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The malaria rebound phenomenon: a literature review

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The malaria rebound phenomenon: a literature review

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Abstract

Background and objectives

The term "rebound malaria" has been used to describe an increase in clinical malaria outcomes after a period of protection due to effective control interventions. The primary objective of this work was to conduct a literature review of studies that specifically evaluated rebound or that presented data on malaria-related outcomes after the malaria interventions were discontinued.

Methods

We defined rebound as a period of increased malaria risk after time-limited protection from malaria (i.e., after chemoprevention, vaccination, vector control), relative to individuals of the same age from the same population who did not receive the intervention. The studies included in this review were identified by searching in academic publications, relevant electronic databases and the grey literature without time frame limitation.

Main results

A total of 50 studies (reported in 67 publications) met the inclusion criteria. Of these, only five drug-based studies reported a significant rebound effect for clinical malaria: three of them after chemoprophylaxis, one after five doses of intermittent preventive treatment in infants and one after three rounds of seasonal malaria chemoprevention.

Conclusions

Some studies have observed a period of increased malaria risk after time-limited protection from malaria, mainly for uncomplicated clinical malaria. Even though a rebound for severe malaria and anaemia has also been found in some studies, those that evaluated the cumulative rate since the beginning of the intervention and during a long follow-up period, found that the overall risk was lower in the intervention group, thus providing a positive "net benefit". Rebound seemed to be associated with interventions that provided more protection and for a longer period of time (e.g. continuous prophylaxis) and/or targeting younger ages, as they interfere more with the development of NAI. There is not enough evidence to conclude that rebound precludes the implementation of malaria control strategies, specially those targeting the most vulnerable populations. However, additional measures might be needed (e.g. improved access to care) after the discontinuation of certain interventions, to mitigate the effect of rebound. Finally, there is a need to define a standardised approach and methodology to assess the rebound phenomenon.

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Abbreviations and acronyms

AQ	Amodiaquine
AS	Artesunate
Bm	Bimonthly
CI	Confidence interval
CP	Chemoprophylaxis
CPG	Chlorproguanil
CR	Cumulative rate
D	Dapsone
DALYs	Disability-adjusted life years
DP	Dihydroartemisinin-piperaquine
GMS	Greater Mekong Subregion
HMM	Home-based management of malaria
HR	Hazard ratio
IPTi	Intermittent preventive treatment in infants
IR	Incidence rate
IRR	Incidence rate ratio
IRS	Indoor residual spraying
ISGlobal	Barcelona Institute for Global Health
ITCs	Insecticide-treated curtains
ITNs	Insecticide-treated nets
m	Monthly
MDA	Mass drug administration
Moz	Mozambique
NAI	Naturally acquired immunity
NR	Not reported
OR	Odds ratio
PE	Protective efficacy
Pf	*Plasmodium falciparum*

PNG	Papua New Guinea
PPY	Per person-year
PQ	Primaquine
PR	Prevalence ratio
Pv	*Plasmodium vivax*
PY	Person-year
PYAR	Person-years-at-risk
RR	Relative risk or Risk ratio (see tables)
Sld	Single low dose
SMC	Seasonal malaria chemoprevention
SP	Sulfadoxine-pyrimethamine
TS	Trimethoprim-sulfamethoxazole
VE	Vaccine efficacy

Background

1.1. Introduction

Children born in an endemic area acquire a natural immunity that, although it is never sterilizing, is quickly developed against death and the severe forms of the disease and progressively protects against non-severe disease and infection. The rate at which the naturally acquired immunity (NAI) is developed is correlated with the transmission intensity (1). In high transmission areas children younger than two years experience the highest incidences of clinical malaria, decreasing rapidly with age, whereas in areas with a lower transmission the age pattern is shifted to older ages. To develop and maintain the level of NAI, continuous exposure to the parasite is needed (what is known as "premunition"), although it is not clear to what level immunity decreases after periods without exposure (2).

Back in 1934, the malariologist Sydney Price James suggested that children in Africa should not be treated for their first malaria attack to enable the development of some immunity. Other malariologists echoed the idea, proposing that in areas of stable malaria transmission, interfering with the established infection-immunity of the population would increase the severity of the clinical manifestations and mortality in older children and adults (3). This debate has continued until recently around the introduction of bednets for malaria control (4). A period of increased malaria risk has indeed been observed following time-limited protective interventions from malaria, relative to individuals of the same age in the same area who did not receive the intervention (5,6). This is known as the "rebound" effect, for which different definitions have been used (7,8).

However, the public health relevance of the rebound effect remains unclear, as it has not been systematically assessed in trials of new tools. Development and policy making on new tools would benefit from a more standardised evaluation of rebound.

The primary objective of this work was to conduct a literature review of studies that specifically evaluated rebound or that presented data on malaria-related outcomes after the malaria interventions were discontinued. We aimed to review the evidence on what happens to the rate of acquisition of NAI (measured through different clinical endpoints, as there is no immune correlate of protection or NAI marker to assess it) in individuals that have been receiving a time-limited malaria control intervention when that intervention is withdrawn, and inform the discussion on how to incorporate the measurement of rebound in the design of studies evaluating new strategies or interventions.

Methods

2.1. Definition of rebound

We defined rebound as a period of increased malaria risk after time-limited protection from malaria (i.e., after chemoprevention, vaccination, vector control), relative to individuals of the same age from the same population who did not receive the intervention.

We did not include studies assessing "age shift", which is a different phenomenon resulting from a permanent reduction in transmission intensity, which leads to a change in the age-pattern towards older children and in the clinical presentation of severe malaria cases. Rebound is also different from malaria resurgence, defined elsewhere as "*an increasing trend in malaria incidence or prevalence following suppression achieved through implementation of control efforts"* (9)), which does not necessarily lead to an increased risk compared to areas not receiving the intervention.

2.2. Eligibility criteria

We included malaria-intervention research that had taken place in malaria-endemic areas, with a control arm or comparison group that did not receive the intervention, regardless of transmission intensity or population age. Studies were included if the follow-up period post-intervention in both the intervention and the comparison arm was >1 month. Randomised controlled trials and non-randomized studies were included, as well as modelling studies. The types of interventions assessed included antimalarial drug-based strategies (i.e., chemoprophylaxis, intermittent preventive treatment in infants (IPTi), seasonal malaria chemoprevention (SMC), mass drug administration (MDA), and chemoprevention in school-aged children), vector control strategies (i.e., insecticide-treated nets (ITNs) and indoor residual spraying (IRS)), the RTS,S vaccine, and other strategies such as combinations of different interventions or cotrimoxazole prophylaxis for HIV-positive patients. For drug-based strategies, we excluded studies that administered one single dose of chemoprevention. We mainly focused on studies that were purposely assessing the presence or absence of a rebound effect after intervention discontinuation, but other studies with follow-up periods post-intervention that met inclusion criteria, were also included. The following outcomes were assessed: mortality, clinical cases, severe malaria, hospital admissions, and anaemia. Immunological and entomological outcomes were not included.

2.3. Information sources and search strategy

The studies included in this review were identified by searching in academic publications, relevant electronic databases and the grey literature without time frame limitation. All studies that met eligibility criteria regardless of language or publication status (published, in progress) were included for consideration in this review.

We searched the following sources on October 14th, 2021: MEDLINE (PubMed), the US National Institute of Health Ongoing Trials Register (clinicaltrials.gov) and the MESA Track database. We also contacted researchers and organisations within the field to identify any relevant published or unpublished studies and reviewed the reference lists of studies identified and included in the review, as well as of systematic reviews on the topic for additional relevant studies.

The following search terms were used: “rebound”, “age-shift”, “intervention withdrawal”, “intervention cessation” and “discontinuation”, combined with the keyword “malaria”.

2.4. Data collection and analysis

The abstract/title screening from the retrieved articles was done using the Rayyan online tool (10). All studies identified as potentially eligible based on the title and abstract screening were retrieved, and the full report was assessed for eligibility.

The data extracted from the studies included both descriptive data and study outcomes. Variables for data extraction included: country, recruitment years, intensity of malaria transmission, study design, intervention(s) assessed, duration of the intervention, age group, lifecycle stage(s) targeted by the intervention, background interventions, duration of follow-up after the intervention was withdrawn, outcome measures and timepoints, efficacy of the intervention, and presence or absence of rebound.

Results

3.1. Study selection

A total of 162 records were identified: 82 via searching databases, and 80 via other methods (e.g., websites, organisations and citation searching). Of these, 97 were assessed for full-text eligibility criteria. After the full-text screening, 67 publications were included in the review.

3.2. Study characteristics

3.2.1. Included studies

A total of 50 studies (reported in 67 publications) met the inclusion criteria (**Table 1**). For drug-based strategies, we identified 12 studies (17 publications), published between 1953 and 2014, assessing the effects of chemoprophylaxis in children of ages ranging from 0 to 14 years. One review analysing the effects of malaria chemoprophylaxis in children (**Prinsen Geerligs 2003** (5)) was also included. Eight studies (11 publications) were included for IPTi, published between 2001 and 2012. In addition, one pooled analysis of six IPTi randomised controlled trials was identified (**Aponte 2009** (11)). Six randomised controlled trials (eight publications) assessing the effect of SMC in children under 5 or 10 years of age were included, published between 2006 and 2015. Lastly, we included three relevant MDA trials (six publications), published between 2017 and 2021, four of them part of a multisite trial conducted in Southeast Asia. For vector control interventions, we only identified one study that met the inclusion criteria, **Okullo 2017** (12), which assessed the effect of IRS cessation in Uganda. The long-term effects of the RTS,S/AS01 or RTS,S/AS02A vaccine were assessed in four of the included studies (eight publications), published between 2011 and 2019. The possibility of a rebound/resurgence effect was assessed in one study evaluating the impact of combining vector control and chemoprophylactic measures: The Garki project in Nigeria (**Molineaux 1980** (3)) and the possibility of rebound after cotrimoxazole discontinuation was assessed in one study (**Homsy 2014** (13)). Seven modelling studies published between 1999 and 2021 were included and we also identified four relevant ongoing studies and one protocol (see Ongoing studies).

Table 1. Included studies

Author and year of publication	Country	Reference	Author and year of publication	Country	Reference
Chemoprophylaxis					
Dobrovolny 1953	Guatemala	(14)	**Saarinen 1988**	Angola	(15)
Archibald 1956	Nigeria	(16)	**Menéndez 1997** **Aponte 2007**	Tanzania	(17) (18)
Bradley-Moore 1985	Nigeria	(19)	**Hogh 1994**	Mozambique	(20)

Oyediran 1993	Nigeria	(21)	**Guinovart 2012**	Mozambique	(22)
Björkman 1986	Liberia	(23)	**Bigira 2014**	Uganda	(24)
Greenwood 1988	The Gambia	(25)	**Kamya 2014**	Uganda	(26)
Menon 1990 **Greenwood 1995**	The Gambia	(27) (28)	**Prinsen Geerligs 2003**	Review	(5)
Otoo 1988 **Otoo 1989**	The Gambia	(29) (30)			
Intermittent preventive treatment in infants (IPTi)					
Schellenberg 2001 **Schellenberg 2005**	Tanzania	(31) (32)	**Grobusch 2007** **Grobusch 2009**	Gabon	(33) (34)
Chandramohan 2005	Ghana	(35)	**Odhiambo 2010**	Kenya	(36)
Kobbe 2007 **Kobbe 2011**	Ghana	(37) (38)	**Senn 2012**	Papua New Guinea	(39)
Mockenhaupt 2007	Ghana	(40)	**Aponte 2009**	Pooled analysis	(11)
Macete 2006	Mozambique	(41)			
Seasonal Malaria Chemoprevention (SMC)					
Cissé 2006	Senegal	(42)	**Kweku 2008**	Ghana	(43)
Dicko 2008	Mali	(44)	**Tagbor 2011**	Ghana	(45)
Dicko 2011 **Dicko 2011b**	Mali	(46) (47)	**Konaté 2011** **Konaté 2011b**	Burkina Faso	(48) (49)
Mass Drug Administration (MDA)					
Landier 2017	Myanmar	(50)	**von Seidlein 2019**	Vietnam	(51)
Pongvongsa 2018	Laos	(52)	**McLean 2021**	Myanmar	(53)
Tripura 2018	Cambodia	(54)	**Morris 2018**	Tanzania	(55)

Indoor Residual Spraying (IRS)					
Okullo 2017	Uganda	(12)			
RTS,S/AS01 or RTS,S/AS02A					
RTS,S Clinical Trials Partnership 2011-2015	Burkina Faso Gabon Ghana Kenya Malawi Mozambique Tanzania	(56–59)	**Olotu 2013** **Olotu 2016**	Kenya	(60)
Sacarlal 2009	Mozambique	(61)	**Tinto 2019**	Tanzania Kenya Burkina Faso	(62)
Other strategies					
Molineaux 1980	Nigeria	(3)	**Homsy 2014**	Uganda	(13)
Modelling studies					
Coleman 1999		(63)	**Águas 2009**		(64)
Gurarie 2007		(65)	**Okell 2011**		(66)
Ross 2008		(67)	**Sallah 2021**	Senegal	(68)
Gosling 2008		(69)			

3.2.2. Excluded studies

30 articles were excluded after full-text screening due to the following reasons: ineligible outcome (n=4), ineligible intervention (n=3), ineligible follow-up period (n=7), uncontrolled study (n=8), ineligible comparison arm (n=1), cross-referenced article (n=6), or because the full report could not be retrieved and no abstract was available (n=1).

None of the ITN trials identified through our search stopped the ITN use, distribution or re-treatment of the nets after the initial intervention periods in the intervention communities, and most of them provided

the control communities with nets when the trials ended. Hence, these studies did not meet our inclusion criteria and were excluded. Nevertheless, a short summary of these trials can be found in the Additional Studies section of this report (see Insecticide-treated nets).

3.3. Community-level versus individual-level rebound

The term "rebound malaria" has been used to describe an increase in clinical malaria outcomes after a period of protection due to effective control interventions. However, this phenomenon can take place at the community level when an intervention is withdrawn (e.g. IRS), or can happen at the individual level when an intervention is no longer provided to children as they grow older and are no longer eligible to receive that intervention (e.g., SMC or IPTi). In this review, most of the included studies focused on the latter, which we have defined as a period of increased malaria risk after time-limited protection from malaria, relative to individuals of the same age in the same area who did not receive the intervention.

3.4. Results by intervention

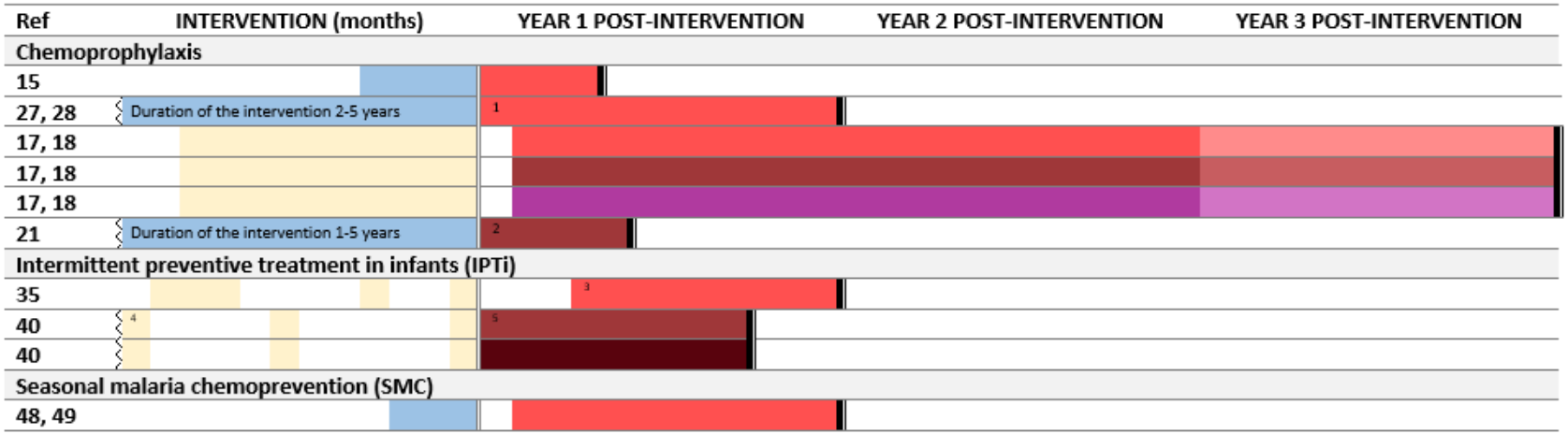
3.4.1. Drug-based strategies

Overall, five drug-based studies reported a statistically significant rebound effect for **clinical malaria**: three of them after chemoprophylaxis discontinuation, one after IPTi and one after three rounds of SMC (**Figure 1**). For chemoprophylaxis, the duration of the interventions implemented ranged between four months to five years, and the follow-up periods during which a rebound in the incidence of clinical malaria effect was observed ranged between four months and three years post-intervention (**Saarinen 1988** (5,15), **Menon 1990** (27)**/Greenwood 1995** (28) and **Menéndez 1997** (17)**/Aponte 2007** (18)). For IPTi, a statistically significant rebound in the incidence of high-density clinical malaria (parasitaemia >5000 parasites/µL) was observed during the year after the intervention in **Chandramohan 2005** (70). During the year after SMC was administered, a statistically significant rebound in the incidence of clinical malaria was observed in one study in Burkina Faso (**Konaté 2011** (48), **Konaté 2011b** (49)).

Three studies reported a significant rebound in **severe malaria**. Two chemoprophylaxis studies found significantly higher incidence of severe malaria in the chemoprophylaxis group during months 1-4 post-intervention (**Oyediran 1993** (5,21)) and during the three years after the intervention (**Aponte 2007** (18)). However, the latter found that cumulative rates since the beginning of the intervention were slightly lower (but not statistically significant) in the intervention group. One IPTi study assessed the incidence of severe malaria during follow-up (**Mockenhaupt 2007** (40)) and found a higher incidence at 1-9 months

post-intervention, which was statistically significant for the first or only episode but not when accounting for all episodes. Two of these studies also found a significant rebound in **severe malarial anaemia.** In the IPTi study, a statistically significant higher incidence of severe malarial anaemia during the period from 1 to 9 months post-intervention was observed among the children that received IPTi (**Mockenhaupt 2007** (40)). One chemoprophylaxis study (**Menéndez 1997** (17)**/Aponte 2007** (18)) found a significant rebound effect for severe anaemia during the three years after chemoprophylaxis, but cumulative rates since the beginning of the intervention were also slightly lower (not statistically significant) in the intervention group (18).

