de l'efficacité protectrice de la chimioprophylaxie du paludisme chez l'enfant montrent que cette stratégie pourrait être envisagée pour des périodes déterminées dans le cadre de programmes de santé intégrés. Une chimioprophylaxie associée intermittente, administrée en routine dès le plus jeune âge, peut convenir pour les enfants vivant dans des zones d'holoendémie. Des études à grande échelle s'étendant sur plusieurs années sont nécessaires pour répondre à ces questions et déterminer l'impact de cette approche sur l'utilisation des services de santé, la mortalité et l'émergence de parasites chimiorésistants.

Resumen

Análisis de los efectos de la quimioprofilaxis antipalúdica infantil en la respuesta hematológica, la morbilidad y la mortalidad

En este artículo se analiza la evidencia disponible respecto a los efectos beneficiosos de la quimioprofilaxis del paludismo en las respuestas hematológicas, la morbilidad, la mortalidad, la utilización de los servicios de salud y el fenómeno de rebote en relación con la situación inmunitaria en los niños. Dado que la anemia puede contribuir en gran medida a la mortalidad infantil, es importante evaluar los datos aportados por los ensayos controlados sobre el potencial de la quimioprofilaxis para reducir la anemia infantil. En un análisis de los ensayos realizados se hallaron pruebas concluyentes de que la quimioprofilaxis del paludismo mejora los niveles medios de hemoglobina y reduce la anemia grave, las crisis clínicas de paludismo, el índice parasitario y el índice esplénico. Se han logrado reducciones significativas de las consultas ambulatorias y los ingresos hospitalarios, y estudios realizados en Gambia han aportado pruebas sólidas de que la mortalidad disminuye. La administración de quimioprofilaxis a los niños no parece alterar de forma sostenida la inmunidad contra el paludismo, pero los efectos de rebote pueden ser mayores en los niños que reciben profilaxis durante la lactancia. Los periodos breves de profilaxis dirigida son probablemente preferibles a la administración continua de medicamentos. La evidencia respecto a la eficacia protectora de la quimioprofilaxis antipalúdica en los niños muestra que esta estrategia podría formar parte de programas de salud integrales durante determinados periodos. La instauración temprana en la infancia de una terapia combinada sistemática intermitente podría ser una medida idónea para quienes viven en entornos de holoendemicidad. Es necesario emprender estudios en gran escala durante varios años para analizar esta cuestión y el impacto de este enfoque en la utilización de los servicios de salud, la mortalidad y la aparición de parásitos farmacorresistentes.

