GiveWell

INTERVENTION REPORT

# Seasonal Malaria Chemoprevention

Version: February 2018

# About GiveWell

**GiveWell** is a nonprofit dedicated to finding outstanding giving opportunities and publishing the full details of our analysis to help donors decide where to give.

Unlike charity evaluators that focus solely on financials, assessing administrative or fundraising costs, we conduct in-depth research aiming to determine how much good a given program accomplishes (in terms of lives saved, lives improved, etc.) per dollar spent. Rather than try to rate as many charities as possible, we focus on the few charities that stand out most (by **our criteria**) in order to find and confidently recommend high-impact giving opportunities (our **list of top charities**).

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This report was originally researched, written, and published by GiveWell. To view the latest version of this report on GiveWell's website, please visit **this page**.

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# Summary


- **What is the program?** Seasonal malaria chemoprevention (SMC) involves giving children under the age of 5 full malaria treatment courses intermittently during the malaria season. In general, we focus our discussion on work similar to that of **Malaria Consortium's SMC program** (one of our **top charities**).
- **What is its evidence of effectiveness?** Seven randomized controlled trials provide strong evidence that this program reduces cases of malaria. The trials were insufficiently powered to detect effects on all-cause mortality.
- **How cost-effective is it?** SMC programs appear to be in the range of cost-effectiveness of our other **priority programs**.
- **Does it have room for more funding?** It appears that there is a large remaining global need for additional funding for SMC programs.
- **Bottom line:** SMC is one of our **priority programs**.


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# What is the problem?

Malaria is one of the leading causes of child deaths in Africa.[1] It is transmitted from person to person by infected mosquitoes.[2] It involves flu-like symptoms including fever.[3] As discussed below, there is evidence connecting malaria with death (particularly in children under 5), anemia, splenomegaly (enlarged spleen), other nutrition-deficiency-related indicators, and low birthweight.

It is also believed that malaria can cause permanent disability (hearing impairment, visual impairment, epilepsy, etc.).[4]

# What is the program?

The World Health Organization (WHO) defines seasonal malaria chemoprevention as "the intermittent administration of full treatment courses of an antimalarial medicine to children during the malaria season in areas of highly seasonal transmission."[5] It "consists of administering a maximum of four treatment courses of SP [sulfadoxine–pyrimethamine] + AQ [amodiaquine] at monthly intervals to children aged 3–59 months in areas of highly seasonal malaria transmission"[6] and "during the high malaria transmission period."[7] SMC was "formerly known as 'intermittent preventive treatment of malaria in children [IPTc].'"[8]

According to the World Health Organization (WHO):

The suitability of an area for SMC is determined by the seasonal pattern of rainfall, malaria transmission and the burden of malaria. SMC is recommended for deployment in areas:

- where more than 60% of the annual incidence of malaria occurs within 4 months;
- where there are measures of disease burden consistent with a high burden of malaria in children (incidence ≥ 10 cases of malaria among every 100 children during the transmission season);
- where SP and AQ retain their antimalarial efficacy.[9]

According to the WHO, "SMC provides protection for up to 1 month after each complete (3-day) course.... Health workers should give the dose of SP and the first dose of AQ to the children

under their direct observation and should advise the children's caregivers on how to give the second and third doses of AQ to the child at home."[10]

# Does the program have strong evidence of effectiveness?

Seven randomized controlled trials provide strong evidence that this program reduces cases of malaria. A 2012 **Cochrane Collaboration** review concluded, "In areas with seasonal malaria transmission, giving antimalarial drugs to preschool children (age [less than] 6 years) as IPTc during the malaria transmission season markedly reduces episodes of clinical malaria, including severe malaria. This benefit occurs even in areas where insecticide treated net usage is high."[11] The trials were insufficiently powered to detect effects on all-cause mortality.

## Evidence from randomized controlled trials

The Cochrane review summarizes the results of seven randomized controlled trials (RCTs). It states:

Seven trials (12,589 participants), including one cluster-randomized trial, met the inclusion criteria. All were conducted in West Africa, and six of seven trials were restricted to children aged less than 5 years. IPTc prevents approximately three quarters of all clinical malaria episodes (rate ratio 0.26; 95% CI 0.17 to 0.38; 9321 participants, six trials, high quality evidence), and a similar proportion of severe malaria episodes (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials, high quality evidence). These effects remain present even where insecticide treated net (ITN) usage is high (two trials, 5964 participants, high quality evidence).