Figure 1. Drug-based studies that found statistically significant rebound in clinical malaria, severe malaria, severe anaemia and/or severe malarial anaemia.



15	Saarinen 1988, Angola
27, 28	Menon 1990, Greenwood 1995, The Gambia
17, 18	Menéndez 1997, Aponte 2007, Tanzania
21	Oyediran 1993, Nigeria
35	Chandramohan 2005, Ghana
40	Mockenhaupt 2007, Ghana
48, 49	Konaté 2011, Konaté 2011b, Burkina Faso

Outcome for which rebound was observed during the follow up period after the intervention was discontinued:	
Clinical malaria	End of follow-up
Severe malaria	Intervention or follow-up longer than shown in figure
Severe anaemia	
Severe malarial anaemia	
Children under 5	
Infants under 1	

[1] Rebound only statistically significant in children who had received the intervention for 5 years, but no difference observed in the children who had received the intervention for 1-4 years.
[2] Only in the group of children treated with chloroquine.
[3] Significant for parasite densities ≥5000 parasites/µL.
[4] IPTi administered at 3, 9 and 15 months of age.
[5] Significant for first or only episode, but not significant for all episodes.

3.4.1.1. Chemoprophylaxis

12 relevant studies (18 publications) assessing the impact of chemoprophylaxis in children were included (**Table 2**). Different drugs (or drug combinations), doses and duration of chemoprophylaxis were tested in children whose ages ranged from 0 to 14 years. Weekly chloroquine or biweekly chlorguanide during seven months and a half was administered to children 0-14 years of age in Guatemala in 1953 (**Dobrovolny 1953** (14)), weekly chloroquine during one or two years was administered to children 0-2 years of age in Nigeria between 1976 and 1979 (**Bradley-Moore 1985** (19)), and **Saarinen 1988** (15) administered daily proguanil to Namibian refugee children aged 5-59 months in Angola for four months. Children aged 2-9 years received monthly chemoprophylaxis with chloroquine, pyrimethamine or chlorproguanil for two years in Liberia (**Björkman 1986** (23)). Between 1953 and 1955, children aged 5-10 years in Nigeria received weekly pyrimethamine for two years and presumptive treatment with amodiaquine at the end of the intervention period (**Archibald 1956** (16)) and between 1976 and 1982, children 6 weeks to 4 years of age received weekly chloroquine or pyrimethamine for periods ranging between one and five years in Nigeria (**Oyediran 1993** (21)). The drug combination pyrimethamine-dapsone was tested in five studies. In The Gambia, children aged 3-59 months received the drugs fortnightly for nine months (**Greenwood 1988** (25)) or for two to five years (**Menon 1990** (27), **Greenwood 1995** (28)) and in Tanzania, children 2-12 months received the drugs weekly for 10 months (**Menéndez 1997** (17), **Aponte 2007** (18)). In the Greenwood 1995 study, once the trial was terminated in 1988, the antimalarial drugs were provided to village health workers until 1991 in case they wished to continue administering chemoprophylaxis to children under 5 years of age. Even though no formal record of the number of doses administered was kept, drug consumption indicated that overall coverage was low (28). Fortnightly chemoprophylaxis for two years with pyrimethamine-dapsone was also tested in children 3-5 years of age in The Gambia (**Otoo 1988** (29), **Otoo 1989** (30)) and weekly administration to children aged 7-12 years was implemented in Mozambique for 12 months (**Hogh 1994** (20)). Also in Mozambique, **Guinovart 2012** (22) administered monthly sulfadoxine-pyrimethamine and artesunate to children from 2.5 to 4.5 months of age or from 5.5 to 9.5 months in 2005. Two randomised controlled trials that evaluated antimalarial chemopreventive regimens in HIV-unexposed and HIV-exposed children tested monthly sulfadoxine-pyrimethamine, monthly dihydroartemisinin-piperaquine, or daily trimethoprim-sulfamethoxazole for 18 months in children from 6-24 months of age in Uganda (**Bigira 2014** (24), **Kamya 2014** (26)). The follow-up periods after the discontinuation of the chemoprophylaxis in the included studies ranged from three months to seven years. One review analysing the effects of malaria chemoprophylaxis in children (**Prinsen Geerligs 2003** (5)) was also included.

These studies suggest that chemoprophylaxis does not result in a sustained impairment of NAI, although rebound effects seemed to be more frequent in children who received the intervention during infancy. Despite differences in study design, antimalarial drug administered, duration and frequency of prophylaxis, and duration of follow-up after intervention withdrawal, only three studies showed a significant rebound effect for **clinical malaria** after the intervention (**Saarinen 1988** (5,15), **Menon 1990** (27)/**Greenwood 1995** (28) and **Menéndez 1997** (17)/**Aponte 2007** (18)). Despite this, the cumulative rates of clinical malaria since the beginning of the intervention in Aponte et al. (18) were slightly higher in the intervention group, but this difference was not statistically significant (**Table 3**). Two studies found significantly higher incidences of **severe malaria** in the chemoprophylaxis group than in the control group (**Oyediran 1993** (5,21), **Aponte 2007** (18)) (**Table 4**), but the latter found that cumulative rates were slightly lower in the intervention group. Similarly, one study (**Menéndez 1997** (17)**/Aponte 2007** (18)) found a significant rebound effect for severe anaemia after chemoprophylaxis (**Table 5**), but cumulative rates were slightly lower in the intervention group (18). No significant rebound effect was found in any of the studies for **parasite prevalence** (**Table 6**). Likewise, no evidence for a significant rebound in **mortality** was found in the studies assessed (**Table 7**). One study found higher incidence of **hospital admissions** in the group that received sulfadoxine-pyrimethamine as compared to the non-treated group (**Bigira 2014** (24), **Table 8**).

Table 2. Characteristics of chemoprophylaxis studies included

Study	Location	Year(s)	Age group	Drug	Frequency of intervention	Duration of intervention	Duration of follow-up post-interv.	Outcomes reported
Dobrovolny 1953[1]	Guatemala	1948 - 1949	Children 0-14 years	Chloroquine or chlorguanide	Weekly or biweekly	7.5 months	3 months	• Prevalence of infection
Archibald 1956	Nigeria	1953 - 1955	Children 5-10 years	Pyrimethamine[2]	Weekly	2 years	3 months	• Prevalence of infection
Bradley-Moore 1985	Nigeria	1976 - 1979	Children 0-2 years	Chloroquine	Weekly	1 or 2 years	6 months	• Incidence of clinical malaria • All-cause mortality
Björkman 1986	Liberia	1976 - 1979	Children 2-9 years	Chloroquine, pyrimethamine or chlorproguanil	Monthly	2 years	12 months	• Prevalence of infection
Greenwood 1988	The Gambia	1982 - 1985	Children 3-59 months	Pyrimethamine-dapsone	Fortnightly	9 months	12 months	• Incidence of clinical malaria • All-cause mortality • Malaria-associated mortality
Menon 1990 Greenwood 1995	The Gambia	1983 - 1989	Children 3-59 months	Pyrimethamine-dapsone	Fortnightly	2-5 years	2-7 years	• Incidence of clinical malaria • Prevalence of infection • All-cause mortality
Saarinen	Angola	1986	Children 5-59	Proguanil	Daily	4 months	4 months	• Incidence of clinical malaria

[1] We were not able to retrieve the full-text. Data as reported in the publically-available abstract and in Prinsen Geerlings, 2003 (5).

[2] Presumptive treatment with amodiaquine at the end of the intervention period.

1988[1]			months					
Otoo 1988 Otoo 1989	The Gambia	1983 - 1985	Children 3-5 years	Pyrimethamine-dapsone	Fortnightly	2 years	6 months 12 months	‣ Incidence of clinical malaria ‣ Prevalence of infection
Oyediran 1993[1]	Nigeria	1976-1982	Children 6 weeks-4 years	Chloroquine or pyrimethamine	Weekly	1-5 years	5 months	‣ Incidence of severe malaria
Hogh 1994	Moz	1989-1991	Children 7-12 years	Pyrimethamine-dapsone	Weekly	12 months	6 months	‣ Prevalence of infection
Menéndez 1997 Aponte 2007	Tanzania	1995-1999	Children 2-12 months	Pyrimethamine-dapsone	Weekly	10 months	12 months 3 years	‣ Incidence of clinical malaria ‣ Incidence of severe malaria ‣ Incidence of severe anaemia ‣ All-cause mortality
Guinovart 2012	Moz	2005-2009	Children 2.5-4.5 months *(late exposure group)* or 5.5-9.5 months *(early exposure group)*	SP+AS	Monthly	3 or 5 months	14 months	‣ Incidence of clinical malaria ‣ Incidence of anaemia ‣ Prevalence of infection ‣ All-cause mortality ‣ Incidence of all-cause hospital admissions
Bigira 2014	Uganda	2010-2013	Children 6-24 months	SP, TS or DP	Monthly (SP and DP), daily (TS)	18 months	12 months	‣ Incidence of clinical malaria ‣ Incidence of severe malaria ‣ All-cause mortality ‣ Incidence of all-cause hospital admissions
Kamya 2014	Uganda	2010-2011	Children 6-24 months HIV-exposed, uninfected	SP, TS or DP	Monthly (SP and DP), daily (TS)	18 months	12 months	‣ Incidence of clinical malaria ‣ Incidence of severe malaria ‣ All-cause mortality ‣ Incidence of all-cause hospital admissions

AS: artesunate; DP: dihydroartemisinin-piperaquine; Moz: Mozambique; SP: sulfadoxine- pyrimethamine; TS: trimethoprim- sulfamethoxazole.

Incidence of clinical malaria

Incidence of clinical malaria after chemoprophylaxis was stopped was assessed in nine studies (**Table 3**). A rebound effect in the incidence of clinical malaria was observed among Namibian refugees in Angola four months after chemoprophylaxis was stopped (**Saarinen 1988** (5,15)). In The Gambia, the attacks of fever with parasitaemia during the year after chemoprophylaxis with pyrimethamine-dapsone was stopped were significantly higher among the children who had received the intervention for five years (from 3 months to 5 years of age) than among the children who had received placebo (p=0.02). However, little difference was observed in the children who had received the intervention for 1-4 years (**Menon 1990** (27), **Greenwood 1995** (28)), providing some evidence for a rebound of clinical malaria among the group of children who received the intervention for a longer period. According to the authors, a plausible explanation for this modest rebound in clinical cases could be the fact that children in the intervention arm still experienced a malaria infection every once in a while due to variable drug compliance during the study (at the age of five years, overall malaria antibody levels were similar in children who had received chemoprophylaxis and children who had received placebo (30)), enabling them to develop a certain level of immunity (28). A clinical malaria rebound during the year after the intervention was stopped was also observed in a trial in Tanzania, where children who had received pyrimethamine-dapsone during the first year of life experienced more episodes of clinical malaria when compared to the group receiving placebo (incidence rate ratio for first or only malaria episode was 1.8, 95% CI 1.3-2.6, p<0.001 and incidence rate ratio for all episodes was 1.8, 95% CI 1.3-2.5, p<0.001) (**Menéndez 1997** (17)). When the children were followed-up until 4 years of age (three years post-intervention), the incidence of clinical malaria after chemoprophylaxis was higher in the intervention group than in the control group, but the cumulative rates since the beginning of the intervention, even though they were still a little higher in the treated group, were not statistically significant in terms of differences (3.22 vs 3.02 episodes, cumulative rate difference 0.20, 95% CI -0.21 to 0.59) (**Aponte 2007** (18)). In Mozambique, the two groups of children who received monthly chemoprophylaxis from 2.5 to 4.5 months of age or from 5.5 to 9.5 months of age experienced a higher incidence of clinical malaria during the second year of life than the control group, but the difference was not statistically significant (although the study was underpowered, as the malaria transmission was lower than expected) (**Guinovart 2012** (22)). A non-statistically significant higher incidence of clinical malaria was also observed in Uganda (**Bigira 2014** (24)).

Table 3. Chemoprophylaxis studies evaluating incidence of clinical malaria

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Bradley-Moore 1985	Passive case detection	1-6 months	Data not shown	No
Saarinen 1988[3]	NR	1-4 months	RR 1.30 (95% CI 1.07-1.57)	**Yes**
Greenwood 1988	Active case detection	1-12 months	4.8/1000 (2/417) vs 8.5/1000 (5/585)	No
Menon 1990 Greenwood 1995	Active case detection	1-12 months	*Children who had received the intervention for 1-4 years:* 212 vs 206 attacks/1000 *Children who had received the intervention for 5 years (from 3 months to 5 years of age):* Attacks of fever + parasitaemia more frequent in the intervention group (p=0.02)	Not significant **Yes**
Otoo 1988 Otoo 1989[4]	Active case detection	1-6 months 1-12 months	4/48 vs 5/47 No increase observed in the intervention arm	No
Menéndez 1997	Passive case detection and cross-sectional surveys	2-12 months	*First or only episode:* IRR 1.8 (95% CI 1.3-2.6), p<0.001 *All episodes:* IRR 1.8 (95% CI 1.3-2.5), p<0.001	**Yes**
Aponte 2007	Passive case detection	2 month-3 years 0-3 years[5]	0.99 vs 0.72 events/PYAR IRR 1.38 (95% CI 1.21-1.59)[6] CR 3.22 vs 3.02 episodes[7] CR difference 0.20 (95% CI -0.21-0.59)	**Yes** Not significant
Guinovart 2012	Passive case detection and cross-sectional surveys	2.5-14 months	*First or only episode, >0 parasites/µL:* 0.50 *(late exposure: CP 2-5-4.5 months of age)*, 0.51 *(early exposure: CP 5.5-9.5 months of age)* vs 0.35 episodes/PYAR, p=0.379 HR *(late exposure vs control)* 1.38 (95%	Not significant

[3] We were not able to retrieve the full-text. Data as reported in the publically-available abstract and in Prinsen Geerlings, 2003 (5).

[4] We were not able to retrieve the full-text. Data as reported in the publically-available abstract.

[5] Includes intervention period.

[6] IRR and CI calculated by the authors of this review.

[7] Cumulative rate since the beginning of the intervention.

			CI 0.83-2.28), p= 0.642 HR *(early exposure vs control)* 1.35 (95% CI 0.81-2.24), p=0.743 HR *(early vs late exposure)* 0.98 (95% CI 0.61-1.59), p=1 *First or only episode, >15 000 parasites/µL:* 0.24 *(late exposure)*, 0.38 *(early exposure)* vs 0.24 episodes PYAR, p=0.244 HR *(late exposure vs control)* 0.92 (95% CI 0.49-1.71), p=1.0 HR *(early exposure vs control)* 1.47 (95% CI 0.82-2.62), p=0.581 HR *(early vs late exposure)* 1.60 (95% CI 0.89-2.89), p=0.359	No or not significant
Bigira 2014	Monthly routine evaluations	1-12 months	All episodes: *SP:* 11.98, *TS:* 10.90, *DP:* 10.77 vs 10.85 episodes/PYAR	Not significant
Kamya 2014	Monthly routine evaluations	1-12 months	*All episodes:* *SP:* 6.75, *TS:* 8.13, *DP:* 6.78 vs 9.08 episodes/PYAR	No

*Month/year 1 is considered the first month post-intervention; ^Adjusted measures when available; CP: chemoprophylaxis; CR: cumulative rate; DP: dihydroartemisinin-piperaquine; HR: hazard ratio; IRR: incidence rate ratio; NR: not reported; PYAR: person-years-at-risk; RR: relative risk; SP: sulfadoxine-pyrimethamine; TS: trimethoprim- sulfamethoxazole.

Incidence of severe malaria

The risk of severe malaria after chemoprophylaxis withdrawal was evaluated in four studies (**Table 4**). In the five months after intervention cessation, significantly more episodes of severe morbidity were recorded in the group treated with chloroquine when compared to the control group in Nigeria (**Oyediran 1993** (21)), but a similar trend in the children that were administered pyrimethamine was not statistically significant (clinical malaria relative risk 3.50, 95% CI 1.17-10.48 for chloroquine and relative risk 1.77, 95% CI 0.54-5.79 for pyrimethamine) (5). It was observed that most of the episodes of severe morbidity in the control group occurred below the age of 4 years, whereas severe morbidity kept occurring at older ages in the children who had received chemoprophylaxis. This difference in the age pattern was statistically significant for the chloroquine group when compared to the control group (21). In Tanzania, in the three years following a chemoprophylaxis trial in children aged 2-12 months, a rebound in the risk of severe malaria was seen in the intervention group after discontinuing chemoprophylaxis, but it decreased over time. By the end of the follow-up period, three years after the intervention, the cumulative rate of severe malaria since the beginning of the intervention was lower in the children who had received

chemoprophylaxis during the first year of life (cumulative rate 0.47 vs 0.59 events, cumulative rate difference -0.12, 95% CI -0.27-0.03 (**Aponte 2007** (18)). No evidence of rebound during the year after the intervention was observed in two chemoprophylaxis trials in Uganda (**Bigira 2014** (24)**, Kamya 2014** (26)).

Table 4. Chemoprophylaxis studies evaluating incidence of severe malaria

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Oyediran 1993[8]	NR	1-5 months	*Chloroquine:* RR 3.50 (95% CI 1.17-10.48) *Pyrimethamine:* RR 1.77 (95% CI 0.54-5.79)	**Yes, for chloro-quine**
Aponte 2007	Passive case detection	2 months-3 years 0-3 years[9]	0.15 vs 0.10 events/PYAR IRR 1.54 (95% CI 1.07-2.2)[10] CR 0.47 vs 0.59 episodes[11] CR difference -0.12 (95% CI -0.27-0.03)	**Yes** No
Bigira 2014♦	Monthly routine evaluations	1-12 months	*All episodes:* *SP:* 0.132, *TS:* 0.046, *DP:* 0 vs 0.046 episodes/PYAR	No
Kamya 2014♦	Monthly routine evaluations	1-12 months	*All episodes:* *SP:* 0.147, *TS:* 0.116, *DP:* 0.044 vs 0.161 episodes/PYAR	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; ♦: severe malaria or danger signs; CR: cumulative rate; DP: dihydroartemisinin-piperaquine; IRR: incidence rate ratio; NR: not reported; PYAR: person-years-at-risk; RR: risk ratio; SP: sulfadoxine-pyrimethamine; TS: trimethoprim-sulfamethoxazole.