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Table A. **Malaria chemoprophylaxis studies in children**

Country	First year of study	Study duration (months)	Placebo controlled?	Children			Chemoprophylaxis				Intention-to-treat analysis	Reference
				Age range	No. treated	No. controls	Antimalarial drug	Frequency	Duration	Dose		
Algeria	1951	3.5	No	0–15 years	249	160	Chloroquine	Weekly	15 weeks	100/300 mg	Yes	(*4*)
Angola	1986	4	Yes	5 months–5 years	484	268	Proguanil	Daily[a]	4 months	50 mg	Yes	(*5*)
Burkina Faso	1984	Rainy season	Yes	0–5 years	1005	1112	Chloroquine	Weekly	Rainy season	<1 years: 50 mg base 1–5 years: 100 mg base	Yes	(*6*)
Cameroon	1973	120	No	5–14 years	388	109	Chloroquine	Weekly	120 months	5 mg/kg	Yes	(*7*)
Ethiopia	1988	2.5	Yes	1–14 years	999	998	Chloroquine	Weekly	10 weeks	5 mg base/kg	Yes	(*8*)
Gabon	1997	6	Yes	4–16 years	125	140	Atovaquone–proguanil	Daily[a]	12 weeks	11–20 kg: 62.5/25 mg 21–30 kg: 125/50 mg 31–40 kg: 187/75 mg >40 kg: 250/100 mg	No	(*9*)
	1999	2.5	Yes	12–20 years	86 84 86 86	84	Tafenoquine	Three-day course	77 days	250 mg 125 mg 62.5 mg 31.2 mg	No	(*10*)
Gambia	1951	42	Yes	0–36 months	26	26	Chloroquine	Weekly	42 months	<2 years: 6 mg base/kg >2 years: 150 mg base	No	(*11*)
	1963	7.5	Yes	7–8 months	7	7	Pyrimethamine	Weekly[a]	7.5 months	12.5 mg	Yes	(*12*)
	1968	6	No	6–10 years	26	32	Pyrimethamine–sulfadoxine	Fortnightly	5–6 months	6–10 years: 2 mg/40 mg	No	(*13*)
					26		Pyrimethamine	Weekly		25 mg		
	1982	12	Yes	3 months–5 years	NR[b]	NR	Pyrimethamine–dapsone	Fortnightly	9 months	3–11 months: 6.25/25 mg 1–4 years: 12.5/50mg	No	(*14*)
	1982	24	Yes	3 months–5 years	352[c]	384[c]	Pyrimethamine–dapsone	Fortnightly	24 months	3–11 months: 6.25/25 mg 1–5 years: 12.5/50 mg	Yes	(*15*)
					384[c]		Chlorproguanil	Fortnightly		20 mg		
	1983	48–62	Yes	3 months–5 years	NR	NR	Pyrimethamine–dapsone	Fortnightly	62 months	3–11 months: 6.25/25 mg 1–4 years: 12.5/50 mg	No	(*16*)
	1983	≈30	Yes	3–5 years	48	47	Pyrimethamine–dapsone	Fortnightly	24 months	3–11 months: 6.25/25 mg 1–4 years: 12.50 mg	Yes	(*17*)
	1983	60	Yes	3–59 months	Variable	Variable	Pyrimethamine–dapsone	Fortnightly	2–3 years	3–11 months: 3.13/25 mg 1–5 years: 6.25/50	No	(*18*)
	1983	6	Yes	3 months–5 years	25 28	26 26	Pyrimethamine–dapsone Chlorproguanil	Fortnightly	6 months	3–11 months 6.25/25 mg 3 months –5 years 25 mg	No	(*19*)
	1984	18	Yes	3 months–5 years	22 25	32 32	Pyrimethamine–dapsone Chlorproguanil	Fortnightly	18 months	As for above	No	(*19*)