IPTc probably produces a small reduction in all-cause mortality consistent with the effect on severe malaria, but the trials were underpowered to reach statistical significance (risk ratio 0.66, 95% CI 0.31 to 1.39, moderate quality evidence). The effect on anaemia varied between studies, but the risk of moderately severe anaemia is probably lower with IPTc (risk ratio 0.71, 95% CI 0.52 to 0.98; 8805 participants, five trials, moderate quality evidence). Serious drug-related

adverse events, if they occur, are probably rare, with none reported in the six trials (9533 participants, six trials, moderate quality evidence).

Amodiaquine plus sulphadoxine-pyrimethamine is the most studied drug combination for seasonal chemoprevention. Although effective, it causes increased vomiting in this age-group (risk ratio 2.78, 95% CI 2.31 to 3.35; two trials, 3544 participants, high quality evidence). When antimalarial IPTc was stopped, no rebound increase in malaria was observed in the three trials which continued follow-up for one season after IPTc.[12]

We have applied two adjustments to the results of the Cochrane meta-analysis on clinical malaria incidence:

- We identified two additional RCTs (**Tagbor et al. 2016**, **Matalinga et al. 2015**) published after the Cochrane review, which compare SMC with placebo. Both found smaller effect sizes on incidence of clinical malaria than the pooled results of the Cochrane meta-analysis.[13] We added **Tagbor et al. 2016** to our updated version of the Cochrane meta-analysis, but did not add **Matalinga et al. 2015** because courses were delivered at three monthly (rather than one monthly) intervals, and so are unlikely to have achieved similar reductions in malaria incidence to Malaria Consortium's SMC program.[14]
- One of the RCTs (**Dicko et al. 2008**) included in the meta-analysis treated participants every eight weeks (rather than monthly, as in the Malaria Consortium program). We have removed this study from the meta-analysis.[15]

After these two adjustments, the pooled estimate of the effect of SMC on clinical malaria episodes increases slightly (rate ratio 0.25; 95% CI 0.18 to 0.37).[16]

A World Health Organization report claims that SMC offers a high level of protection for about four weeks after the last treatment, after which protection appears to decline.[17] We have not independently vetted this claim. We note that some of the trials continued to collect malaria incidence up to six weeks after the last treatment was administered, which could underestimate the level of protection over a four week period. We have not included an adjustment to account for this underestimate because the trials do not report sufficiently granular data to separately estimate protective efficacy for the period up to four weeks after the last treatment.[18]

The Cochrane review also notes there is substantial heterogeneity between the program results, meaning the variance between results of different trials is unlikely to have occurred by chance.[19] The authors note there are insufficient trials to make meaningful conclusions about the causes

of this heterogeneity.[20] We reviewed two of the studies which find substantially lower reductions in malaria incidence (**Dicko et al. 2008**; **Tagbor et al. 2016**), and note possible causes in this footnote.[21]

## How does the Malaria Consortium SMC program compare to the programs addressed in these studies?

We examined the individual studies included in the Cochrane review to better understand how they compared to the **Malaria Consortium SMC program** (one of our **top charities**).

We found:

- Six of the seven trials delivered treatment on a monthly basis, as in Malaria Consortium's program.[22]
- Four of the seven trials treated children with a combination of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ), as in Malaria Consortium's program.[23]
- All seven trials were conducted in West Africa, where Malaria Consortium operates.[24]
- Six of the seven trials only treated children under 59 months of age, as in Malaria Consortium's program.[25]
- The number of courses ranged between two and five. Malaria Consortium typically delivers four courses.[26]
- Coverage of insecticide treated nets (ITNs) varied widely between <5% and 93%.[27]
- Weighted average coverage of SMC was ~90%, higher than our estimate of Malaria Consortium's coverage.[28]

We conclude that the trials in the Cochrane review are reasonably similar to Malaria Consortium's SMC program. We have included an adjustment in our cost-effectiveness analysis to account for differences in coverage between the RCTs and Malaria Consortium’s program.[29]

## Does the reduction in malaria incidence cause a similar reduction in mortality?

The trials included in the Cochrane review were underpowered to detect a significant effect on all-cause mortality.[30]

Our best guess is that the reduction in malaria incidence results in a similar reduction in mortality. We have limited evidence to support this claim but note that:

- We would expect that a reduction in clinical malaria from SMC results in a similar reduction in malaria mortality unless there was evidence that SMC was disproportionately likely to prevent non-severe cases of malaria.
- The Cochrane review finds that SMC prevents a similar proportion of severe malaria episodes and all clinical malaria episodes, though only two trials measured effects on severe malaria.[31]
- The Cochrane review notes that "IPTc probably produces a small reduction in all-cause mortality consistent with the effect on severe malaria, but the trials were underpowered to reach statistical significance (risk ratio 0.66, 95% CI 0.31 to 1.39, moderate quality evidence)."[32]

We have included an optional downward adjustment (which some contributors use) in our cost-effectiveness analysis to account for the possibility that SMC causes a smaller reduction in malaria mortality than malaria incidence.[33]

## Evidence of implementation at scale

We haven't seen rigorous evaluations of SMC's impact on mortality at large scale. However, we discuss implementation of SMC at scale and the coverage achieved by such programs in our **Malaria Consortium review**.

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## Possible developmental effects

Reducing exposure to malaria during childhood may have an effect on long term productivity and earnings, although we are uncertain about the magnitude of this effect. We have reviewed the evidence for the developmental effects of malaria prevention **here**.

## Possible negative / offsetting impacts

- **Possible development of drug resistance**. Resistance to Amodiaquine (AQ), and sulphadoxine-pyrimethamine (SP) may reduce the effectiveness of SMC over time. We spoke with Professor Sir Brian Greenwood (Professor of Clinical Tropical Medicine at London School of Hygiene & Tropical Medicine) about timelines for possible development of drug resistance. He told us:
  - Timelines are uncertain, but he believes based on historical experience that resistance to AQ/SP is unlikely to develop in the next 5-10 years.[34]
  - Some resistance to SP may have emerged in East Africa[35], but AQ has relatively little history of resistance.[36]
  - If resistance to SP/AQ did develop, dihydroartemisinin-pipearquine (DHAPQ) may be a viable alternative, although we have not carefully reviewed the evidence for DHAPQ.[37]

  We have not vetted these claims but they are consistent with our general impressions from reviewing relevant literature.
- **Possible rebound effects.** One potential issue with SMC is the possibility of disease rebound after treatment ends. We have not investigated this possibility in depth, but note that the Cochrane review includes three RCTs with post-intervention follow-up, none of which find evidence of a rebound effect.[38] We are not aware of any studies done to measure rebound effects after multiple years of treatment.[39]
- **Possible interaction with insecticide treated nets (ITNs).** Two of the RCTs in the Cochrane review promoted the use of ITNs to both the intervention and control group.[40] These trials found similar *proportional* reductions in malaria incidence to trials which did not promote ITNs.[41] If SMC and ITN coverage are expanded in the same area at the same

time, it is possible that the *absolute* reduction in malaria incidence attributable to each would be reduced. We have not carefully considered whether Malaria Consortium's SMC program is operating in areas where ITN coverage is being expanded.

# How cost-effective is the program?

SMC programs appear to be in the range of cost-effectiveness of our other **priority programs**. See our most recent **cost-effectiveness model** for estimates of the cost per life saved through **Malaria Consortium**-supported SMC programs. See our **Malaria Consortium review** for more details on the cost-per-treatment for SMC.

Note that our cost-effectiveness analyses are simplified models that do not take into account a number of factors. For example, our model does not include the short-term impact of non-fatal cases of malaria prevented. It also does not include possible **offsetting impacts** or other harms.[42]

There are limitations to this kind of cost-effectiveness analysis, and we believe that **cost-effectiveness estimates such as these should not be taken literally**, due to the significant uncertainty around them. We provide these estimates (a) for comparative purposes and (b) because working on them helps us ensure that we are thinking through as many of the relevant issues as possible.

# Does the program appear to have room for more funding?

For information on the global need for treatment and other potential funders of this program, see **this section of our Malaria Consortium review**.

# Our process

## 2016

In 2016 we completed an interim intervention report on SMC. We reviewed the Cochrane Collaboration review (discussed above), the ACCESS-SMC website, the section of the WHO website devoted to SMC, and some documents provided to us by **Malaria Consortium**.