<u>Incidence of moderate or severe anaemia</u>

Two studies assessed the risk of severe anaemia after chemoprophylaxis discontinuation (**Table 5**). A higher rate of severe anaemia was observed after weekly chemoprophylaxis with pyrimethamine-dapsone given to children 2-12 months of age in Tanzania (incidence rate ratio during the year post-intervention 2.2, 95% CI 1.3-2.7, p<0.01) (**Menéndez 1997** (17)), but by the third year post-intervention the magnitude of this rebound effect was relatively small (**Aponte 2007** (18)). By the age of 4 years (three years post-intervention), the children that received chemoprophylaxis had a lower risk of severe anaemia

[8] We were not able to retrieve the full-text. Data as reported in the publically-available abstract and in Prinsen Geerlings, 2003 (5).

[9] Includes intervention period.

[10] IRR and CI calculated by the authors of this review.

[11] Cumulative Rate since the beginning of the intervention.

than control children (cumulative rate in the intervention group since the beginning of the intervention 0.93 (95% CI 0.79 to 0.97) vs 1.12 events (95% CI 0.97 to 1.28) in the control group) (**Aponte 2007** (18)). In a trial in Mozambique that administered chemoprophylaxis with sulfadoxine-pyrimethamine plus artesunate to children aged 2.5-4.5 months (late exposure group) or 5.5-9.5 months (early exposure group), the incidence of moderate or severe anaemia over the period 2.5-14 months post-intervention was slightly higher in the late exposure group than in the control group (0.15 vs 0.14 episodes per year at risk) and lower in the early exposure group when compared to the control group (0.12 vs 0.14 episodes per year at risk), but these differences were not statistically significant (p=0.848) (**Guinovart 2012** (22)).

Table 5. Chemoprophylaxis studies evaluating incidence of severe anaemia

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Menéndez 1997	Passive case detection and cross-sectional surveys	2-12 months	IRR 2.2 (95% CI 1.3-2.7), p<0.01	**Yes**
Aponte 2007	Hospital-based passive case detection	2 months-3 years	0.24 vs 0.15 events/PYAR IRR 1.59 (95% CI 1.19-2.14)[13]	**Yes**
		0-3 years[12]	CR 0.93 vs 1.12 events[14] CR difference -0.19 (95% CI -0.40-0.01)	No
Guinovart 2012⧫	Passive case detection and cross-sectional surveys	2.5-14 months	0.15 *(late exposure: CP 2.5-4.5 months of age)*, 0.12 *(early exposure: CP 5.5 to 9.5 months of age)* vs 0.14 episodes/ PYAR, p=0.848 HR *(late exposure vs control)* 1.16 (95% CI 0.52-2.59), p=1 HR *(early exposure vs control)* 0.91 (95% CI 0.40-2.11), p=1 HR *(early vs late exposure)* 0.79 (95% CI 0.34-1.82), p=1	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; ⧫: moderate or severe anaemia; CP: chemoprophylaxis; CR: cumulative rate; HR: hazard ratio; IRR: incidence rate ratio; PYAR: person-years-at-risk.

<u>Prevalence of infection</u>

[12] Includes intervention period.

[13] IRR and CI calculated by the authors of this review.

[14] Cumulative Rate since the beginning of the intervention.

No evidence of rebound was observed in the seven studies that assessed parasite prevalence at different time points after the intervention (**Table 6**).

Table 6. Chemoprophylaxis studies evaluating prevalence of infection

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Dobrovolny 1953[15]	NR	3 months	*Chloroquine:* RR 0.41 (95% CI 0.26-0.64) *Chlorguanide:* RR 0.85 (95% CI 0.63-1.15)	No
Archibald 1956	Monthly follow-up visits	1 month 2 months 3 months	24% vs 14.8% 16.8% vs 17.3% 25.7% vs 33.8% (p-values not shown)	No or not significant
Björkman 1986	Cross-sectional surveys	6 months 12 months	Parasite rates comparable in all groups	No
Menon 1990 Greenwood 1995	Cross-sectional surveys	12 months	*2 years of CP♣:* 61% vs 84%, p<0.05 *3 years of CP:* 33% vs 14% *4 years of CP:* 32% vs 10% *5 years of CP:* 37% vs 23%	No or not significant
Otoo 1988	Cross-sectional surveys	6 months	61% vs 84% (95% CI -33-(-13))	No
Hogh 1994	Cross-sectional surveys	6 months	Data not shown	No
Guinovart 2012	Cross-sectional surveys	14 months	13.04% (*late exposure: CP 2.5-4.5 months of age*), 13.95% (*early exposure: CP 5.5-9.5 months of age*) vs 7.45%, p=0.302	Not significant

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; ♣: number of years for which medication had been received before it was stopped at 5 years of age; CP: chemoprophylaxis; NR: not reported; RR: relative risk.

Mortality

None of the five studies that recorded the number of deaths after the intervention was stopped found a significant rebound in mortality after chemoprophylaxis (**Table 7**). When accounting for all the deaths that occurred during the entire follow-up period of a trial administering monthly pyrimethamine-dapsone to children aged 2-12 months in Tanzania (17), the difference in deaths between the chemoprophylaxis and control group was not statistically significant (19 versus 13 deaths, p=0.512). However, a higher (but non-

[15] We were not able to retrieve the full-text. Data as reported in the publically-available abstract and in Prinsen Geerlings, 2003 (5).

statistically significant) number of deaths was found in children aged 2-4 years that had received the intervention when compared to the control group (10 vs three deaths, p=0.088) (**Aponte 2007** (18)). In The Gambia, a similar probability of dying during the two years of follow-up post-intervention was found for children who had entered the trial when they were aged 3-16 months and who received medication or placebo for at least 4 rainy seasons (4 vs 5 deaths, risk ratio 0.80, 95% CI 0.22-2.95). Similarly, when accounting for all children who had entered the trial at the beginning regardless of age, and that received prophylaxis until they were aged 5 years (duration of prophylaxis varied depending on how old they were when they entered the trial), it was observed that the probability of dying during the four years post-intervention (ages 5 to 9 years) was the same for both groups (probability of dying 0.008). However, the probability of dying during the year after chemoprophylaxis (between the ages of 5 and 6 years) was higher in the intervention group than in the control (10 vs 4 deaths, risk ratio 2.43, 95% CI 0.77-7.68, p=0.12), but this difference was not statistically significant. A similar pattern was observed when accounting for all the children (children who were enrolled at the beginning of the trial or later on (duration of the follow-up varied depending on recruitment date): the probability of dying during the five years post-intervention (ages 5-10 years) was lower - but not statistically significant - in the intervention group (probability of dying 0.040 vs 0.052, rate ratio 0.87, 95% CI 0.50-1.60, p=0.37), but the probability of dying during the year after chemoprophylaxis was higher - but not statistically significant - in the intervention group when compared to the control (11 vs 5 deaths, rate ratio 2.20, 95% CI 0.70-8.10, p=0.21) (**Greenwood 1995** (28)).

Table 7. Chemoprophylaxis studies evaluating mortality

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Malaria-associated mortality				
Greenwood 1988	All deaths recorded by village reporters and recorders	12 months	1 death/222 vs 1 death/230	No
All-cause mortality				
Bradley-Moore 1985	Active investigation of all deaths among study children	6 months	Only 1 death/94 in the chemoprophylaxis group	No

Greenwood 1988	All deaths recorded by village reporters and recorders	12 months	2 deaths/222 vs 2 deaths/230	No
Menon 1990 Greenwood 1995	Deaths recorded by village reporters and field workers	2 years (ages 5-7 y)	*Children recruited at trial start when they were aged 3-16 months and received CP for ≥4 rainy seasons:* Probability of dying 0.020 vs 0.025 (4 vs 5 deaths), RR 0.80 (95% CI 0.22-2.95)	No
		12 months (ages 5-6 y)	*All children recruited at trial start:* 0.005 vs 0.002 (10 vs 4 deaths), RR 2.43 (95% CI 0.77-7.68), p=0.12	Not significant
		4 years (ages 5-9 y)	Probability of death between ages 5-9 years was identical for the 2 groups (0.008 for both)	No
		12 months (ages 5-6 y)	*Children recruited at trial start or over the following 5 years:* Probability of dying 0.015 vs 0.007 (11 vs 5 deaths), RR 2.20 (95% CI 0.70-8.10), p=0.21	Not significant
		5 years (ages 5-10 y)	Probability of dying 0.040 vs 0.052, RR 0.87 (95% CI 0.50-1.60), p=0.37	No
		0-9 years	282 deaths (261 before age 5 and 21 after) vs 339 deaths (315 before age 5 and 24 after)	No
Aponte 2007	Deaths recorded through monthly home visits	0-3 years	*All ages:* 19 deaths/208 vs 13 deaths/207, p=0.512	Not significant
			2-4 years age group: 10 vs 3 deaths, p=0.088	Not significant
Guinovart 2012	Passive surveillance and monthly home visits	2.5-14 months	2 deaths/194 vs 3 deaths/103	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; CP: chemoprophylaxis; RR: rate ratio.

Hospital admissions

In terms of hospital admissions during the follow-up period after the intervention was stopped (**Table 8**), **Bigira 2014** (24) found a significantly higher incidence of hospitalisation in the group that had received monthly sulfadoxine-pyrimethamine compared to the control group (0.452 vs 0.046 episodes per person-years-at-risk (PYAR), incidence rate ratio 10.7, 95% CI 2.17–53.2, p=0.004), but this trend was not observed

in the trimethoprim-sulfamethoxazole or the dihydroartemisinin-piperaquine arms (0.091 and 0.023 episodes per PYAR, respectively, vs 0.046 episodes per PYAR in the control group).

Table 8. Chemoprophylaxis studies evaluating hospital admissions

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Incidence of all-cause hospital admissions				
Guinovart 2012	Passive surveillance and monthly home visits	2.5-14 months	0.19 *(late exposure: CP 2.5-4.5 months of age)*, 0.20 *(early exposure: CP 5.5-9.5 months of age)* vs 0.19 episodes/PYAR, p=0.91 HR *(late exposure vs control)* 1.14 (95% CI 0.50-2.62), p=1 HR *(early exposure vs control)* 1.19 (95% CI 0.52-2.69), p=1 HR *(early vs late exposure)* 1.04 (95% CI 0.46-2.36), p=1	Not significant
Bigira 2014	Passive surveillance	1-12 months	*All episodes:* *SP:* 0.452, *TS:* 0.091, *DP:* 0.023 vs 0.046 episodes/PYAR *SP:* IRR 10.7 (95% CI 2.17–53.2), p=0.004 *TS:* IRR 1.99 (95% CI 0.36–11.1), p=0.43 *DP:* IRR 0.51 (95% CI 0.06–4.14), p=0.52	**Yes, for SP**
Kamya 2014	Passive surveillance	1-12 months	*All episodes:* *SP:* 0.318, *TS:* 0.186, *DP:* 0.089 vs 0.459 episodes/PYAR *SP* PE 0.99 (95% CI 0.18-5.58), p=0.99 *TS* PE 0.41 (95% CI 0.07-2.40), p=0.32 *DP* PE 0.20 (95% CI 0.03-1.29), p=0.09	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; CP: chemoprophylaxis; DP: dihydroartemisinin-piperaquine; HR: hazard ratio; IRR: incidence rate ratio; PE: protective efficacy; PYAR: person-years-at-risk; SP: sulfadoxine-pyrimethamine; TS: trimethoprim-sulfamethoxazole.

3.4.1.2. Intermittent preventive treatment in infants (IPTi)

Eight relevant randomised controlled trials (11 publications) assessing the effects of IPTi were identified (**Table 9**). SP was administered at 2, 3 and 9 months of age in Tanzania (**Schellenberg 2001** (31), **Schellenberg 2005** (32)), at 2, 3, 4, 9 and 12 months of age in Ghana (**Chandramohan 2005** (70)), at 3, 4 and 9 months of age in Mozambique (**Macete 2006** (41)), and at 3, 9 and 15 months of age in two trials in Ghana (**Kobbe 2007** (37), **Kobbe 2011** (38), **Mockenhaupt 2007** (40)) and one trial in Gabon (**Grobusch**

2007 (71), **Grobusch 2009** (34)). The combinations of sulfadoxine-pyrimethamine+artesunate (SP+AS), amodiaquine+artesunate (AQ+AS) and chlorproguanil+dapsone administered at 10 weeks, 14 weeks and 9 months of age were compared in a trial in Kenya (**Odhiambo 2010** (36)), whereas **Senn 2012** (39) compared SP+AQ and SP+AS administered at 3, 6, 9 and 12 months of age in Papua New Guinea. The duration of the follow-up after the intervention ranged from nine months to three years. In addition, one pooled analysis of six randomised controlled trials was included (**Aponte 2009** (11)).

Table 9. Characteristics of IPTi studies included

Study	Location	Year(s)	Age at which IPTi was administered	Drug	Duration of follow-up post-interv.	Outcomes reported
Aponte 2009	Tanzania Moz Gabon Ghana	1999 - 2007	Pooled analysis of 6 IPTi trials		6-12 months	‣ Incidence of clinical malaria ‣ Incidence of anaemia ‣ Incidence of all-cause hospital admissions ‣ Incidence of malaria-associated hospital admissions
Schellenberg 2001 Schellenberg 2005	Tanzania	1999 - 2001	2, 3, 9 months of age	SP	9-15 months	‣ Incidence of clinical malaria • Incidence of severe anaemia ‣ Prevalence of infection ‣ Prevalence of anaemia
Chandramohan 2005	Ghana	2000 - 2004	2, 3, 4, 9, 12 months of age	SP	8 months	‣ Incidence of clinical malaria • Incidence of anaemia • Malaria mortality • All-cause mortality • Incidence of all-cause hospital admissions • Incidence of malaria-associated hospital admissions
Macete 2006	Moz	2002 - 2004	3, 4, 9 months of age	SP	12 months	‣ Incidence of clinical malaria
Kobbe 2007 Kobbe 2011	Ghana	2003 - 2007	3, 9, 15 months of age	SP	3 years	‣ Incidence of clinical malaria • Prevalence of infection • Incidence of anaemia • Prevalence of anaemia ‣ Prevalence of all-cause hospital admissions ‣ All-cause mortality

Grobusch 2007 Grobusch 2009	Gabon	2002 - 2006	3, 9, 15 months of age	SP	15 months	‣ Incidence of clinical malaria ‣ Incidence of anaemia
Mockenhaupt 2007	Ghana	2003 - 2005	3, 9, 15 months of age	SP	9 months	‣ Incidence of clinical malaria ‣ Incidence of severe malaria ‣ Incidence of anaemia ‣ Incidence of severe malarial anaemia ‣ All-cause mortality ‣ Incidence of all-cause hospital admissions
Odhiambo 2010	Kenya	2004 - 2008	10 weeks, 14 weeks and 9 months of age	SP+AS, AQ+AS or CPG+D	15 months	‣ Incidence of clinical malaria ‣ Incidence of moderate-to-severe anaemia
Senn 2012	PNG	2016 - 2010	3, 6, 9, 12 months of age	SP+AQ or SP+AS	9 months	‣ Incidence of clinical malaria • Incidence of moderate-to-severe anaemia ‣ Prevalence of infection

AQ: amodiaquine; AS: artesunate; CPG: chlorproguanil; D: dapsone; Moz: Mozambique; PNG: Papua New Guinea; SP: sulfadoxine-pyrimethamine.

A statistically significant rebound in the incidence of clinical malaria in the period after the intervention was observed in one study (**Chandramohan 2005** (70), **Table 10**) for high-density malaria cases, but this was not significant when accounting for all densities. However, this was a cluster randomised trial, which is not fully comparable to the other IPTi studies that were individual randomised controlled trials. the Four additional studies including the pooled analysis reported higher rates of clinical malaria in the intervention arm when compared to the control group, but these differences were not statistically significant (**Aponte 2009** (11), **Grobusch 2007** (71), **Grobusch 2009** (34), **Mockenhaupt 2007** (40), **Odhiambo 2010** (36)). Only one study assessed the incidence of severe malaria during follow-up (**Mockenhaupt 2007** (40)) and found a higher incidence during the period 1-9 months post-intervention, which was statistically significant for the first or only episode but not when accounting for all episodes. No evidence of rebound was observed for hospital admissions (**Table 16**), parasite prevalence, incidence of anaemia, incidence of malarial anaemia, or incidence of severe anaemia (**Tables 11-14**), but **Mockenhaupt 2007** (40) reported a statistically significant higher incidence of severe malarial anaemia during the period 1-9 months post-intervention among the children that received the intervention in Ghana. No evidence of rebound in mortality was observed in any of the studies assessed (**Table 15**).

<u>Incidence of clinical malaria</u>

Eight trials assessed the presence or absence of rebound in the incidence of clinical malaria (**Table 10**). **Chandramohan 2005** (70) found a significantly higher incidence of high-density clinical malaria (parasitaemia ≥5000 parasites/µl) in the intervention arm when compared to the control arm during the period from 4 to 12 months post-intervention (incidence rate ratio 1.19, 95% CI 1.02-1.39). When accounting for all malaria episodes, the incidence was still higher in the intervention arm but the effect was not statistically significant (incidence rate ratio 1.05, 95% CI 0.91-1.21). Aponte et al. conducted a pooled analysis for a possible rebound effect with the data from six trials with extended follow-up periods and found very similar incidences of clinical malaria in the five months post-IPTi in the two arms (1.10 vs 1.09 events/PYAR, pooled estimate of protective efficacy by combined estimates -1%, 95% CI -11.9-8.7, p=0.843) (**Aponte 2009** (11)). Higher incidences in the intervention arm - but not statistically significant - were observed in two other studies: over the period 3-15 months post-intervention for all malaria episodes in **Grobusch 2007** (71) and **Grobusch 2009** (34) (0.17 vs 0.14 events/PYAR, protective effect -18.0%, 95% CI -97.4-29.5, p=0.53) (34) and 1-15 months post-intervention in **Odhiambo 2010** (36), with the highest incidence observed in the chlorproguanil-dapsone arm (0.82 vs 0.75 events/PYAR, protective effect -7.3%, 95% CI -34.6-14.5, p=0.54). Similar incidences in both arms were observed over the period 1-9 months after the intervention in **Mockenhaupt 2007** (40) when accounting for all episodes (1.78 vs 1.77 events/PYAR, protective effect -1.0 (95% CI -17.6-13.2, p=0.89).