	1986	12	Yes	3–5 years	52	45	Pyrimethamine–dapsone	Fortnightly	3 years	12.5/50 mg	Yes	(*20*)
	1989	12	Yes	6 months–5 years	952	946	Pyrimethamine–dapsone	Weekly	20 weeks	12.5/50 mg	Yes	(*21, 22*)
Ghana	1953	24	Yes	7 years	88	88	Pyrimethamine–amodiaquine[a]	Weekly	36 weeks	25 mg	Yes	(*23*)
	1955	Three school terms	No	12–20 years	297	248	Chloroquine	Each school term	3 school terms	<84 lb: 300 mg base 84–140 lb: 450 mg >140 lb: 600 mg	Yes	(*23*)
	1959	6	Yes	5–14 years	170	145	Chlorproguanil	Weekly[a]	6 months	20 mg	Yes	(*24*)
Guatemala	1948	24	Yes	0–14 years	240 371	252	Chloroquine Chlorguanide	Weekly or fortnightly	7 months	<2 years: <75 mg 2–5 years: 75 mg 6–11 years: 150 mg ⩾12 years: 300 mg	Yes	(*25*)
Kenya	1952	12	No	School	221	168	Pyrimethamine	Monthly	12 months	37–75 mg	Yes	(*26*)
	1954	5	No	5 months–8 years	23	8	Amodiaquine	Weekly	5 months	100/200 mg	Yes	(*27*)
	1985	5	Yes	7–14 years	78	40	Chlorporguanil	Weekly[a]	20 week	20 mg	No	(*28*)
	1986	6	Yes	8–9 years	40 30 39	37	Chlorproguanil Chlorproguanil Proguanil	Daily[a] Weekly[a] Daily[a]	26 weeks	7.5 mg 50 mg 100 mg	No	(*29*)

Country	First year of study	Study duration (months)	Placebo controlled?	Children			Chemoprophylaxis				Intention-to-treat analysis	Reference
				Age range	No. treated	No. controls	Antimalarial drug	Frequency	Duration	Dose		
	1988	School term	Yes	6–18 years	59	68	Proguanil	Daily[a]	School term	100 mg	No	(*30*)
	1992	4	Yes	9–14 years	79	34	Primaquine	Three doses a week[a]	12 weeks	15 mg base	No	(*31*)
	1993	4	Yes	9–14 years	37		Doxycycline	Daily[a]	11 weeks	50 mg		
					32		Primaquine	Daily[a]	11 weeks	15 mg		
					32		Mefloquine	Weekly[a]	11 weeks	125 mg		
					30		Proguanil–chloroquine	Daily/weekly[a]	11 weeks	200 mg/150 mg base		
Liberia	1953	3	Yes	6–14 years	49	27	Pyrimethamine	Weekly	12 weeks	12.5 mg	Yes	(*32*)
					36		Chloroquine			150 mg base		
					36		Amodiaquine			200 mg		
	1955	8	Yes	5–14 years	60	23	Pyrimethamine	Monthly	8 months	25 mg	Yes	(*33*)
					33		Primaquine	Weekly	12 months	15 mg		
			Yes		32	20	Chloroquine	Monthly	8 months	150 mg base		
			No		45	7	Pyrimethamine–chloroquine	Monthly	6 months	25 mg/150 mg base		
	1976	24	No	2–9 years	64	42	Pyrimethamine	Every 4 weeks	24 months	2 mg/kg	No	(*34*)
					70		Proguanil			1.5 mg/kg		
	1976	36	Yes	2–9 years	90	58	Chloroquine	Monthly	24 months	8–15 mg base/kg	Yes	(*35*)
					70		Proguanil	Monthly	24 months	1–2 mg base/kg		
					64		Pyrimethamine	Monthly	24 months	1.3–2.5 mg base/kg		
	1987	12	Yes	6 months –6 years	158	104	Chloroquine	Every 3 weeks	12 months	5 mg base/kg	No	(*36*)