## 2017

We investigated a small number of high-priority research questions based on our impression of the likelihood that they could substantively change our view of SMC:

- We reviewed the individual studies in the Cochrane Collaboration review and removed one (**Dicko et al. 2008**) because it delivered treatments bi-monthly rather than monthly.
- We searched for additional RCTs published after the Cochrane Collaboration review and added one (**Tagbor et al. 2016**) to the meta-analysis.
- We investigated possible **negative / offsetting impacts** including (i) possible emergence of drug resistance, (ii) possible interaction with ITNs, (iii) rebound effects.
- We updated our coverage adjustment to account for imperfect coverage in the trials in the Cochrane Collaborate review.
- We explored possible sources of heterogeneity in the effects of SMC, which we will use to inform our questions for potential top charities.

Research originally published on **GiveWell.org**

# Sources

| Document | Source |
|---|---|
| ACCESS-SMC: Partners | **Source** (**archive**) |
| Catholic Relief Services: ACCESS-SMC in the Sahel | **Source** (**archive**) |
| Cissé et al. 2006 | **Source** (**archive**) |
| Cochrane: Identifying and measuring heterogeneity | **Source** (**archive**) |
| Dicko et al. 2008 | **Source** (**archive**) |
| Dicko et al. 2011 | **Source** (**archive**) |
| GiveWell update of Meremikwu et al. 2012 meta-analysis (Forest plot) | **Source** |
| GiveWell update of Meremikwu et al. 2012 meta-analysis (RevMan file) | **Source** |
| GiveWell's analysis of SMC coverage in RCTs | **Source** |
| GiveWell's non-verbatim summary of a conversation with Professor Sir Brian Greenwood, January 4 2017 | **Source** |
| GiveWell's SMC cost-effectiveness analysis | **Source** |
| Jamison et al. 2006 | **Source** (**archive**) |
| Konaté et al. 2011 | **Source** (**archive**) |
| Kweku et al. 2008 | **Source** (**archive**) |
| Malaria Consortium: Seasonal Malaria Chemoprevention | **Source** (**archive**) |
| Management Sciences for Health. The cost and impact of ACCESS-SMC | **Source** (**archive**) |
| Matalinga et al. 2015 | **Source** (**archive**) |
| Meremikwu et al. 2012 | **Source** (**archive**) |

| | |
|---|---|
| Seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in children: a field guide | **Source** (**archive**) |
| Sesay et al. 2011 | **Source** (**archive**) |
| Tagbor et al. 2016 | **Source** (**archive**) |
| WebMD. Malaria: Topic overview | **Source** (**archive**) |
| Wilson 2011 | **Source** (**archive**) |
| World Health Organization. Seasonal Malaria Chemoprevention | **Source** (**archive**) |
| World Health Organization. Seasonal Malaria Chemoprevention. A Field Guide. 2013 | **Source** (**archive**) |
| World Health Organization. World Malaria Report (2015) | **Source** (**archive**) |
| Zongo et al. 2015 | **Source** (**archive**) |

1. "In 2015, malaria was the fourth highest cause of death, accounting for 10% of child deaths in sub-Saharan Africa." **World Health Organization. World Malaria Report (2015)**, Pg x.

2. "Human infection begins when the malaria vector, a female anopheline mosquito, inoculates plasmodial sporozoites from its salivary gland into humans during a blood meal. The sporozoites mature in the liver and are released into the bloodstream as merozoites. These invade red blood cells, causing malaria fevers. Some forms of the parasites (gametocytes) are ingested by anopheline mosquitoes during feeding and develop into sporozoites, restarting the cycle." **Jamison et al. 2006**, Pg 413.

3. "Most malaria infections cause symptoms like the flu, such as a high fever, chills, and muscle pain. Symptoms tend to come and go in cycles. Some types of malaria may cause more serious problems, such as damage to the heart, lungs, kidneys, or brain. These types can be deadly." **WebMD. Malaria: Topic overview**.

4. See **Jamison et al. 2006**, Pg 416, Table 21.3 for estimates of cases of hearing impairment, visual impairment, epilepsy, etc. caused by malaria.

5. **World Health Organization. Seasonal Malaria Chemoprevention**.

6. **Seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in children: a field guide**, Pg 7.

7. **Seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in children: a field guide**, Pg 7.

8. **Seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in children: a field guide**, Pg 7.

9. **Seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in children: a field guide**, Pg 8.

10. **Seasonal malaria chemoprevention with sulfadoxine–pyrimethamine plus amodiaquine in children: a field guide**, Pg 9.

11. **Meremikwu et al. 2012**, Pg 2.

12. **Meremikwu et al. 2012**, Pg 2.