Table 10. IPTi studies evaluating incidence of clinical malaria

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Aponte 2009	*See each of the 6 studies for details*	35 days-5 months	1.10 vs 1.09 events/PYAR PE¶ -1% (95% CI -11.9-8.7), p=0.843 PE§ -3.9% (95% CI -13.9-5.2), p=0.409	No
Schellenberg 2001 Schellenberg 2005	Passive case detection	1-15 months	*First or only episode:* 0.28 vs 0.43 events/PYAR PE 36% (95% CI 11-53), p=0.006 *All episodes:* 0.33 vs 0.42 PYAR PE 23% (95% CI -5-43), p=0.097	No
Chandramohan 2005	Passive case detection	4-12 months	*>0 parasites/µl:* 843.9 vs 790.8 events/1000 PYAR IRR 1.05 (95% CI 0.91-1.21) *≥5000 parasites/µl:*	Not significant **Yes**

			558.4 vs 460.3 events/1000 PYAR IRR 1.19 (95% CI 1.02-1.39)	
Macete 2006	Passive case detection	1-12 months	No evidence of increase in episodes of clinical malaria after discontinuation of IPTi (data not shown)	No
Kobbe 2007	Active and passive case detection	1-6 months	*First or only episode:* PE 4.2% (95% CI -17.6-22.0), p=0.68 *Multiple episodes:* PE -5.2% (95% CI -24.5-11.1), p=0.56	No
Grobusch 2007 Grobusch 2009	Active case detection	3-15 months	*All episodes:* 0.17 vs 0.14 events/PYAR PE -18.0% (95% CI -97.4-29.5), p=0.53	Not significant
Mockenhaupt 2007	Active and passive case detection	1-9 months	*First or only episode:* 0.59 vs 0.60 events/PYAR PE 1.8% (95% CI -8.5-11.0), p=0.73 *All episodes:* 1.78 vs 1.77 events/PYAR PE -1.0 (95% CI -17.6-13.2), p=0.89	No No
Odhiambo 2010	Passive case detection	1-15 months	*SP+AS:* 0.74, *AQ+AS:* 0.77, *CPG+D:* 0.82 vs 0.75 events/PYAR *SP+AS:* PE 1.5% (95% CI -23.1-21.2), p=0.89 *AQ+AS:* PE -1.1% (95% CI -26.3-19.0), p=0.92 *CPG+D:* PE -7.3% (95% CI -34.6-14.5), p=0.54	No or not significant
Senn 2012	Passive case detection	3-9 months	*SP+AQ:* 1.05, *SP+AS:* 1.06 vs 1.15 events/PYAR *SP+AQ:* IRR 0.91 (95% CI 0.70-1.20) *SP+AS:* IRR 0.92 (95% CI 0.70-1.21), p=0.76 (p for comparison across all three treatment groups)	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; ¶Pooled estimate of protective efficacy by combined estimates; §Pooled estimate of protective efficacy by sensitivity analysis removing the trial with the highest protective efficacy; AQ: amodiaquine; AS: artesunate; CPG: chlorproguanil; D: dapsone; IRR: incidence rate ratio; PE: protective efficacy; PYAR: person-years-at-risk; SP: sulfadoxine-pyrimethamine.

Incidence of severe malaria

One study assessed the risk of rebound in the incidence of severe malaria. In Ghana, incidence of severe malaria over the period 1-9 months post-intervention was higher in the group of children who had received three doses of sulfadoxine-pyrimethamine, but this difference was statistically significant when accounting only for first or only episodes (0.05 vs 0.02 events/PYAR, protective effect -101.5, 95% CI -

298.9-(-1.8), p=0.04), but not significant when considering all episodes (0.07 vs 0.04 events/PYAR, protective effect -97.2%, 95% CI -296.6–2.0, p=0.06) (**Mockenhaupt 2007** (40)). According to the authors, the estimated number of averted severe malaria cases by IPTi would balance the total number of such events between the SP and control group over the complete follow up period (40).

Prevalence of infection

None of the studies that assessed prevalence of infection at three months, nine months or three years after the intervention was stopped found evidence of a significant rebound (**Table 11**). **Kobbe 2011** (38) also assessed the prevalence of clinical disease three years after the intervention and, even though prevalence was slightly higher in the intervention arm, this difference was not statistically significant.

Table 11. IPTi studies evaluating prevalence of infection

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Schellenberg 2001 Schellenberg 2005	Cross-sectional surveys	9 months	Prevalence did not differ among arms (data not shown)	No
Kobbe 2011	Cross-sectional survey	3 years	33.2% vs 34.3%, p=0.91	No
Senn 2012	Cross-sectional survey?	3 months 9 months	No significant differences observed (data not shown)	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available.

Incidence of anaemia and malarial anaemia

Three out of the five studies that assessed incidence of anaemia after the intervention and two out of the four that measured severe anaemia observed higher incidences in the intervention arm, but none of these differences was significant (**Tables 12 and 13**). On the other hand, the incidence of severe malarial anaemia was significantly higher in the treated children in a study in Ghana (0.04 vs 0.02 events/PYAR for first of only episode and 0.07 vs 0.03 events/PYAR for all episodes) (**Mockenhaupt 2007** (40)).

Table 12. IPTi studies evaluating incidence of anaemia

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Aponte 2009	*See each of the 6 studies*	35 days-5	0.14 vs 0.14 events/PYAR	No

	for details	months	PE¶ 2.1% (95% CI -8-11.2), p=0.673 PE§ 0.9% (95% CI -9.5-10.2), p=0.864	
Chandramohan 2005	Passive case detection	4-12 months	PE -6.4% (95% CI -76.8-35.9)	Not significant
Kobbe 2007	Active and passive case detection	1-6 months	*First or only episode:* PE -4.4 (95% CI -34.5-18.9), p=0.74 *Multiple events:* PE -9.9% (95% CI -37.0-11.9), p=0.4	Not significant
Grobusch 2007 Grobusch 2009	Active case detection	3-15 months	PE -45.3% (95% CI -234.5-36.3), p=0.38	Not significant
Mockenhaupt 2007	Active and passive case detection	1-9 months	*First or only episode:* 0.29 vs 0.31 events/PYAR PE 7.2% (95% CI -11.7–22.9), p=0.43 *All episodes:* 0.64 vs 0.66 events/PYAR PE 3.8% (95% CI -21.1–23.6), p=0.74	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; ¶Pooled estimate of protective efficacy by combined estimates; §Pooled estimate of protective efficacy by sensitivity analysis removing the trial with the highest protective efficacy; PE: protective efficacy; PYAR: person-years-at-risk.

Table 13. IPTi studies evaluating incidence of severe anaemia and severe malarial anaemia

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Incidence of severe anaemia				
Schellenberg 2001 Schellenberg 2005	Passive case detection	1-15 months	0.11 vs 0.11 events/PYAR PE -5% (95% CI -77-38), p=0.852	No
Kobbe 2007	Active and passive case detection	1-6 months	*First or only episode:* PE -141.1% (95% CI -1143.1-53.2), p=0.29 *Multiple events:* PE -147.2% (95% CI -1147.1-52.0), p=0.28	Not significant
Odhiambo 2010	Passive case detection	1-15 months	0.20 *(SP+AS)*, 0.23 *(AQ+AS)*, 0.23 *(CPG+D)* vs 0.26 events/PYAR *SP+AS* PE 22.2% (95% CI -11.7-45.8),	No

			p=0.17 *AQ+AS* PE 11.2% (95% CI -25.6-37.2), p=0.5 *CPG+D* PE 8% (95% -31.1-35.5), p=0.64	
Senn 2012	Passive case detection	3-9 months	0.27 *(SP+AQ)*, 0.27 *(SP+AS)* vs 0.27 events/PYAR IRR 1.01 (95% CI 0.63-1.61) *(SP+AQ)*, 1.03 (95% CI 0.64-1.63) *(SP+AS)*, p=0.99	No
Incidence of severe malarial anaemia				
Mockenhaupt 2007	Active and passive case detection	1-9 months	*First or only episode:* 0.04 vs 0.02 events/PYAR PE -131.8% (95% CI -382.3-(-11.4)), p=0.03 *All episodes:* 0.07 vs 0.03 events/PYAR PE -124.2 (95% CI -373.0-(-6.2)), p=0.03	**Yes**

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; AQ: amodiaquine; AS: artesunate; CPG: chlorproguanil; D: dapsone; IRR: incidence rate ratio; PE: protective efficacy; PYAR: person-years-at-risk; SP: sulfadoxine-pyrimethamine.

Prevalence of anaemia

No evidence of rebound in the prevalence of anaemia was observed at 9 months or 3 years post-intervention (**Table 14**).

Table 14. IPTi studies evaluating prevalence of anaemia

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Schellenberg 2001 Schellenberg 2005	Cross-sectional surveys	9 months	Prevalence did not differ among arms (data not shown)	No
Kobbe 2011	Cross-sectional survey	3 years	*Moderate anaemia:* 2.9% vs 2.9%, p=0.98 *Severe anaemia:* 0.5% vs 0%, p=0.39	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available.

Mortality

No evidence of rebound in mortality was observed among the trials that recorded the number of deaths during the follow-up period (**Table 15**). Nonetheless, a higher rate of both malaria or anaemia mortality and all-cause mortality was seen in the intervention arm in the 4 to 12 months following the last dose of IPTi in Ghana, but these differences were not statistically significant (18.5/1000 vs 15.7/1000, incidence rate ratio 1.17, 95% CI 0.54-2.53 for malaria or anaemia mortality and 43.7/1000 vs 34.1/1000,incidence rate ratio 1.27, 95% CI 0.76-2.13 for all-cause mortality) (**Chandramohan 2005** (70)).

Table 15. IPTi studies evaluating mortality

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Malaria or anaemia mortality				
Chandramohan 2005	Hospital diagnosis or verbal autopsy	4-12 months	18.5/1000 vs 15.7/1000 IRR 1.17 (95% CI 0.54-2.53)	Not significant
All-cause mortality				
Chandramohan 2005	Hospital diagnosis or verbal autopsy	4-12 months	43.7/1000 vs 34.1/1000 IRR 1.27 (95% CI 0.76-2.13)	Not significant
Kobbe 2007	Not reported	1-6 months	PE 51.3% (95% CI -436.5-95.6), p=0.56	No
Mockenhaupt 2007	Not reported	1-9 months	0.01 vs 0.02 events/PYAR PE 53.1% (95% CI -22.4–82.1), p=0.12	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; IRR: incidence rate ratio; PE: protective efficacy; PYAR: person-years-at-risk.

Hospital admissions

No evidence of rebound in all-cause and malaria-associated hospital admissions was observed in the period after IPTi was administered in any of the studies assessed (**Table 16**).

Table 16. IPTi studies evaluating hospital admissions

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Incidence of all-cause hospital admissions				
Aponte 2009	*See each of the 6 studies for details*	35 days-5 months	0.28 vs 0.29 events/PYAR PE¶ -2.7% (95% CI -20.2-12.1), p=0.735	No

			PE§ -6.6% (95% CI -25.9-9.6), p=0.446	
Chandramohan 2005	Passive surveillance	4-12 months	179.8/1000 vs 182.2/1000 IRR 1.0 (95% CI 0.98-1.31)	No
Kobbe 2007	Active and passive surveillance	1-6 months	PE -58.6% (95% CI -163.7-4.6), p=0.08	Not significant
Mockenhaupt 2007	Passive case detection	1-6 months	PE 13.3% (95% CI -26.9-40.8), p=0.46	No
Prevalence of all-cause hospital admissions				
Kobbe 2011	Retrospective interviews with mothers and caretakers and consultation of medical records♦	3 years	*Participants reporting no hospital admissions:* 80.3% vs 79.1%, p=0.36	No
Incidence of malaria-associated hospital admissions				
Aponte 2009	*See each of the 6 studies for details*	35 days-5 months	0.10 vs 0.08 events/PYAR PE¶ -20.2% (95% CI -59.3-9.3), p=0.199 PE§ -28.2% (95% CI -74.7-6.0), p=0.116	Not significant
Chandramohan 2005	Passive surveillance	4-12 months	42.3/1000 vs 45.9/1000 RR 0.92 (95% CI 0.54-1.56)	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; ¶Pooled estimate of protective efficacy by combined estimates; §Pooled estimate of protective efficacy by sensitivity analysis removing the trial with the highest protective efficacy; ♦: frequencies since last follow-up of core study; IRR: incidence rate ratio; PE: protective efficacy; PYAR: person-years-at-risk.

3.4.1.3. Seasonal malaria chemoprevention (SMC)

We included six randomised controlled trials (eight publications) assessing the effects of SMC on malarial outcomes (**Table 17**). **Cissé 2006** (42) assessed the administration of three monthly rounds of AS+SP to children aged 2 to 59 months in Senegal, **Dicko 2008** (44) administered two rounds of SP at eight-week intervals to children aged 6 months to 10 years of age in Mali, and **Kweku 2008** (43) compared the effect of three versus six rounds of AS+AQ or SP when administered to children aged 3 to 59 months in Ghana. Two trials assessed the effects of administering three monthly rounds of SP+AQ to children aged 3 to 59 months, one in Mali (**Dicko 2011** (46), **Dicko 2011b** (47)) and one in Burkina Faso (**Konaté 2011** (48), **Konaté 2011b** (49)). One trial compared the impact of administering three bimonthly rounds of AS+AQ to children aged 3 to 59 months and home-based management of malaria (HMM) to HMM alone in Ghana (**Tagbor 2011** (45)). Duration of follow-up post-intervention ranged between 12 and 17 months.

During the year after SMC was administered, a statistically significant rebound in the incidence of clinical malaria was observed in one study in Burkina Faso (**Konaté 2011** (48), **Konaté 2011b** (49)). Slightly higher incidences in the intervention arm were also observed in two SMC studies that took place in Ghana (**Kweku 2008** (43)) and Mali (**Dicko 2011** (46), **Dicko 2011b** (47)), but these differences were not statistically significant (**Table 18**). The differences in the prevalence of infection at follow-up were only statistically significant at five months after the last round of SMC in the arm administering amodiaquine plus artesunate monthly in **Kweku 2008** (43), but this rebound was not significant in the survey conducted seven months later (12 months post-intervention) (**Table 19**). No significant rebound following SMC was observed for severe malaria, anaemia (**Table 20**), or hospital admissions (**Table 21**).

Table 17. Characteristics of SMC studies included

Study	Location	Year(s)	Age group	Drug	Frequency of intervention	Duration of intervention	Duration of follow-up post-interv.	Outcomes reported
Cissé 2006	Senegal	2002 - 2003	Children 2-59 months	AS+SP	3 rounds, monthly for 1 year	SMC for 3 months	12 months	◦ Incidence of clinical malaria • Prevalence of anaemia
Dicko 2008	Mali	2002 - 2004	Children 6 months-10 years	SP	2 rounds, 8 weeks interval for 1 year	SMC for 2 months	17 months	◦ Incidence of clinical malaria
Kweku 2008	Ghana	2005 - 2006	Children 3-59 months	AS+AQ or SP	3 or 6 rounds, monthly or bimonthly for 1 year	SMC for 6 months	12 months	◦ Incidence of clinical malaria ◦ Incidence of anaemia ◦ Prevalence of infection ◦ Prevalence of anaemia ◦ Incidence of malaria admissions ◦ Incidence of hospital admissions
Dicko 2011 Dicko 2011b	Mali	2008 - 2009	Children 3-59 months	SP+AQ	3 rounds, monthly for 1 year	SMC for 3 months	12 months	◦ Incidence of clinical malaria ◦ Incidence of severe malaria • Prevalence of infection • Prevalence of anaemia • Incidence of hospital admissions
Konaté 2011 Konaté 2011b	Burkina Faso	2008 - 2009	Children 3-59 months	SP+AQ	3 rounds, monthly for 1 year	SMC for 3 months	12 months	• Incidence of clinical malaria ◦ Prevalence of infection ◦ Prevalence of anaemia ◦ Incidence of hospital admissions
Tagbor 2011	Ghana	2007 - 2008	Children 3-59 months	AS+AQ	3 rounds, bimonthly for 1 year	SMC for 5 months	14 months	• Prevalence of infection • Prevalence of anaemia

AQ: amodiaquine; AS: artesunate; DP: dihydroartemisinin-piperaquine; SP: sulfadoxine-pyrimethamine.

Incidence of clinical malaria

In Senegal, no rebound in the incidence of clinical malaria was seen overall in children who had received three monthly rounds of preventive treatment during the rainy season (**Cissé 2006** (42)), but it was observed that children who had received the intervention in the first year of life maintained some persisting protection in the year after the intervention, whereas this effect was reversed in older children (negative protective efficacies, but not statistically significant). In Burkina Faso, three monthly rounds of intermittent preventive treatment during the rainy season with sulfadoxine-pyrimethamine were associated with a small increase in the incidence of clinical malaria during the year after the intervention (incidence rates 2-12 months post-intervention 1.48 vs 1.33 episodes in the intervention and control groups, respectively, incidence rate ratio 1.12, 95% CI 1.04-1.20, p=0.002) (**Konaté 2011b** (49)). This increased risk of clinical malaria was slightly higher for children who were 24 months of age or older at the beginning of the intervention than for children who were younger than 24 months when the intervention commenced, but there was no evidence that the effect of the intervention at follow-up varied with age. The incidence of clinical malaria during the year after SMC was also higher in the intervention group in a study in Mali (incidence rates 2-12 months post-intervention 0.82 vs 0.77 in the intervention and control groups, respectively, incidence rate ratio 1.09, 95% CI 0.99-1.20, p=0.07) (**Dicko 2011b** (47)), but these differences were not statistically significant. Similarly to the findings in Burkina Faso, a marginally higher incidence of clinical malaria was observed in children who had received the intervention when they were 24 months of age or older, but again no evidence was found for an interaction between the effect of SMC in the post-intervention year and age (47). In Ghana, a non-significant increase in the risk of clinical malaria was observed the year after SMC, but when stratifying by age, a statistically significant higher incidence of clinical malaria during the rainy season following the intervention was observed in the group of children who received monthly artesunate+amodiaquine when they were between 3 and 11 months of age (**Kweku 2008** (43)), differing from the age effect observed in Senegal, Burkina Faso and Mali.