Malaya	1972	9	Yes	6–12 years	75	38	Pyrimethamine–sulfadoxine[a]	Every 4 weeks	9 months	<2 years: 6.25/125 mg 2–4 years: 12.5/250 mg 5–9 years: 25/500 mg 10–12 years: 50/1000 mg	Yes	(*37*)
					37		Chloroquine	Weekly	9 months	<4 years: 75 mg base 5–9 years: 125 mg base		
Mali	1977	16	Yes	0–9 years	Variable	Variable	Chloroquine Pyrimethamine–sulfalene	Fortnightly	16 months	5 mg base/kg 25/500 mg	No	(*38*)
Morocco	1954	4	No	0–>12 years	76	53	Amodiaquine	Monthly	4 months	10 mg/kg	No	(*39, 40*)
					74		Chloroquine			10 mg/kg		
			No	0–>1 years	66	65	Pyrimethamine	Monthly	4 months	25/50 mg	No	
Central Congo	1949	5	No	0–15 years	33	24	Chloroquine	Weekly	5 months	37–115 mg base	Yes	(*41*)
					36		Proguanil					
	1952	6	No	7–16 years	83	67	Pyrimethamine	Fortnightly	3 months	0.5 mg/kg	Yes	(*42*)
	1953	12	No	0–12 years	179	160	Amodiaquine	Fortnightly	12 months	<1 years: 100 mg 1–5 years: 200 mg 6–12 years: 400 mg	Yes	(*43*)
Mozambique	1985	3,7	Yes	7–14 years	82	26	Chloroquine	Weekly[a]	15 weekly	<30 kg: 150 mg ⩾30 kg: 300 mg	No	(*44*)
		5,5			81	26	Chlorproguanil			<30 kg: 10 mg ⩾30 kg: 20 mg	No	
	1986	24	Yes	7–14 years	66	26	Chlorproguanil	Weekly[a]	17 weeks	As above	No	(*45*)
	1989		Yes	7–12 years	195	197	Pyrimethamine–dapsone	Weekly	12 months	25/100 mg	No	
	1989	5	Yes	7–12 years	83	83	Pyrimethamine–dapsone	Weekly[a]	17 weeks	18–29 kg: 6.25/50 mg ⩾30 kg: 12.5/100 mg	Yes	(*46*)
Nigeria	1953	24	No	5–10 years	119	100	Pyrimethamine	Weekly	24 months	25 mg	Yes	(*47*)
	1966	12	Yes	8–17 years	56	57	Pyrimethamine	Weekly	12 months	25 mg	No	(*48*)
					54		Pyrimethamine–dapsone	Weekly	12 months	12.5/100 mg		
					113		Pyrimethamine–sulphomethoxine	Weekly	12 months	12.5/125 mg or 12.5/250 mg		
	1968?	4.5	No	6–12 years	114	11	Cycloguanil–chloroquine	Single injection	18 weeks	7.3–10.8 mg/kg	No	(*49*)
					35		Chloroquine	Single dose	70 days	300/600 mg		

Country	First year of study	Study duration (months)	Placebo controlled?	Children			Chemoprophylaxis				Intention-to-treat analysis	Reference
				Age range	No. treated	No. controls	Antimalarial drug	Frequency	Duration	Dose		
	1969?	2.3	Yes	5–12 years	36	40	Trimethoprim–sulfamethoxazole	Single dose		8 mg/40 mg/kg 4 mg/20 mg/kg	No	(*50*)
					55		Trimethoprim–sulfamethoxazole			15 mg base/kg		
					52		Chloroquine					
	1976	24	Yes	2 weeks–2 years	198	185	Chloroquine	Weekly	24 months	<1 years 100 mg base 1–2 years 200 mg base	No	(*51, 52, 69*)
					30		Pyrimethamine	Weekly	24 months	<1 years 3.13 mg		
					36		Pyrimethamine	Monthly	12 months	1–2 years 6.25 mg		
	1976	6 years		6 weeks–4 years	226		Pyrimethamine	Weekly	1–5 year	65.25–12 mg	Yes	(*53*)
					235		Chloroquine			5 mg/kg		