Table 18. SMC studies evaluating incidence of clinical malaria

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Cissé 2006	Active and passive case detection	9-12 months	IRR 0.98 (95% CI 0.82-1.17)	No

Dicko 2008	Active and passive case detection	12-17 months	23/1000 vs 21.5/1000 PYAR IRR 1.07 (95% CI 0.90-1,27), p=0.46	No
Kweku 2008	Passive case detection	1-5 months (dry season)	*SPbm:* PE -35.1% (95% CI -237.3-14.4), p=0.870 *AQ+ASbm:* PE -56.8% (95% CI -201.6-27-3), p=0.720 *AQ+ASm:* PE 32.4% (95% CI -125.9-55.8), p=0.257	Not significant
		6-12 months (rainy season)	*SPbm:* PE -38.8% (95% CI -108.6-5.6), p=0.094 *AQ+ASbm:* PE -5.3% (95% CI -65.3-30), p=0.740 *AQ+ASm:* PE -38.2% (95% CI -115.8-1.4), p=0.059	
			15–23 months age group (formerly 3–11 months): *SPbm:* PE -50% (95% CI -34-84), p=0.07 *AQ+ASbm:* PE -40% (95% CI -68-81), p=0.152 *AQ+ASm:* PE -62% (95% CI -3-88), p=0.014	**Yes, for AQ+ASm**
			24–71 months age group (Formerly 12–59 months): *SPbm:* PE -22% (95% CI -23-51), p=0.131 *AQ+ASbm:* PE 6% (95% CI -56-44), p=0.405 *AQ+ASm:* PE -7% (95% CI -48-42), p=0.369	No or not significant
Dicko 2011	Passive case detection	9-12 months	IR 1.87 vs 1.73 episodes/PYAR IRR 1.09 (95% CI 0.99-1.21), p=0.08	Not significant
Dicko 2011b		2-12 months	IR 0.82 vs 0.77 episodes/PYAR IRR 1.09 (95% CI 0.99-1.20), p=0.07	Not significant
Konaté 2011	Passive case detection	9-12 months	IR 3.84 vs 3.45 episodes/PYAR IRR 1.12 (95% CI 1.04–1.20), p=0.003	**Yes**
Konaté 2011b		2-12 months	IR 1.48 vs 1.33 episodes/PYAR IRR 1.12 (95% CI 1.04-1.20), p=0.002	

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; AQ: amodiaquine; AS: artesunate; bm: bimonthly; IR: incidence rate; IRR: incidence rate ratio; m: monthly; PE: protective efficacy; PYAR: person-years-at-risk;. SP: sulfadoxine-pyrimethamine.

Incidence of severe malaria

No evidence of a rebound in the incidence of severe malaria was observed in the study that assessed this outcome during follow-up (**Dicko 2008** (44)).

Prevalence of infection

Only one study found evidence of rebound in the parasite prevalence during the follow-up period (**Table 19**). In Ghana, the prevalence of infection at five months after the intervention was higher in the group that received monthly amodiaquine+artesunate when compared to the other arms, but this difference was not statistically significant when the outcome was measured again at 12 months post-intervention (**Kweku 2008** (43)). Parasite prevalence was also slightly higher in the intervention group in a trial in Mali (**Dicko 2011b** (47)), but this difference was not statistically significant either.

Table 19. SMC studies evaluating prevalence of infection

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Kweku 2008	Cross-sectional surveys	5 months (end of dry season)	*SPbm:* 0%, p=0.365 *AQ+ASbm:* 9.5%, p=0.067 *AQ+ASm:* 10.4%, p=0.035 vs 6.2% (*placebo*)	**Yes, for AQ+ASm**
		12 months (end of rainy season)	*SPbm:* 39.2%, p=0.532 *AQ+ASbm:* 40.4%, p=0.856 *AQ+ASm:* 42.0%, p=0.579 vs 39.7% (*placebo*)	Not significant
Dicko 2011 Dicko 2011b	Cross-sectional survey	12 months	16.3% vs 14.1% PR 1.17 (95% CI 0.96-1.14), p=0.12	Not significant
Konaté 2011 Konaté 2011b	Cross-sectional survey	12 months	37.6% vs 42.1% PR 0.88 (95% CI 0.79–0.98), p=0.04	No
Tagbor 2011	Cross-sectional survey	2 months	29.2% vs 41.2%, p=0.045	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; AQ: amodiaquine; AS: artesunate; bm: bimonthly; DP: dihydroartemisinin-piperaquine; m: monthly; PR: prevalence ratio; SP: sulfadoxine-pyrimethamine.

Incidence and prevalence of anaemia

No evidence of a rebound in the incidence and prevalence of anaemia was observed (**Table 20**). Three studies found higher prevalences in the intervention arm at 12 months post-intervention, but these differences were not statistically significant (**Kweku 2008** (43), **Dicko 2011b** (47), **Konaté 2011b** (49)).

Table 20. SMC studies evaluating incidence and prevalence of anaemia

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Incidence of anaemia				
Kweku 2008	Active and passive case detection	1-5 months (dry season)	*SPbm:* PE 23.4 (95% CI -105.6-75.4), p=0.472 *AQ+ASbm:* PE 30.4 (95% CI -125.1-76.0), p=0.410 *AQ+ASm:* PE 65.2 (95% CI -263.0-91.0), p= 0.893	No
		6-12 months (rainy season)	*SPbm:* PE 7.3 (95% CI -71.0-49.8), p=0.193 *AQ+ASbm:* PE 21.7 (95% CI -61.6-62.0), p=0.491 *AQ+ASm:* PE 21.0 (95% CI -51.1-58.7), p=0.523	
Prevalence of anaemia				
Cissé 2006	Cross-sectional surveys	12 months	No increase in the prevalence of anaemia in the intervention arm (data not shown)	No
Kweku 2008	Cross-sectional surveys	12 months	*SPbm:* 11.9%, p=0.987 *AQ+ASbm:* 14.7%, p=0.405 *AQ+ASm:* 9.57%, p=0.281 vs 12% *(placebo)*	Not significant
Dicko 2011 Dicko 2011b	Cross-sectional survey	12 months	56.2% vs 55.6% PR 1.01 (95% CI 0.91-1.12), p=0.84	Not significant
Konaté 2011 Konaté 2011b	Cross-sectional survey	12 months	51.2% vs 48.4% PR 1.06 (95% CI 0.95-1.18), p=0.29	Not significant
Tagbor 2011	Cross-sectional survey	2 months	46.4% vs 47.2%, p=0.67	No

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; AQ: amodiaquine; AS: artesunate; bm: bimonthly; DP: dihydroartemisinin-piperaquine; m: monthly; OR: odds ratio; PR: prevalence ratio; SP: sulfadoxine-pyrimethamine.

Incidence of hospital admissions

No evidence of rebound was found in the studies that assessed all-cause hospital admissions and malaria-associated hospital admissions during the period after the intervention (**Table 21**), even though some found non-statistically significant higher incidences in the group receiving SMC.

Table 21. SMC studies evaluating incidence of all-cause hospital admissions

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Incidence of all-cause hospital admissions				
Kweku 2008	Active and passive case detection	1-5 months (dry season)	*SPbm:* PE -6.4 (95% CI -107.1-90.3), p=0.961 *AQ+ASbm:* PE -15.8 (95% CI -442.5-97.7), p=0.938 *AQ+ASm:* PE -3.8 (95% CI -155.9-93.5), p=0.979	No or not significant
		6-12 months (rainy season)	*SPbm:* PE -21.9 (95% CI -592-83.6), p=0.950 *AQ+ASbm:* PE 6.3 (95% CI -567.6-79.9), p=0.871 *AQ+ASm:* PE 15.6 (95% CI -391.1-78.0), p=0.962	
Dicko 2011	Passive surveillance	9-12 months	IRR 1.16 (95% CI 0.42–3.23), p=0.77	Not significant
Dicko 2011b		2-12 months	IRR 1.55 (95% CI 0.78–3.11), p=0.21	
Konaté 2011	Passive surveillance	9-12 months	IRR 0.98 (95% CI 0.61–1.56), p=0.93	No
Konaté 2011b		2-12 months	IRR 0.78 (95% CI 0.55–1.09), p= 0.14	
Incidence of malaria-associated hospital admissions				
Kweku 2008	Active and passive case detection	1-5 months (dry season)	*SPbm:* PE -6.4% (95% CI -159.8-93.4), p=0.996 *AQ+ASbm:* PE 13.5% (95% CI -174.9-92.8), p=0.918 *AQ+ASm:* PE 37.8% (95% CI -513.3-97.9), p=0.985	No or not significant
		6-12 months (rainy season)	*SPbm:* PE -6.2% (95% CI -463.8-79.9), p=0.943 *AQ+ASbm:* PE 10% (95% CI -783.4-84.9), p=0.888 *AQ+ASm:* PE 20% (95% CI -542.9-83.2), p=0.968	

*Month 1 is considered the first month post-intervention; ^Adjusted measures when available; AQ: amodiaquine; AS: artesunate; bm: bimonthly; DP: dihydroartemisinin-piperaquine; IRR: incidence rate ratio; m: monthly; PE: protective effect; PR: prevalence rate; SP: sulfadoxine-pyrimethamine.

3.4.1.4. Mass drug administration (MDA)

We identified three relevant MDA trials (six publications) that evaluated the impact of administering two or three monthly rounds of sulfadoxine-pyrimethamine with or without low dose primaquine to the

overall population (older than six months or older than one year) (**Table 22**). **McLean 2021** (53) took place in Myanmar and **Morris 2018** (55) in Zanzibar, Tanzania. We also included four publications that analysed the results of a multi-site cluster-randomised trial in Vietnam (**von Seidlein 2019** (51)), Myanmar (**Landier 2017** (50)), Cambodia (**Tripura 2018** (54)), and Laos (**Pongvongsa 2018** (52)). Duration of follow-up post-intervention ranged from nine to 33 months, however none of the studies analysed the risk of malaria during the post-intervention period only, as they all included the intervention period in the analysis. Thus, they are not comparable to the other studies presented in the review, and the possibility of a rebound in the post-intervention period cannot be ruled out.

Table 22. Characteristics of MDA studies included

Study	Location	Year(s)	Age group	Drug	Frequency of intervention	Duration of intervention	Follow-up period since beginning of interv.*	Outcomes reported
Landier 2017	Myanmar	2013 - 2015	Age >6 months	DP+sldPQ	3 rounds, monthly for 1 year	MDA for 3 months	9 months	• Incidence of clinical malaria • Prevalence of *Pf* infection
Tripura 2018	Cambodia	2014 - 2016	Age >6 months	DP	3 rounds, monthly for 1 year	MDA for 3 months	12 months	• Incidence of clinical malaria • Prevalence of *Pf* infection
Pongvongsa 2018	Laos	2016 - 2017	Age >6 months	DP+sldPQ	3 rounds, monthly for 1 year	MDA for 3 months	12 months	• Incidence of clinical malaria • Prevalence of *Pf* infection
von Seidlein 2019	Vietnam	2013 - 2015	Age >6 months	DP+sldPQ	3 rounds, monthly for 1 year	MDA for 3 months	12 months	• Prevalence of *Pf* infection
Morris 2018	Tanzania	2016 - 2017	Age >6 months	DP+sldPQ	2 rounds, 4 weeks apart for 1 year	MDA for 6 weeks	16 months	• Incidence of clinical malaria • Prevalence of infection
McLean 2021	Myanmar	2014 - 2017	Age >1 year	DP+sldPQ	3 rounds, monthly for 1 year	MDA for 3 months	33 months	• Prevalence of *Pf* infection

*Month 0 is considered the first month of the intervention; DP: dihydroartemisinin-piperaquine; *Pf*: *Plasmodium falciparum*; PQ: primaquine; sld: single low dose .

Incidence of clinical malaria

Only one study (**Landier 2017** (50)) found a statistically significant higher incidence of *Plasmodium vivax* clinical malaria during the seven months follow up, which included the MDA period (8.6 cases/1000 person-months vs 5.6 cases/1000 person-months, p=0.03) (**Table 23**). However, this rebound was not seen for *Plasmodium falciparum* (1 case/1000 person-months vs 1.3 cases/1000 person-months, p=0.49).

Table 23. MDA studies evaluating incidence of clinical malaria

Study	Measurement	Follow-up period since beginning of interv.*	Effect (intervention vs control)^	Rebound?
Incidence of clinical malaria				
Landier 2017	Passive case detection at malaria posts	0-9 months[a]	1 case/1000 person-months vs 1.3 cases/1000 person-months, p=0.49 (*Pf*) 8.6 cases/1000 person-months vs 5.6 cases/1000 person-months, p=0.03 (*Pv*)	**Yes, for *Pv***
Tripura 2018	Passive case detection through village malaria workers	0-12 months[a]	1.5 cases/1000 per year vs 37.1 cases/1000 per year IRR 24.5, 95% CI 3.4-177, p=0.002 (*Pf*) 21 cases/1000 per year vs 29 cases/1000 per year IRR 1.4 (95% CI 0.7-2.5), p=0.322 *(Pv)*	No
Pongvongsa 2018	Passive case detection	0-12 months[a]	0 vs 0 events/PYAR (*Pf*)	No
Morris 2018	Passive case detection at health facilities	0-12 months[a] 0-16 months[a]	5.3 events/1000 vs 5.8 events/1000, p=0.382 13.1 events/1000 vs 16.9 events/1000, p=0.13	No

*Month 0 is considered the first month of the intervention; ^Adjusted measures when available; [a]Incidence includes the intervention period; IRR: incidence rate ratio; *Pf: Plasmodium falciparum*; *Pv: Plasmodium vivax*.

Prevalence of infection

No evidence of a rebound (or higher prevalence but not significant), was found in the studies that assessed the prevalence of *Plasmodium falciparum* infection at different timepoints after MDA (**Table 24**).

Table 24. MDA studies evaluating prevalence of Pf infection ✢

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Landier 2017	Cross-sectional surveys	7 months	2.0% vs 0.9%, p=0.10	Not significant
Tripura 2018	Cross-sectional surveys	10 months	0.2% vs 0.9% OR 0.78, 95% CI 0.07-8.84, p=0.84	No
Pongvongsa 2018	Cross-sectional surveys	10 months	0.7% vs 11.6% OR 0.13 (95% CI 0.01-2.37), p=0.170	No
von Seidlein 2019	Cross-sectional surveys	10 months	8.5% vs 5.5% RR 1.55 (95% CI 0.77-3.13)[16]	Not significant
Morris 2018	Cross-sectional survey	3 months	1.7% vs 1.4% OR 1.0, 95% CI 0.5–2, p=0.94	Not significant
McLean 2021	Cross-sectional surveys	13 months 19 months 25 months 31 months	3.2% vs 3.7% 1.5% vs 3.2% 3% vs 3% 2.8% vs 2.7% (p-values not shown)	No

*Month 0 is considered the first month of the intervention; ^Adjusted measures when available; ✢Including asymptomatic infections; OR: odds ratio; RR: risk ratio.

3.4.2. Vector control

3.4.2.1. Indoor residual spraying

Only one study assessing IRS was included in this review, as the majority of the IRS studies identified had to be excluded due to the absence of a comparison arm where the intervention was not included. **Okullo 2017** (12) assessed the trends in malaria incidence among children less than five years of age after the cessation of IRS in Northern Uganda, where 5 rounds of IRS had been conducted. A secondary data analysis was conducted using health facility data as reported through the electronic health management information system, population data from census reports, and IRS implementation data from project reports. A group of districts that had not received IRS was used as a comparison. Unadjusted incidence risk ratios (IRR) were calculated by dividing the incidence for each month after the last IRS campaign by the incidence of the month when the last IRS was conducted within each group of districts. Fourteen months after the date when IRS was withdrawn, the IRR in the intervention districts was 2.62 (95% CI

[16] As reported in Shah 2021 (72).

2.20-3.12) and 1.27 in the comparison districts (95% CI 1.05-1.54) (12). These results indicate that there was an increase in the incidence of clinical malaria in children under 5 in all districts, although this increase was larger in the districts where IRS was discontinued, suggesting there was a rebound. However, the lack of direct comparison between intervention and comparison districts and the potential confounding by differences in rainfall and coverage of other malaria control strategies make the interpretation of the results difficult.

3.4.3. RTS,S/AS01 or RTS,S/AS02A vaccine

4 trials (eight publications) assessing the long-term effects of the RTS,S/AS01 or RTS,S/AS02A vaccine were included (**Table 25**). **Olotu 2013** (60) and **Olotu 2016** (73) reported on the four and seven-year extended follow-up studies of an RTS,S/AS01 phase 2b trial in Kenya, where children aged 5-17 months received three monthly doses of the vaccine. To adjust for variations in malaria exposure within the trial cohort, the distance-weighted local prevalence of malaria was used as a marker of a person's exposure to malaria (referred to as the "malaria exposure index"), and children were categorised as having lower or higher exposure according to whether they were at or below the cohort mean or above the cohort mean, respectively (60). **Sacarlal 2009** (61) reported on the 45-month surveillance period of a phase 2b trial of the RTS,S/AS02A vaccine in children aged 1-4 years in Mozambique. We also included the follow-up results of the multisite phase 3 trial of the RTS,S vaccine in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania (**RTS,S Clinical Trials Partnership 2011-2015**(56–59)), where infants 6-12 weeks and children 5-17 months received three monthly doses with or without a fourth booster dose, and its 3 year extension studies (with a total follow-up of 6-7 years) in Tanzania, Kenya and Burkina Faso (**Tinto 2019** (62)).

These extension studies aimed to detect changes in malaria susceptibility and assess the possibility of a rebound following administration of the RTS,S vaccine (62). Acknowledging that vaccine efficacy wanes and that the risk of malaria is not constant over time, the reduction in the incidence of malaria that could be attributable to the vaccine was calculated as the difference between the incidence in the control and intervention groups and was expressed as the number of cases averted per year of follow-up in **Olotu 2013** (60) and **Olotu 2016** (73). The cumulative cases averted were obtained by summing the cases averted up to and including each given year (73). **Tinto 2019** (62) estimated vaccine efficacy as 1-rate ratio for the different follow-up periods (three-years extension period only and total 6-7 years period since first dose).