	1979	1.5	Yes	1–14 years	16	96	Proguanil	Daily[a]	6 weeks	50 mg	No	(*54*)
Papua New Guinea	1980	5	Yes	7–14 years	125	66	Pyrimethamine–dapsone	Weekly[a]	13 weeks	16–30 kg: 6.25/25 mg ⩾30 kg: 12.5/50 mg	Yes	(*55*)
					127		Amodiaquine			10 mg/kg		
	1977	12	No	0 months–7 years	1304	201	Amodiaquine	Weekly	12 months	0–6 months: 25 mg	Yes	(*56*)
Senegal	1971	12	No	0–60 months	686	804	Chloroquine	Weekly	4 months per year	<1 years: 50 mg base	Yes	(*57*)
	1972	12			375	634				1–3 years: 100 mg base		
	1973	12			144	331				3–5 years: 200 mg base		
Sierra Leone	1992	12	Yes	3 months–6 years	436	450	Pyrimethamine–dapsone	Fortnightly	12 months	3–11 months: 3.125/25 mg 1–4 years: 6.25–50 mg ⩾ 5 years: 12/5/100 mg	Yes	(*58*)
Sri Lanka	1978?	3	Yes	0 months–14 years	27	26	Chloroquine	Monthly	3 months	0–4 years: 75 mg base	No	(*59*)
					23		Chloroquine	Once in 2 months	3 months	5–9 years: 150 mg base		
					29		Chloroquine	Once in 3 months	3 months	10–14 years: 300 mg base		
United Republic of Tanzania	1989?	4.5	Yes	2–9 years	25	25	Proguanil	Daily[a]	13 weeks	100 mg	Yes	(*60*)
					26		Chloroproguanil	2 doses a week		20 mg		
	1993	12	Yes	1–9 years	126	123	Pyrimethamine–dapsone	Weekly	52 weeks	1–4 years: 3.125/25 mg 5–9 years: 6.25/50 mg	No	(*61*)
	1995	23	Yes	2–23 months	421	411	Pyrimethamine–dapsone	Weekly	12 months	1.56/12.5 mg	No	(*62*)
	1999	9	Yes	2–18 months	350	351	Pyrimethamine–sulfadoxine	Three intermittent treatments	10 months	<5 kg: 6.25/125 mg 5–10 kg: 12.5/250 mg >10 kg: 25/500 mg	Yes	(*63*)
Thailand	1986	4	Yes	5–16 years	92	90	Proguanil	Daily	4 months	20 kg: 100 mg	No	(*64*)
					99		Proguanil + sulfisoxazole	Daily + single dose	4 months	100 mg/75 mg/kg		
	1988?	2	Yes	6–15 years	116	101	Proguanil–sulfafurazole	Daily	7.4 weeks	<20 kg: 100 ⩾20 kg: 200 mg	No	(*65*)
		5					Sulfamethoxazole	Daily	11 weeks	25 mg		
Uganda	1974	36	No	0–3 years	36	26	Pyrimethamine	Monthly[a]	36 months	25 mg	Yes	(*66*)
Upper Volta	1961	4	No	0–9 years	148	99	Chloroquine	Fortnightly	3 months	100/200 mg	No	(*67*)
					141		Chloroquine + primaquine + pyrimethamine	Fortnightly		100/200 mg 10/20 mg 10/20 mg		

[a] Treated with therapeutic dose before prophylaxis commenced.
[b] NR, not reported.
[c] Child years at risk.

Table B. **Morbidity effects**

Year of study	Reference	Antimalarial	Percentage reduction				
			Clinical malaria	Fever (>37.5°C)	Parasitaemia	High density parasitaemia[a]	Splenomegaly
1950	(*41*)	Proguanil	NR[b]	NR	97.9[c]	NR	54.7[d]
		Chloroquine	NR	NR	100.0 [c]	NR	50.1[e]
1952	(*4*)	Chloroquine	NR	NR	NR	NR	53.4[c]
1953	(*42*)	Pyrimethamine	NR	NR	76.9 [c]	NR	82.1[e]