Table 25. Characteristics of RTS,S studies included

Study	Location	Year(s)	Age group	Frequency of intervention	Duration of follow-up*	Outcomes reported
Olotu 2013 Olotu 2016	Kenya	2007 - 2014	Children 5-17 months^	3 monthly doses	4 years 7 years	• Incidence of clinical malaria • Prevalence of infection
Sacarlal 2009	Moz	2003 - 2007	Children 1-4 years^	3 monthly doses	3.6 years (43 months)	• Incidence of clinical malaria • Incidence of severe malaria • Prevalence of infection • All-cause mortality • Malaria-associated hospital admissions • All-cause hospital admissions
RTS,S Clinical Trials Partnership 2011 2012 2014 2015	Burkina Faso Gabon Ghana Kenya Malawi Moz Tanzania	2010 - 2013	Infants 6-12 weeks and children 5-17 months^	3 monthly doses with or without a 4th booster dose at month 20	2 years 2.5 years 3 years	• Incidence of clinical malaria • Incidence of severe malaria • Prevalence of infection • All-cause mortality • Malaria-associated hospital admissions • All-cause hospital admissions
Tinto 2019	Tanzania Kenya Burkina Faso	2014 - 2016	Infants 6-12 weeks and children 5-17 months^	3 monthly doses with or without a 4th booster dose around month 20	6-7 years	• Incidence of clinical malaria • Incidence of severe malaria • Prevalence of infection

*Duration of follow-up after last dose of the vaccine; ^at the time of the first vaccine dose; Moz: Mozambique.

A decrease in the vaccine efficacy for clinical malaria that waned over the four and seven years of follow-up was observed in Kenya (**Olotu 2013** (60), **Olotu 2016** (73)), and a statistically significant negative vaccine efficacy was observed during the fifth year of follow-up among children in the higher malaria exposure group (**Olotu 2016** (73)). A rebound effect in the incidence of clinical malaria was also observed in one of the sites during the three-year extension study (4-7 years post-vaccination) conducted by **Tinto 2019** (62) in the group of children that received the vaccine at 5-17 months of age (**Table 26**). No evidence of rebound in the incidence of severe malaria, prevalence of infection, all-cause mortality or hospital admissions was documented (**Tables 27-30**).

Incidence of clinical malaria

Despite a waning efficacy over time and the fact that incidence of clinical malaria increased in both intervention and control groups at follow-up, in Kenya overall vaccine efficacy against first or only malaria episode over a period of four years following vaccination was 29.9% (incidence rate 0.24 vs 0.34 episodes/PYAR, p=0.005) and 32.1% (0.24 vs 0.36 episodes/PYAR, p=0.004) in the intention-to-treat and per-protocol analyses, respectively. For all malaria episodes, vaccine efficacies were 16.8% (incidence rate 0.65 vs 0.78 episodes/PYAR, intention-to-treat, p=0.18) and 24.3% (0.65 vs 0.77 episodes/PYAR, per-protocol, p=0.04) (**Olotu 2013** (60), **Table 26**). Vaccination resulted in a total of 65 cases averted per 100 vaccinated children over a period of 4 years (26, 22, 18, and −1 cases averted in the four successive years). When vaccine efficacy estimates were stratified by year post-vaccination, negative vaccine efficacy was observed for year four, but this effect was not statistically significant (vaccine efficacy -1.2, 95% CI -46.8-31.2, p=0.95) (**Olotu 2013** (60)). Over seven years of follow-up (**Olotu 2016** (73)), vaccine efficacy against first or only episode of clinical malaria was 27% (incidence rate 0.22 vs 0.31 episodes/PYAR, p=0.006, intention-to-treat) and 33.8% (incidence rate 0.22 vs 0.33 episodes/PYAR, p=0.001, per-protocol), and for all episodes it was 4.4% (incidence rate 0.73 vs 0.77 episodes/PYAR, p=0.66, intention-to-treat) and 7% (0.73 vs 0.76 episodes PYAR, p=0.52, per-protocol). Nonetheless, when stratifying by year, a rebound in the incidence of clinical malaria during the fifth year was observed for the group of children that had a higher-than-average exposure to malaria (vaccine efficacy -56.8%, 95% CI -118.7-(-12.3), p=0.008) (73). In the three sites where an additional three-year extension of the phase 3 RTS,S/AS01 efficacy study was conducted (Tanzania, Kenya and Burkina Faso) (**Tinto 2019**, (62)), vaccine efficacy over the extension period (4-7 years post-vaccination) in the older age group (aged 5-17 months at first dose) was -5.26% (1.079 vs 1.016 episodes/PYAR, 95% CI for VE -20.0-7.69) in the 4-dose group and -8.10% (1.108 vs 1.016 episodes/PYAR, 95% CI for VE -23.9-5.70) in the 3-dose group. Vaccine efficacy during the entire follow-

up period (seven years post-vaccination) in the same age group was 23.7% (95% CI 15.93-30.71) in the 4-dose group and 19.1% (95% CI 10.8-26.7) in the 3-dose group. In Burkina Faso, a statistically significant increase in the incidence of clinical malaria was observed in the older children group during the three-years extension period (2.444 vs 1.998 episodes/PYAR, vaccine efficacy -30.26%, 95% CI -59.5-(-6.35), 4-dose group; 2.411 vs 1.998 episodes/PYAR, vaccine efficacy -26.04%, 95% CI -56.0-(-1.84), 3-dose group), but a benefit was still observed when accounting for the entire seven-year follow-up (vaccine efficacy 13.78%, 95% CI 3.29-23.14, p=0.012 in the 4-dose group and 7.24%, 95% CI -4.23-17.45, p=0.21 in the 3-dose group). No significant differences in the risk during the extension periods were observed in the children that had received the vaccine at 6-12 weeks in any of the sites (62).

Table 26. RTS,S studies evaluating incidence of clinical malaria

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Olotu 2013	Active and passive case detection	R-4 years§	*>2500 parasites/mm^3*: *First or only episode*§: 0.24 vs 0.34 episodes/PYAR Unadjusted VE 29.9% (95% CI 10-3-45.3), p=0.005 *All episodes*§: 0.65 vs 0.78 episodes/PYAR Unadjusted VE 16.8% (95% CI -8.6-36.3), p=0.18 (*Andersen-Gil model*); VE 18.6% (95% CI -7.2-38.3), p=0.14 (*negative binomial regression model*)	No
		2 weeks-4 years post-3rd dose◤	*>2500 parasites/mm^3*: *First or only episode*◤: 0.24 vs 0.36 episodes/PYAR VE 32.1% (95% CI 11.6-47.8), p=0.004 *All episodes*◤: 0.65 vs 0.77 episodes/PYAR VE 24.3% (95% CI 1.9-41.6), p=0.04 (*Andersen-Gil model*); VE 23.5% (95% CI -0.7-41.9), p=0.06 (negative binomial regression model)	
		Year 2 Year 3 Year 4	*Stratified efficacy estimates*◤*:* VE 24.7% (95% CI -19.1-52.3), p=0.225 VE 22.0%, 95% CI -17.0-48.0), p=0.23 VE -1.2 (95% CI -46.8-31.2), p=0.95	No or not significant

Olotu 2016		R-7 years§	*>2500 parasites/mm^3*: *First or only episode*§: 0.22 vs 0.31 episodes/PYAR VE 27.0% (95% CI 8.5-41.8), p=0.006 *All episodes*§: 0.73 vs 0.77 episodes/PYAR VE 4.4% (95% CI -17.0-21.9), p=0.66	No
		2 weeks-7 years post-3rd dose◤	*>2500 parasites/mm^3*: *First or only episode*◤: 0.22 vs 0.33 episodes/PYAR VE 33.8% (95% CI 16.4-47.6), p=0.001 *All episodes*◤: 0.73 vs 0.76 episodes/PYAR VE 7.0% (95% CI -14.5-24.6), p=0.52	
		Year 5 Year 6 Year 7	*Stratified efficacy estimates*◤*:* VE -34.4% (95% CI -83.9-1.8), p=0.06 *Low exposure:* VE -0.8% (95% CI -100.7-49.3), p=0.98 *High exposure:* VE -56.8% (95% CI -118.7-(-12.3)), p=0.008 VE -29.9% (95% CI -91.9-12.1), p=0.19 VE 4.9% (95% CI -27.0-28.9), p=0.73	**Yes, for year 5 in high exposure cohort**
Sacarlal 2009	Passive case detection	0.5-43 months post-3rd dose	*First or only episode*◤: 0.19 vs 0.26 episodes/PYAR VE 30.5% (95% CI 18.9-40.4), p<0.001 *All episodes*◤: 0.30 vs 0.36 episodes/PYAR VE 25.6% (95% CI 11.9-37.1), p<0.001	No
RTS,S Clinical Trials Partnership 2011 2012	Passive case detection	2 weeks-12 months post-3rd dose	*Older children (5-17 months):* *First or only episode*◤: 0.435 vs 0.833 episodes/PYAR PE 55.8% (97.5% CI 51.3-59.9), p<0.001 *All episodes*◤: 0.735 vs 1.468 episodes/PYAR PE 55.1% (95% CI 50.5-59.2), p<0.001 *Younger children (6-12 weeks):* *First or only episode*◤: 0.37 vs 0.48 episodes/PYAR PE 31.5% (97.5% CI 24.7-37.6), p<0.001 *All episodes*◤: 0.91 episodes/PYAR PE 33.0% (95% CI 26.4-38.9), p<0.001	No or not significant

2014		1-18 months post-3rd dose	*Older children (5-17 months):* *All episodes*▾: 0.69 vs 1.17 episodes/PYAR PE 45.7% (95% CI 41.7-49.5), p<0.001 *Younger children (6-12 weeks):* *All episodes*▾: 0.71 vs 0.92 episodes/PYAR PE 26.6% (95% CI 20.3-32.4), p<0.001	
2015		13-28 months post-4th dose *(older children)*	*Older children (5-17 months):* 0.89 vs 0.97 episodes/PYAR VE 12.3% (95% CI 3.6-20.1), p=0·0062 *(4-dose group)*§ 0.94 vs 0.97 episodes/PYAR VE 2.9% (95% CI -6.4-11.4), p=0.53 *(3-dose group)*§	
		13-19 months post-4th dose *(younger children)*	*Younger children (6-12 weeks):* 1.17 vs 1.27 episodes/PYAR VE 10.5% (95% CI 0.2-19.7), p=0.046 *(4-dose group)*§ 1.29 vs 1.27 episodes/PYAR VE 4.4% (95% CI -6.7-14.3), p=0.42 *(3-dose group)*§	
Tinto 2019	Passive case detection and retrospective data collection from routine medical charts in the health services	4-7 years post-1st dose *(older children)*	*Older children (5-17 months), all sites:* 1.079 vs 1.016 episodes/PYAR VE -5.26% (95% CI -20-7.69) *(4-dose group)*§ 1.108 vs 1.016 episodes/PYAR VE -8.10% (95% CI -23.9-5.70) *(3-dose group)*§	No or not significant
			Older children, Burkina Faso site: 2.444 vs 1.998 episodes/PYAR, p=0.011 VE -30.26% (95% CI -59.5-(-6.35)), *(4-dose group)*§ 2.411 vs 1.998 episodes/PYAR, p=0.034 VE -26·04% (95% CI -56·0-(-1·84)) *(3-dose group)*§	**Yes, only for older children in Burkina Faso site**
		1st dose-7 years *(older children)*	*Older children (5-17 months), all sites:* 1.277 vs 1.555 episodes/PYAR VE 23.7% (95% CI 15.93-30.71) *(4-dose group)*§ 1.348 vs 1.555 episodes/PYAR VE 19.1% (95% CI 10.8-26.7) *(3-dose group)*§	No
			Older children, Burkina Faso site:	

		2.411 vs 2.803 episodes/PYAR VE 13.78% (95% CI 3.29-23.14), p=0.012 *(4-dose group)*§ 2.563 vs 2.903 episodes/PYAR VE 7.24% (95% CI -4.23-17.45), p=0.21 *(3-dose group)*§
	3.5-6.5 years post-1st dose *(younger children)*	*Younger children (6-12 weeks), all sites:* 1.632 vs 1.686 episodes/PYAR VE 0.62% (95% CI -13.7-13.13) *(4-dose group)*§ 1.563 vs 1.686 episodes/PYAR VE 5.32% (95% CI -8.12-17.09) *(3-dose group)*§
	1st dose-6.5 years *(younger children)*	*Younger children (6-12 weeks), all sites:* 1.662 vs 1.921 episodes/PYAR VE 15.55% (95% CI 6.72-23.54) *(4-dose group)*§ 1.723 vs 1.921 episodes/PYAR VE 13.15% (95% CI 4.05-21.39) *(3-dose group)*§

*Vaccine received on Year 1; ^Adjusted measures when available; ◤: per protocol cohort; §: intention-to-treat population; PYAR: person-years-at-risk; PE: protective efficacy; R: randomization; VE: vaccine efficacy.

Incidence of severe malaria

No evidence of a rebound in the incidence of severe malaria was observed in any of the studies assessed (**Table 27**). However, severe malaria was more frequent, even though not significant, over the period from 12 to 18 months after the third dose in the younger age group that received the intervention compared to controls (p=0.17) (**RTS,S 2014** (58)).

Table 27. RTS,S studies evaluating incidence of severe malaria

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Sacarlal 2009	Passive case detection	0.5-43 months post-3rd dose	VE 38.3% (95% CI 3.4-61.3)◤	No
RTS,S Clinical Trials Partnership 2011 2012	Passive case detection	2 weeks-12 months post-3rd dose	*Older children (5-17 months):* Affected rate 2% vs 3.8%, PE 47.3% (95% CI 22.4-64.2)◤ *Younger children (6-12 weeks):* Affected rate 1.5% vs 2.3%,	No

			PE 36.6 (95% CI 4.6-57.7)◤	
2014		1-18 months post-3rd dose	*Older children (5-17 months):* Affected rate 2.6% vs 4.1%, PE 35.5% (95% CI 14.6-51.1)◤ *Younger children (6-12 weeks):* Affected rate 2.5% vs 2.9%, PE 14.9% (95% CI -19.5-38.9)◤	
		12-18 months post-3rd dose	*Younger children (6-12 weeks):* More frequent in the intervention group, p=0.17	Not significant
2015		13-28 months post-4th dose *(older children)*	*Older children (5-17 months):* Affected rate 0.01% vs 0.01%, VE -18.8% (95% CI -128.0-37.6) *(4-dose group)*§ Affected rate 0.01% vs 0.01%, VE -57.9% (95% CI -192.0-12.8) *(3-dose group)*§	
		13-19 months post-4th dose *(younger children)*	*Younger children (6-12 weeks):* Affected rate 0.01% vs 0.01%, VE 24.9% (95% CI -69.3-67.6) *(4-dose group)*§ Affected rate 0.01% vs 0.01%, VE 12.6% (95% CI -91.2-60.5) *(3-dose group)*§	
Tinto 2019	Passive case detection and retrospective data collection from medical charts in the routine health services	4-7 years post-1st dose *(older children)*	*Older children (5-17 months), all sites:* IR 0.004 vs 0.009 episodes/PY, VE 53.68% (95% CI -13.7-81.13) *(4-dose group)*§ IR 0.007 vs 0.009 episodes/PY, VE 23.33% (95% CI -67.1-64.82) *(3-dose group)*§	No
		1st dose-7 years *(older children)*	IR 0.015 vs 0.023 episodes/PY, VE 36.69% (95% CI 14.60-53.07) *(4-dose group)*§ IR 0.021 vs 0.023 episodes/PY, VE 10.14% (95% CI -18.1-31.64) *(3-dose group)*§	
		3.5-6.5 years post-1st dose *(younger children)*	*Younger children (6-12 weeks), all sites:* IR 0.007 vs 0.011 episodes/PY, VE 32.08% (95% CI -53.1-69.87) *(4-dose group)*§ IR 0.007 vs 0.011 episodes/PY, VE 37.57% (95% CI -44.4-73.01) *(3-dose*	

		group)§	
	1st dose-7 years *(younger children)*	IR 0.019 vs 0.028 episodes/PY, VE 30.99% (95% CI 4.67-50.04) *(4-dose group)*§ IR 0.019 vs 0.028 episodes/PY, VE 34.24% (95% CI 8.74-52.61) *(3-dose group)*§	

*Vaccine received on Year 1; ^Adjusted measures when available; §: intention-to-treat population, including all participants who received at least one dose of study vaccine; ◤: per protocol cohort; IR: incidence rate; PY: person-year; VE: vaccine efficacy.

Prevalence of infection

No evidence of rebound in the prevalence of infection at different post-intervention periods was observed in any of the studies assessed (**Table 28**).

Table 28. RTS,S studies evaluating prevalence of infection

Study	Type of follow-up	Follow-up period post-intervention	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Prevalence of infection				
Olotu 2013 Olotu 2016	Cross-sectional surveys◤	8 months 12 months 15 months 25 months 38 months 49 months 65 months 78 months 91 months -post 3rd dose	1% vs 4%, p=0.06 5% vs 14%, p=0.005 1% vs 6%, p=0.03 4% vs 7%, p=0.21 9% vs 20%, p=0.008 7% vs 5%, p=0.47 12.4% vs 11.9%, p=0.9 7.3% vs 6.3%, p=0.76 16.5% vs 21.8%, p=0.34	No Not significant at 49, 65 and 78 months
Sacarlal 2009	Cross-sectional surveys	31 months 43 months -post 3rd dose	15.8% vs 20.3%, p=0.049 12.2% vs 18.5%, p=0.004	No
RTS,S Clinical Trials Partnership 2014	Cross-sectional surveys	18 months - post 3rd dose	*Older children (5-17 months):* 7.4% vs 10.7%, PE 30.7 (95% CI 17.3-41.9)◤ *Younger children (6-12 weeks):* 6.9% vs 7.9%, PE 12.7% (95% CI -8.1-29.4)◤	No
Tinto 2019	Cross-sectional surveys	5 years post-	*Older children (5-17 months), all sites:*	No

	1st dose *(older children)*	0.34% vs 0.58%, VE 40.80% (95% CI 15.70-58.80) *(4-dose group)*§ 0.33% vs 0.58%, VE 42.70% (95% CI 17.40-60.80) *(3-dose group)*§
	4 years post-1st dose *(younger children)*	*Younger children (6-12 weeks), all sites:* 0.29% vs 0.36%, VE 20.80% (95% CI -17.5-46.90) *(4-dose group)*§ 0.37% vs 0.36%, VE -2.30% (95% CI -47.6-29.00) *(3-dose group)*§
	6 years post-1st dose *(older children)*	*Older children (5-17 months), all sites:* 0.23% vs 0.28%, VE 16.00% (95% CI -6.60-33.90) *(4-dose group)*§ 0.24% vs 0.28%, VE 13.00% (95% CI -10.7-31.7) *(3-dose group)*§
	5 years post-1st dose *(younger children)*	*Younger children (6-12 weeks), all sites:* 0.27% vs 0.29%, VE 9.20% (95% CI -18.0-30.10) *(4-dose group)*§ 0.31% vs 0.29%, VE -4.40% (95% CI -34.5-18.90) *(3-dose group)*§
	7 years post-1st dose *(older children)*	*Older children (5-17 months), all sites:* 0.24% vs 0.29%, VE 16.40% (95% CI -5.90-34.00) *(4-dose group)*§ 0.29% vs 0.29%, VE 0.10% (95% CI -25.8-20.70) *(3-dose group)*§
	6 years post-1st dose *(younger children)*	*Younger children (6-12 weeks), all sites:* 0.24% vs 0.24%, VE -1.40% (95% CI -34.7-23.60) *(4-dose group)*§ 0.26% vs 0.24%, VE -6.80% (95% CI -42.0-19.60) *(3-dose group)*§

^Adjusted measures when available; ◤: per protocol cohort; §: intention-to-treat population, including all participants who received at least one dose of study vaccine; PE: protective efficacy; VE: vaccine efficacy.

All-cause mortality

No evidence of rebound in all-cause mortality over different post-intervention periods was observed in any of the studies assessed (**Table 29**).

Table 29. RTS,S studies evaluating all-cause mortality

Study	Type of follow-up	Follow-up period post-intervention	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Sacarlal 2009	Active and passive surveillance	0.5-43 months	1.2% (12 deaths/1012) vs 2.2% (22 deaths/1010), p=0.087§	No

		post-3rd dose		
RTS,S Clinical Trials Partnership 2011	Passive surveillance	12 months post-1st dose	*Older children (5-17 months)§:* 0.9% (56 deaths/5949, 95% CI 0.7-1.2) vs 0.9% (28 deaths/2974, 95% CI 0.6-1.4) *Younger children (6-12 weeks)§:* 1.1% (49 deaths/4358, 95% CI 0.8-1.5) vs 0.8% (18 deaths/2179, 95% CI 0.5-1.3)	No
2012	Passive surveillance	14 months post-1st dose	*Younger children (6-12 weeks)§:* 1.5% (66 deaths/4358, 95% CI 1.2-1.9) vs 1.3% (28 deaths/2179, 95% CI 0.9-1.9)	Not significant
2014	Passive surveillance	18 months post-3rd dose	*Older children (5-17 months)◤:* 0.8% (40 deaths/4557)vs 0.9% (22 deaths/2328) PE -7.1% (95% CI -64.1-46.1), p=0.788 *Younger children (6-12 weeks)◤:* 1.3% (52 deaths/3996) vs 1.1% (23 deaths/2007) PE -13.6% (95% CI -94.4-31.7), p=0.712	
2015	Active and passive surveillance	48 months post-1st dose (*older children*)	*Older children (5-17 months)§:* 2% (61 deaths/2976) vs 1.5% (46 deaths/2974) VE -32.5 (95% CI -98.7-11.1), p=0.17 *(4-dose group)* 1.7% (51 deaths/2972) vs 1.5% (46 deaths/2974) VE -10.9% (95% CI -69.0-27.0), p=0.61 *(3 dose group)*	
		39 months post-1st dose (*younger children*)	*Younger children (6-12 weeks)§:* 2.3% (51 deaths/2180) vs 1.9% (42 deaths/2179) VE -21.4% (95% CI -87.2-20.9), p=0.40 *(4-dose group)* 2.5% (54 deaths/2178) vs 1.9% (42 deaths/2179) VE -28.6% (95% CI -97.3-15.6), p=0.22 *(3 dose group)*	

^Adjusted measures when available; ◤: per protocol cohort; §: intention-to-treat population; PE: protective efficacy.

Hospital admissions

No rebound in hospital admissions during the follow-up period post-intervention was observed (**Table 30**).

Table 30. RTS,S studies evaluating hospital admissions

Study	Type of follow-up	Follow-up period post-intervention	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Malaria-associated hospital admissions				
Sacarlal 2009	Passive surveillance	0.5-43 months post-3rd dose	VE 23% (95% CI -1.7-41.9), p=0.078	No
RTS,S Clinical Trials Partnership 2014	Passive surveillance	18 months post-3rd dose	*Older children (5-17 months):* 5.2% vs 8.8%, PE 41.5% (95% CI 29.1-51.7)◤ *Younger children (6-12 weeks):* 4.1% vs 5%, PE 17.1% (95% CI -7.3-35.7)◤	No
All-cause hospital admissions				
Sacarlal 2009	Passive surveillance	0.5-43 months post-3rd dose	175 vs 194 admissions VE 22.2% (95% CI -3.8-41.7), p=0.088	No
RTS,S Clinical Trials Partnership 2014	Passive surveillance	18 months post-3rd dose	*Older children (5-17 months):* 15.5% vs 19.1%, PE 19.0 (95% CI 8.5-28.1)◤ *Younger children (6-12 weeks):* 17.9% vs 19.1%, PE 6.1% (95% CI -6.6-17.2)◤	No

^Adjusted measures when available; ◤: per-protocol cohort; PE: protective efficacy; VE: vaccine efficacy.

3.4.4. Other strategies

3.4.4.1. Combination of strategies

In Nigeria, the Garki project assessed the impact of three or four rounds of residual spraying with propoxur at intervals of two months before and during each of the two main transmission seasons of 1972 and 1973 in combination with MDA with sulfalene-pyrimethamine every 10 weeks (low-frequency areas) or every

two weeks in the wet seasons and every 10 weeks in the dry season (high-frequency areas) (**Molineaux 1980** (3)). After the 18-month intervention period, children less than 10 years that lived in the high-frequency areas (the ones that received the most intensive strategy) received four rounds of chloroquine every five weeks during the main transmission season of 1974, and all villages that had received MDA were provided with chloroquine treatment for people reporting fever. The high-frequency areas together with one cluster of untreated villages (control) were followed up for two additional years (post-intervention phase). Demographic-parasitological surveys that included the collection of a thick blood film were conducted every 10 weeks during the intervention period and local residents were employed as collectors of data on births, deaths and migration. During the post-intervention phase, infants were examined every five weeks in the dry season and every two weeks in the wet season. In the first wet season after the intervention phase, overall parasite prevalence reached the baseline or control level, went down during the following dry season, and increased back to baseline levels in the subsequent wet season, but no clear evidence of rebound was observed. However, when looking at age-specific data, a temporary increase in parasite prevalence above that in the control area was observed in the first post-intervention wet season in the population aged more than 10 years that had received the intervention, but these differences were "not very large and tended to disappear over time". No clear indication of a rebound in mortality was reported either (3,5).

3.4.4.2. Cotrimoxazole

One RCT that assessed the effect of prolonging cotrimoxazole prophylaxis until four years of age in HIV-exposed children in eastern Uganda was included (**Homsy 2014** (13)). Daily cotrimoxazole was administered to HIV-exposed infants aged 6 weeks to 9 months until breastfeeding cessation and HIV-status confirmation. At the end of breastfeeding, children who remained HIV-uninfected were assigned to discontinue cotrimoxazole or to continue prophylaxis until two years of age. At age two years, those children who continued cotrimoxazole prophylaxis were randomly assigned to discontinue or continue prophylaxis until four years of age. A cohort of 100 HIV-unexposed uninfected children who never received prophylaxis was included for indirect comparisons[17]. All children were followed-up until five years of age. When comparing the incidence of clinical malaria among groups according to cotrimoxazole randomization and ages, the following was observed: incidence of clinical malaria from cessation of breastfeeding to two years of age was 4.60 episodes per person-year (PPY) (95% CI 4.17-5.07) in HIV-

[17] Although HIV-exposed treatment groups were randomly assigned, the HIV-infected and HIV-unexposed children were not randomised and thus were not directly comparable to HIV-exposed children (13).

exposed children who stopped cotrimoxazole prophylaxis after breastfeeding cessation, as compared to an incidence from enrolment (6 weeks-12 months of age) to two years of age of 4.63 PPY (95% CI 4.29-4.99) in the group that never received cotrimoxazole. Incidences at 2-4 years of age were 5.95 episodes per PPY (95% CI 5.57-6.35) in HIV-exposed children who stopped cotrimoxazole prophylaxis after breastfeeding cessation, 5.60 episodes per PPY (95% CI 5.12-6.1) in HIV-exposed children who stopped prophylaxis at two years of age, and 5.82 episodes per PPY (95% CI 5.46-6.2) in the unexposed, untreated group. Between four and five years of age, incidences were 5.32 episodes per PPY (95% CI 4.8-5.89) in the HIV-exposed children who stopped cotrimoxazole prophylaxis after breastfeeding cessation, 4.81 episodes per PPY (95% CI 4.18-5.51) in HIV-exposed children who stopped prophylaxis at two years of age, 4.61 episodes per PPY (95% CI 3.95-5.35) in HIV-exposed children who stopped prophylaxis at four years of age, and 4.99 episodes per PPY (95% CI 4.51-5.5) in the HIV unexposed, untreated group. According to these data, no evidence of rebound in the incidence of clinical malaria was observed in the year after cotrimoxazole prophylaxis was discontinued after breastfeeding cessation. However, the incidence of clinical malaria was higher (but not statistically significant) in the HIV-exposed children who discontinued cotrimoxazole after the end of breastfeeding both between age 2 to 4 years and between age 4 to 5 years when compared to the untreated cohort. This rebound effect was not observed in the incidence of complicated malaria in the year after cotrimoxazole discontinuation at any age.

3.5. Duration of rebound

The long follow-up periods after chemoprophylaxis in **Greenwood 1995** (28) and **Aponte 2007** (18) provide some valuable information on the duration of rebound and its relationship with age. **Figure 2**, reprinted from **Aponte 2007** (doi:10.1371/journal.pmed.0040242.g002) (18), shows the age-specific incidence of clinical manifestations of malaria (clinical malaria, severe malaria and severe anaemia) from age 2 months until 4 years in the group receiving weekly chemoprophylaxis with pyrimethamine- dapsone from age 2-12 months and the control group (17). The malaria risk in the control group was highest in infants and declined slowly during the first 4 years of life, while in children receiving chemoprophylaxis there was a reduced risk of malaria during the first year of life (although the protective effect decreased as infants grew older) and a rebound during the second and third years of life.

Figure 2. Incidence of clinical manifestations of malaria by age in the group of children who received chemoprophylaxis and the group of children who received placebo. (A) Clinical malaria, (B) severe malaria, and (C) severe anaemia. Reprinted from Aponte 2007 (doi:10.1371/journal.pmed.0040242.g002) (18).

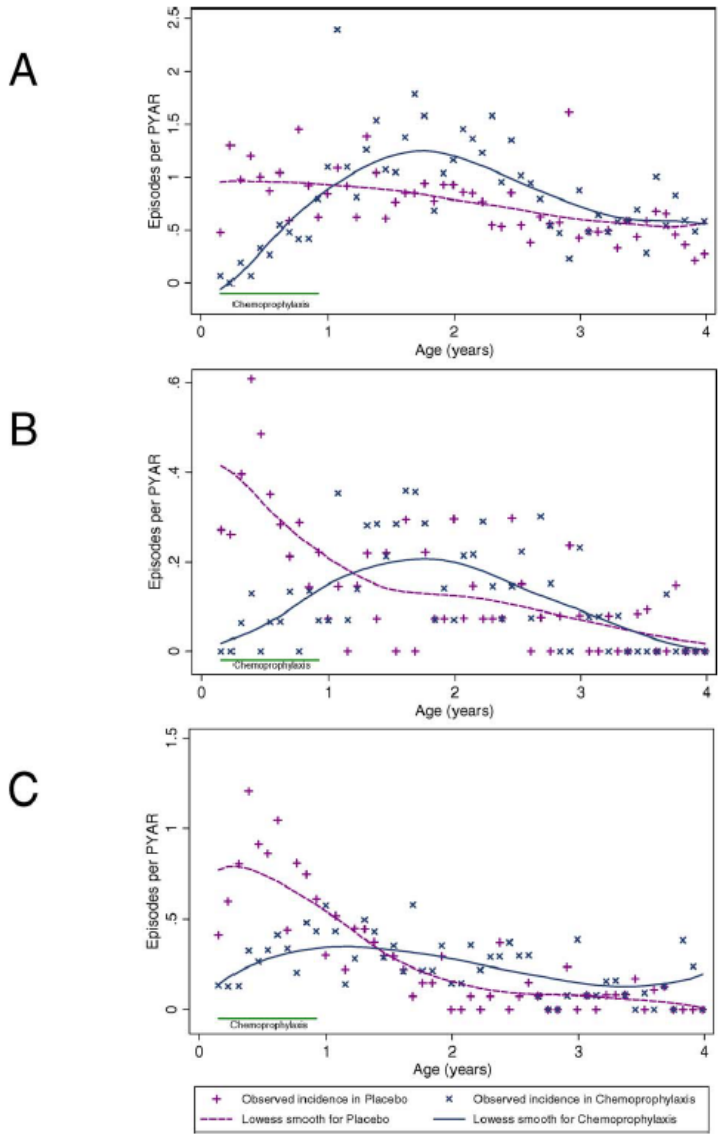
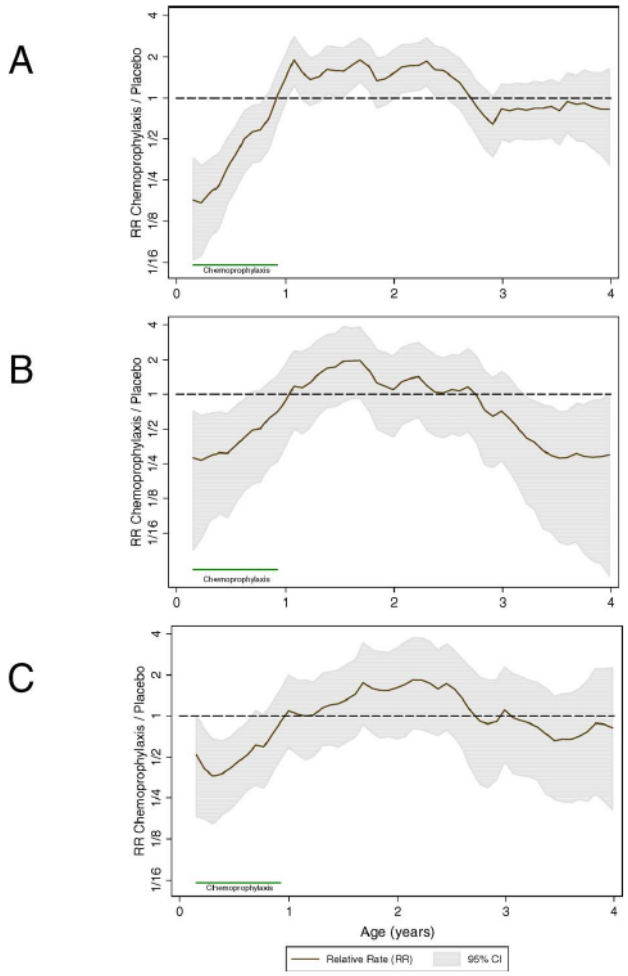


Figure 3, also reprinted from **Aponte 2007** (doi:10.1371/journal.pmed.0040242.g003) (18), shows the relative rates of clinical manifestations of malaria by age. Once prophylaxis was stopped, children in the

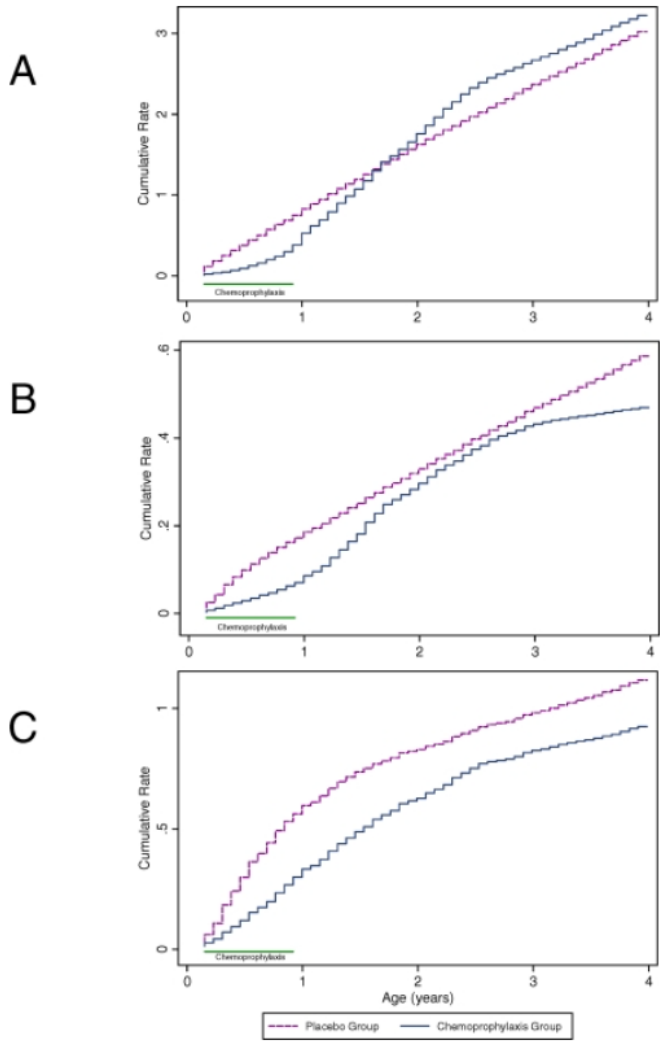
chemoprophylaxis arm had a significantly higher rate of clinical malaria compared with the children that had received placebo, which lasted for at least 18 months (**Figure 3A**). Similar patterns are seen for severe malaria and severe anaemia in **Figures 3B** and **3C**, respectively, although the rebound is shorter or smaller.

Figure 3. Relative rates of clinical manifestations of malaria by age. (A) Clinical malaria, (B) severe malaria, and (C) severe anaemia. Relative-rate values higher than 1 indicate a higher incidence in the chemoprophylaxis group, whereas relative-rate values lower than 1 indicate a higher incidence in the placebo group. Reprinted from Aponte 2007 (doi:10.1371/journal.pmed.0040242.g003) (18).