	(*25*)	Chloroquine	NR	NR	85.8[c]	NR	9.5[e]
		Chlorguanide	NR	NR	51.1[e]	NR	8.8[e]
1954	(*39,40*)	Amodiaquine	NR	NR	76.8[c]	NR	36.5[c]
		Chloroquine	NR	NR	86.9 [c]	NR	49.1[c]
		Primethamine	NR	NR	100[c]	NR	2.3
	(*32*)	Pyrimethamine	NR	NR	100[c]	NR	19.1[e]
		Chloroquine	NR	NR	100[c]	NR	19.0[e]
		Amodiaquine	NR	NR	100[c]	NR	19.0[e]
1955	(*43*)	Amodiaquine	NR	NR	77.1[c]	NR	79.2 [c]
	(*27*)	Amodiaquine	NR	NR	100[e]	NR	NR
	(*33*)	Pyrimethamine	NR	NR	100[d]	NR	No change
		Primaquine	NR	NR	42.5	NR	NR
		Chloroquine	NR	NR	100	NR	No change
		Pyrimethamine–chloroquine	NR	NR	95.5[d]	NR	No change
	(*23*)	Pyrimethamine	90.5[c]	NR	100[c]	NR	90.5[c]
	(quoted by 23)	Chloroquine	83.3[c]	NR	NR	NR	NR
1956	(*47*)	Pyrimethamine	NR	NR	100[c]	NR	91.9[c]
	(*11*)	Chloroquine	NR	NR	100[c]	NR	100[c]
1958	(*26*)	Pyrimethamine	NR	NR	76.8[c]	NR	NR
1961	(*24*)	Chlorproguanil	NR	NR	90.7[c]	NR	55.5[d]
1962	(*67*)	Chloroquine	NR	NR	100[c]	NR	NR
		Chloroquine, primaquine, pyrimethamine	NR	NR	100[c]	NR	NR
1969	(*48*)	Pyrimethamine	NR	NR	77.9[c]	NR	
		Pyrimethamine–dapsone	NR	NR	82.2[c]	NR	85.5[c, f]
		Pyrimethamine–sulphormethoxine	NR	NR	95.0[c]	NR	
1970	(*49*)	Cycloguanil–chloroquine	NR	0	37[e]	NR	NR
		Chloroquine	NR	11.2	29[e]	NR	NR
	(*13*)	Pyrimethamine–sulfadoxine	NR	NR	68.0[e]	NR	71[e]
		Pyrimethamine	NR	NR	68.0[e]		61[e]
1971	(*50*)	Trimethoprim–sulfamethoxazole	NR	NR	<21 (NS[g])	NR	NR
		Chloroquine	NR	NR	25.7 (NS)	NR	NR
1975	(*37*)	Pyrimethamine–sulfadoxine	NR	NR	86.3[c]	NR	24.3
		Chloroquine	NR	NR	54.0[d]	NR	27.1
1979	(*57*)						
	Study year						
	1971	Chloroquine	NR	NR	88.1[c]	NR	43.4[c]
	1972	Chloroquine	NR	NR	81.8[c]	NR	71.5[c]
	1978	Chloroquine	NR	NR	83.1[c]	NR	88.5[c]
1980	(*59*)	Chloroquine (1 dose)	NR	NR	63.2[e]	NR	NR
		Chloroquine (2 doses)	NR	NR	62.3 (NS)	NR	NR
		Chloroquine (3 doses)	NR	NR	70.1 (NS)	NR	NR
1981	(*38*)	Chloroquine–pyrimethamine–sulfalene	NR	NR	33.7	NR	32.4
	(*56*)	Amodiaquine	NR	NR	93.1[c]	NR	71.1[c]
1984	(*7*)	Chloroquine	NR	NR	88.9	NR	NR
1985	(*52, 69*)	Chloroquine	73.3[c]	NR	78.5[c]	NS	NR
		Pyrimethamine (weekly)	NR	NR	93.7[c]	NR	NR
		Pyrimethamine (monthly)	NR	NR	83.5[c]	NR	NR
1986	(*35*)	Pyrimethamine	NR	50[a]	NR	NR	NR
		Chloroquine	NR	45.7[c, h]	65[c]	NR	45[c]
		Proguanil	NR	29.3[e, h]	NR	NR	NR
1987	(*28*)	Chlorproguanil	NR	NR	34.6[d]	NR	NR
1988	(*6*)	Chloroquine	NR	NR	32 (approximately)[c]	NR	NR
	(*14*)	Pyrimethamine–dapsone	68.7[d]	0.0	69.4[c]	80.0[c]	74.1[c]

Year of study	Reference	Antimalarial	Percentage reduction				
			Clinical malaria	Fever (>37.5°C)	Parasitaemia	High density parasitaemia[a]	Splenomegaly
1988	(*30*)	Proguanil	NR	NR	77.1[c]	NR	NR