Cumulative rates (CRs) of clinical manifestations of malaria are shown in **Figure 4**, reprinted from **Aponte 2007** (https://doi.org/10.1371/journal.pmed.0040359.g001) (18). These show that, even though the CR from age 2 months until 4 years for clinical malaria was slightly higher in the chemosuppressed group compared to the control group (**Figure 4A**), for severe malaria and severe anaemia it was lower in the chemosuppressed group (see results in Tables 3 and 4).

Figure 4. Cumulative rates of clinical manifestations of malaria(A) Clinical malaria, (B) severe malaria, and (C) severe anaemia. Reprinted from Aponte 2007 (https://doi.org/10.1371/journal.pmed.0040359.g001) (18).



In The Gambia, the incidence of malaria during the first year after chemoprophylaxis was stopped was higher in the intervention group (including all participants who had received chemoprophylaxis from age 3 months to 5 years) compared to the control group (p=0.02). No evidence of a significant rebound in mortality was found after chemoprophylaxis was stopped at the age of 5 years (**Figure 5**, reprinted from **Greenwood 1995** (28)). However, the probability of dying between the ages of 5 and 6 years (the first year after chemoprophylaxis was stopped) was higher in the chemoprevention group than in the control group (see Table 6). This difference was not statistically significant, but the number of deaths was small, so we cannot rule out a rebound during that first year. The probability of dying between the ages of 5 and

10 years was similar in both groups (when including only those recruited at trial start) or lower in the chemoprevention group (when including all participants, whether recruited at trial start or over the following 6 years). During the overall surveillance period (from trial start to end of follow up) mortality among children in the chemoprophylaxis group was 15% less than among children in the placebo group, showing that the intervention provided a positive "net benefit" in averting deaths.

Figure 5. Probability of dying in a cohort of children who received chemoprophylaxis from the age of 3 months to 5 years. Reprinted from Greenwood 1995, edited (28).

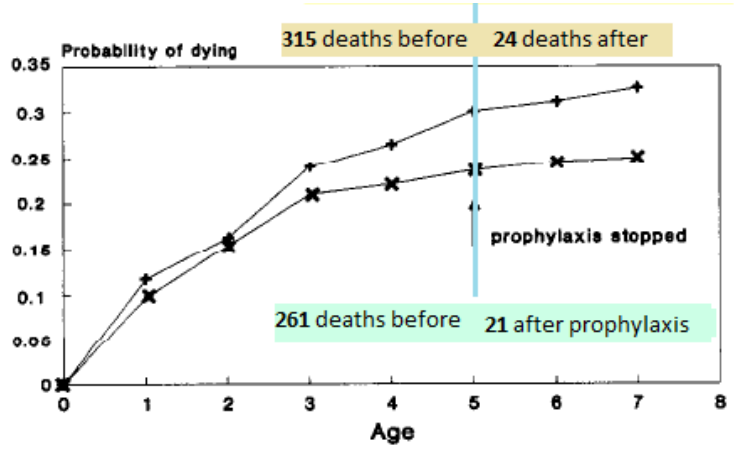
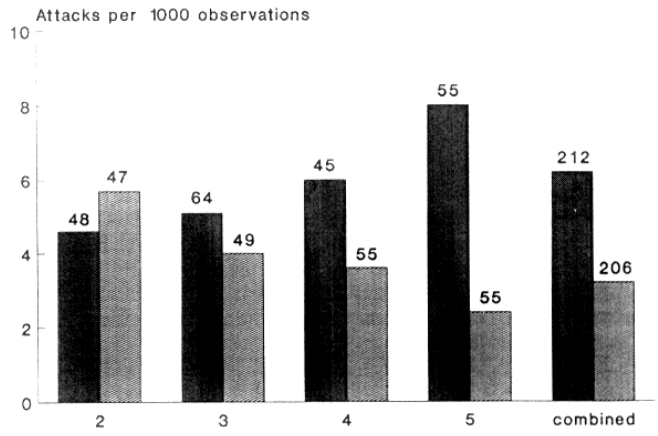


Fig. 1. The probability of dying from birth to the age of 7 years in a cohort of children who received chemoprophylaxis with Maloprim® (×) or placebo (+) from the age of 3 months to 5 years.

Figure 6. Number of malaria "attacks " (fever with parasitaemia) during the year after the intervention was discontinued (5 to 6 years of age). Reprinted from Greenwood 1995 (28).



The prevalence of fever (axillary temperature >37.5ºC) accompanied by malaria parasitaemia ('Attacks') in children visited weekly between the ages of 5 and 6 years who had received either chemoprophylaxis with Maloprim" (dark bars) or placebo (light bars) for the previous 2-5 years. Figures above the bars indicate the number of children in each group.

This study in The Gambia is also the only one that had participants with different durations of exposure to chemoprevention. As shown in **Figure 6**, the longer the chemoprevention received, the larger the rebound seems to be.

Both studies point towards a time-limited rebound effect after chemoprophylaxis discontinuation, which seems longer and larger for clinical malaria than for severe malaria. There is no evidence of a rebound in mortality, although the small numbers do not allow to completely rule it out. Both studies show that overall, when taking into account the cases or deaths averted during the intervention period by chemoprophylaxis, the benefit of the interventions outweighs the rebound, with a lower cumulative risk in the intervention group compared to the control.

3.6. Effect of age on the development of immunity

The effect of age on the development of malaria immunity is not fully understood, as this relationship may be confounded by the intensity of transmission. People that live in high transmission settings are exposed to malaria at earlier ages than those living in less intense transmission areas. The clinical presentation of severe malaria varies with age, with severe anaemia being more frequent in young children and cerebral malaria in older children, but it is unclear if this is driven by the frequency of infection or age itself (18,74). A study in Indonesia that compared two groups of people living in the same area, where one group had little previous exposure to malaria and the other had life-long intensive exposure, found that the degree of protection was determined by recent exposure and age, independently of the history of intensive exposure over the previous years (75) and suggested that adults may need fewer malaria episodes to develop immunity than children (76). Results from a four-year follow-up of a chemoprophylaxis trial in Tanzania suggested that a reduction in exposure during the first year of life could delay the development of immunity and result in a rebound in clinical disease (including clinical malaria, severe malaria and severe anaemia) (18), similar to what was observed in other chemoprophylaxis studies (28). Nevertheless, when accounting for all the cumulative cases since the beginning of the intervention, this shift in the age pattern of disease was not associated with an increase in severe malaria or severe anaemia (18), hence supporting the hypothesis that older individuals may develop effective responses to the disease more efficiently than younger individuals.

3.7. Additional studies

3.7.1. Insecticide-treated nets

More than 20 years ago, a series of randomised controlled trials in different sites in Africa demonstrated that ITNs and insecticide-treated curtains (ITCs) were effective in reducing child mortality (77–81), with six lives saved per year for every 1000 children protected (82). Around that same time, it was suggested that the short-term mortality improvements gained through transmission control strategies such as ITNs in areas of high endemicity could reduce the acquisition of natural immunity and result in increased severe disease and mortality in older ages (4,83). At the end of the original ITN trials, which had a duration of two years, the control groups were provided with ITNs or ITCs, as the efficacy of the intervention was proven (84). Even though a control arm without the intervention was not available at follow-up anymore to assess whether a rebound effect was seen, some ITN trials followed the children for longer periods, providing further evidence on the topic. Binka and colleagues (84) presented the results of a seven and a half year follow-up of the initial ITN trial conducted in Ghana (79). During the two years follow-up included in the main trial, the nets in the intervention compounds were reimpregnated every six months and at the end of the trial, ITNs were also provided to the control areas. After five years and a half, no evidence of delayed mortality or severe disease was observed (84). In a study in Burkina Faso, half of the population received ITCs to cover doors, windows and eaves, and the other half received ITCs two years later. Over six years of implementation, during which curtains were annually re-treated or replaced, no evidence of increased mortality in older children was observed either (85). Similar results were found in an extended evaluation of the impact of ITNs in Kenya, where nets were distributed to control villages at the end of the trial and demographic surveillance continued (86). After up to six years of ITN use, no differences in mortality were observed between the children that had received the intervention during the trial and the former control group. In rural Tanzania, socially marketed ITNs were associated with a 27% increase in survival in children aged 1 month to 4 years over three years of implementation (87). To estimate the association between use of ITNs during the first years of life and survival to adulthood, a 22-year follow-up of this same cohort was conducted, showing that the survival benefit from early-life use of treated nets persisted to adulthood (88).

3.7.2. Modelling studies

Seven relevant modelling studies were identified. **Coleman 1999** (63) presented a model that estimated the cost and disability-adjusted life years (DALYs) per child aged 1–119 months with and without an ITN

intervention. The threshold at which the intervention would no longer be cost-effective was dependent on the age range at which reductions in mortality and morbidity due to ITNs and then rebound occurred. Based on empirical estimates of age-specific malaria mortality in Sub-Saharan Africa, the study concluded that if mortality and morbidity reductions occurred in children aged 1-59 months and rebound in the 5-9 years age group, it was unlikely that this threshold rate would be reached, so the ITNs are likely to be DALY-averting. On the other hand, if reductions occurred in children aged 1-35 months and rebound in ages 3-6 years, ITNs might not be DALY-averting. **Gurarie 2007** (65) presented a model to study the effects of drug and vaccine interventions on frequency, severity and age pattern of disease and found possible rebound effects following intervals of drug treatment, but not after vaccination. Three studies assessed the effects of intermittent preventive treatment: **Ross 2018** (67) predicted a modest increase in susceptibility to malaria between IPTi doses and following the last dose, but these were outweighed by the cumulative benefits; **Gosling 2008** (69) noted that a decline in transmission intensity during the study period would increase the protective efficacy of IPTi (and potentially other interventions) and extend it into the second year of life (as observed in the Tanzania IPTi study (**Schellenberg 2001** (31)) and thus decrease the possibility of a rebound; and **Águas 2009** (64) predicted that the benefits of implementing IPTi in infants would surpass the drawbacks of having more cases in older children. For SMC, a rebound in clinical cases could be expected less than one year after the last dose of SP, but of marginal magnitude. **Okell 2011** (66) and **Sallah 2021** (68) modelled the effects of MDA and found increases in transmission (i.e., malaria resurgence) after the intervention, but no rebound (i.e. higher transmission in the intervention areas when compared to no intervention).

3.7.3. Ongoing studies

We identified four relevant ongoing studies, expected to be completed between 2022 and 2023. The risk of malaria rebound after MDA is being investigated in the Greater Mekong Subregion (GMS), utilising data from malaria intervention trials in Myanmar (50,89) and other trials in the GMS (90). Rebound is also being assessed in a two-year extension of the RTS,S/AS01 plus SMC trial taking place in Burkina Faso and Mali (91). In Tanzania, a randomised controlled trial of intermittent preventive treatment in school-aged children includes a second non-interventional year to assess possible rebound effects (92,93). The impact of withdrawing IRS and MDA is also being assessed in a study in Uganda, planned to be completed in May 2022 (94).

Discussion

Even though the rebound phenomenon has been a topic of discussion for a long time, the majority of studies assessed in this review were not specifically designed to evaluate the presence or absence of a rebound after withdrawal of the intervention, hence did not have a specific methodology to assess it, but rather measured the impact of the interventions during an extended follow-up period. It is important to differentiate between the duration of protection of an intervention and the presence of a rebound after intervention withdrawal. While the former may result in an increase in the risk of disease due to waning of protection over time that may be similar to the risk observed in the population that has not received the intervention (i.e. resurgence), the latter refers to an increased risk in the population that has received the intervention as compared to the control group.

The studies assessed in this review used different types of interventions, with different efficacies and durations, study designs, target age groups, duration of follow-up, outcomes and methods to measure the outcomes, which made it difficult to compare across all of them and draw general conclusions. Overall, the evidence reviewed suggests there may be rebound in some outcomes, mainly uncomplicated clinical malaria. For more severe forms of the disease, there is more discrepancy in the results. However, we need to take into account that most of the studies were not powered to evaluate the rebound for severe malaria or mortality during the post-intervention period, as the sample size was mostly powered to evaluate intervention efficacy for clinical malaria as the primary outcome. Thus a non-significant increase in the risk of the more severe outcomes during the post-intervention period in some studies (for example mortality during the initial post-intervention period in the chemoprophylaxis studies in The Gambia (**Greenwood** (28)) and Tanzania (**Aponte 2007** (18)) might be due to chance, but we cannot rule out a rebound. Additionally, given that malaria risk, and especially severe malaria, decreases with increasing age, a complete analysis of the risk over time is needed when evaluating an intervention targeting children, to be able to assess how the effect of the intervention changes with time. Also, the analysis should take into account the cases averted during the intervention period, to understand the "net benefit" of the intervention. This should be addressed by analysing not only the outcome of interest over different time periods, but also estimating the cumulative effect since the beginning of the intervention, hence taking into account the cases averted due to the intervention and the difference in risk of specific outcomes as children grow older. For example, in the **Menéndez 1997** (17) chemoprophylaxis trial in Tanzania, a rebound in severe malaria and severe anaemia was found after the intervention was discontinued, but the cumulative rates from the beginning of the intervention until the end of follow up

(three years post-intervention) were lower in the chemoprophylaxis group than in the control group (**Aponte 2007** (18)). This suggests that overall, the benefit of the intervention in averting severe malaria outcomes outweighed the additional risk caused during the rebound period. It also leads to hypothesising that delaying the acquisition of immunity against severe malaria outcomes to older ages might be beneficial, as children might be better able to build NAI. Finally, when interpreting rebound results, there should also be consistency in the findings of a study: an increase in both the risk of clinical malaria and severe malaria is plausible, but an increase in the risk of severe malaria without evidence of an increase in the risk of clinical malaria -as observed in an IPTi trial (**Mockenhaupt 2007** (40))- could be due to chance.

Whether rebound occurs or not depends on several factors such as the efficacy and duration of the intervention, the transmission intensity, and the rate of NAI acquisition, among others. Overall, rebound seems to be associated with interventions that provide more protection and for a longer period of time (e.g. continuous prophylaxis), whose protection wanes rapidly (i.e., drug-based strategies) and/or that target younger ages. So, the larger the degree of reduction in exposure provided by the intervention, the slower the development of NAI and the higher the possibility of a rebound. Among the studies assessed, five drug-based studies reported a significant rebound effect for clinical malaria: three of them after discontinuation of chemoprophylaxis, one after IPTi and one after three rounds of SMC. The level of transmission before, during and after the period of protection may also have an effect on the size of the rebound, as if the intervention targets all ages and results in a reduction in malaria transmission at the community level, the overall risk of malaria once the intervention is withdrawn will be lower than it was before the intervention. On the contrary, for interventions that don't result in an overall decrease in transmission or in cases where gains can't be sustained, the risk of rebound might be higher. Seasonality may also have an effect on the risk of rebound, and it is important to adequately account for seasonal transmission differences in the design and analysis. The size of the rebound may also be lower when other malaria control interventions are in place, as some level of protection will be provided and therefore the risk of malaria won't be as high as it would be without any control intervention in place.

Studies aiming to assess the risk of rebound should also be vigilant of other potential biases and limitations regarding the choice of the comparison group/area; the change in transmission intensity over the study period (due to the scale up of other control strategies or climatic factors); the duration of the follow up period post-intervention; etc. For example, in many implementation programmes the intervention is targeted to the highest risk populations, thus after withdrawal of that intervention, this population will still have higher incidence because of its higher original risk compared to other populations. Also, some

of the studies included in this review had follow-up periods shorter than one year, which limited the ability to detect a rebound that might have occurred after the end of the follow-up. This is especially important in highly seasonal transmission settings, where the rebound would be seen during the following transmission season one year later. Therefore, there's a need to quantify the rebound phenomenon in a standardised manner across studies, and the approach and methodology to be used needs to be defined.

We have not identified any studies with follow-up periods after ITN and IRS discontinuation in both intervention and control arms, likely due to the fact that these strategies are already proven to be effective and part of routine control strategies. Also, no MDA studies evaluating the risk of malaria in the post-intervention period were found, those included only evaluated cumulative risks since the beginning of the intervention and over an extended follow-up. However, the possibility of a rebound phenomenon should be evaluated and needs further research.

Finally, we have not included any studies specifically evaluating rebound in pregnant women. This would require a separate literature search and might need a different definition of rebound. In pregnant women receiving malaria control interventions, rebound might need to be evaluated during the following pregnancy rather than (or in addition to) the period post-intervention, as rebound would be related to the interference with the development of pregnancy-specific malaria immunity.

Conclusions

Some studies have observed a period of increased malaria risk after time-limited protection from malaria, mainly for uncomplicated clinical malaria. Even though a rebound for severe malaria and anaemia has also been found in some studies, those that evaluated the cumulative rate since the beginning of the intervention and during a long follow-up period, found that the overall risk was lower in the intervention group, thus providing a positive "net benefit". Rebound seemed to be associated with interventions that provided more protection and for a longer period of time (e.g. continuous prophylaxis) and/or targeting younger ages, as they interfere more with the development of NAI. There is not enough evidence to conclude that rebound precludes the implementation of malaria control strategies, specially those targeting the most vulnerable populations. However, additional measures might be needed (e.g. improved access to care) after the discontinuation of certain interventions, to mitigate the effect of rebound. Finally, there is a need to define a standardised approach and methodology to assess the rebound phenomenon.

Methodological recommendations

- There is a need to standardise the definition of rebound and differentiate this phenomenon from similar concepts such as malaria resurgence and age shift.
- When evaluating rebound in studies of new strategies or interventions, it should be taken into consideration that risk changes over time as children grow older. Also, the "net benefit" of the intervention should be evaluated, taking into account the cases averted during the intervention period. Risks should therefore be assessed both for the post-intervention period and for the whole follow-up period since the beginning of the intervention, through the use of cumulative risks.
- The evaluation of rebound should use the same methods and outcomes as the evaluation of the efficacy of the intervention.
- It seems like if there is a rebound effect, it will occur soon after the intervention stops, but it can last for several months and even longer than one year. Therefore, studies should plan for at least one year of follow-up after intervention cessation and, in case an increased risk is still observed by the end of that year, continue the follow-up until the risk is equal or less than in the control arm.
- Sample size estimations should take into consideration that, during the post-intervention follow-up, the malaria risk might decrease as children grow older and thus the sample size needed to be able to detect a rebound will be higher.
- The most frequent clinical presentations of severe malaria in children will change over time as children grow older, with severe anaemia and respiratory distress being more frequent at younger ages and cerebral malaria at older ages. Thus, the choice of the outcome or definition of severe malaria needs to take this into account and the sample size should be powered accordingly.

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