	(*17*)	Pyrimethamine–dapsone	NR	34.8	27.4[e]	NR	8.8
	(*5*)	Proguanil	34[c]	24[c]	32[e]	NR	NR
	(*44*)	Chloroquine (Maputo)	NR	NR	24.0	NR	NR
		Chlorproguanil (Maputo)	NR	NR	14.6	NR	NR
		Chlorproguanil (Xai-xai)	NR	NR	70–100 (range)	NR	NR
1989	(*15*)	Dapsone–pyrimethamine	NR	40.6	84.6[c]	NR	60 (approximately)
		Chlorproguanil	NR	–3.1	38.5[c]	NR	60 (approximately)
	(*20*)	Pyrimethamine–dapsone	NR	NR	33.6	NR	42.1
	(*64*)	Proguanil	NR	NR	44.2	NR	NR
		Sulfisoxazole	NR	NR	23.9	NR	NR
		Proguanil–sulfisoxazole	NR	NR	94.9	NR	NR
1990	(*65*)	Proguanil–sulfafurazole	NR	NR	89	NR	NR
		Proguanil–sulfamethoxazole	NR	NR	78	NR	NR
	(*16*)	Pyrimethamine–dapsone	73[e]	NS	83.4[c]	NR	89.6[c]
1991	(*60*)	Chloproguanil	NR	NR	100[c]	NR	NR
		Proguanil	NR	NR	100[c]	NR	NR
1992	(*46*)	Pyrimethamine–dapsone	NR	NR	100[c]	NR	NR
	(*55*)	Pyrimethamine–dapsone	NR	NR	92.1[c]	NR	60.5[e]
		Amodiaquine	NR	NR	70.9[c]	NR	48.9[e]
1993	(*21, 22*)	Pyrimethamine–dapsone	100[e]	83.9	88.5[c]	94.4[c]	62.2[c]
	(*36*)	Chloroquine	S[i]		NR	NR	NR
	(*54*)	Chloroquine	59.1[d, j]	NR	S	NR	NR
		Pyrimethamine	22.9[e, j]	NR	NS	NR	NR
1994	(*45*)	Pyrimethamine–dapsone	87.1[c]	NR	90.7 (wet)[e] 100 (dry)[e]	NR	NR
	(*8*)	Chloroquine	4.2	NR	2.5	NR	3.4
	(*29*)	Chlorproguanil (daily)	NR	NR	55.8[c]	NR	NR
		Chlorproguanil (weekly)	NR	NR	36.5[c]	NR	NR
		Proguanil (weekly)	NR	NR	61.5[c]	NR	NR
1995	(*18*)	Pyrimethamine–dapsone	NR	NR	20.8	NR	42[e]
	(*31*)	Intermittent study					
		Primaquine	58.5[d]	NR	S	NR	NR
		Daily study					
		Primaquine	83[d]	NR	85[d]	NR	NR
		Doxycycline	91[d]	NR	84[d]	NR	NR
		Mefloquine	81[d]	NR	77[d]	NR	NR
		Chloroquine–proguanil	72[d]	NR	54[d]	NR	NR
1997	(*61*)	Pyrimethamine–dapsone					
		At 24 weeks	67[c]	NR	NR	NR	49.1[c]
		At 52 weeks	12	24.2[d]	12.8[e]	6.6	41.7
	(*62*)	Pyrimethamine–dapsone	First or only episode, 60.5[c]	NR	NR	NR	NR
1998	(*9*)	Atovaquone–proguanil	22.5	NR	100[c]	NR	NR
	(*58*)	Pyrimethamine–dapsone	42.0[d]	NR	29.0[d]	NR	8.6[e]
2000	(*10*)	Tafenoquine					
		31.2 mg	NR	NR	0	NR	NR
		62.5 mg	NR	NR	80[e]	NR	NR
		125 mg	NR	NR	93[e]	NR	NR
		250 mg	NR	NR	100[e]	NR	NR
2001	(*63*)	Pyrimethamine–sulfadoxine	First or only episode, 59.3[e]	13[e]	NR	NR	NR

[a] High-density parasitaemia for references *14*, *21* and *22* is ⩾5000 parasites/μl and for reference *52* is 10 parasites or more per high power field.
[b] NR, not reported.
[c] $P<0.001$.
[d] $P<0.01$.
[e] $P<0.05$.
[f] Average reduction for three groups.
[g] NS, not significant.
[h] Reported fever.
[i] S, significant decrease.
[j] Severe malaria morbidity reduction in children receiving maximum prophylactic doses in preceding two months.