13.
    - "IPTc prevents approximately three quarters of all clinical malaria episodes (rate ratio 0.26; 95% CI 0.17 to 0.38; 9321 participants, six trials, high quality evidence), and a similar proportion of severe malaria episodes (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials, high quality evidence)" **Meremikwu et al. 2012**, Pg 2.
    - "Relative to the AL only group, the adjusted hazard ratio (aHR) was 0.62 (95% CI: 0.41, 0.93), P = 0.020 in the SMC group, a protective efficacy of 38.5% (95% CI 7.28%, 59.2%)" **Tagbor et al. 2016**, Pg 229.

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- "In endemic areas, malaria and its adverse effects in schoolchildren may be prevented by intermittent preventive treatment (IPTsc). However, the most appropriate drug regimen for IPTsc remains to be identified. A randomised controlled trial was conducted in Kinshasa, DRC. Enrolled schoolchildren were assigned to a passive control arm (n = 212), sulfadoxine/pyrimethamine (SP) (n = 202) or SP plus piperaquine (SP/PQ) (n = 202). The primary endpoint was haemoglobin (Hb) change. Secondary endpoints were anaemia, parasitaemia prevalence and clinical malaria incidence. Analysis was by modified intention-to-treat (mITT) and per-protocol. A linear mixed mode was used due to repeated measurements. Of 616 enrolled children, 410 (66.6%) were eligible for mITT analysis. The control arm was used as reference. After 12 months, the Hb level increased by 0.20 g/dL (95% CI -0.61 to 0.47; P = 0.168) and 0.39 g/dL (0.12-0.66; P < 0.01) in the SP and SP/PQ arms, respectively. SP treatment reduced anaemia, malaria parasitaemia and clinical malaria by 10% (0-20%; P = 0.06), 19% (2-33%; P = 0.042) and 25% (-32 to 57%; P = 0.37), respectively. The corresponding values for SP/PQ were 28% (19-37%; P < 0.001), 40% (26-52%; P < 0.001) and 58% (17-79%; P < 0.01). No deaths or severe adverse events (SAEs) were observed. SP/PQ offered substantial protection against anaemia, malaria parasitaemia and clinical malaria and showed no SAEs. SP/PQ, a combination of two long-acting non-artemisinin-based antimalarials, may be a valuable option for IPTsc in Africa." **Matalinga et al. 2015**, Abstract.

**14.**

- "IPTsc with SP or SP/PQ was given at baseline (November 2012), at Month 4 (March 2013) and at Month 7 (June 2013)." **Matalinga et al. 2015**, Pg 340.
- Six of the seven RCTs included in delivered treatment on a monthly basis. See **this section** for more information.
- For our updated meta-analysis, see the updated **RevMan** file at **GiveWell update of Meremikwu et al. 2012 meta-analysis (RevMan file)** and **GiveWell update of Meremikwu et al. 2012 meta-analysis (Forest plot)**

**15.**

"262 children 6 months-10 years in Kambila, Mali were randomized to receive either IPT with SP twice at eight weeks interval or no IPT during the transmission season of 2002 and were followed up for 12 months." **Dicko et al. 2008**, Pg 1.

**16.**

For our updated meta-analysis, see the updated **RevMan** file at **GiveWell update of Meremikwu et al. 2012 meta-analysis (RevMan file)** and **GiveWell update of Meremikwu et al. 2012 meta-analysis (Forest plot)**

**17.**

"The results of clinical trials indicate that a high level of protection against uncomplicated clinical malaria is likely to be maintained for only 4 weeks after administration of each treatment course of SP+ AQ; thereafter, protection appears to decay rapidly." **World Health Organization. Seasonal Malaria Chemoprevention. A Field Guide. 2013**, Pg 4.

**18.**

- **Cissé et al. 2006** followed up for 13 weeks, for three months of SMC treatment.
  - "During 13 weeks of follow-up, the intervention led to an 86% (95% CI 80–90) reduction in the occurrence of clinical episodes of malaria" Pg 663.
  - "one dose of artesunate and one dose of sulfadoxine-pyrimethamine, given on three occasions during the malaria transmission season, was undertaken in 1203 Senegalese children aged 2–59 months." Pg 659.
- **Dicko et al. 2011** followed up 6-7 weeks after the last round of SMC.
  - "Passive surveillance for clinical malaria started at the time of the administration of the first dose of IPTc in August 2008 and continued until the end of the malaria transmission season in November/December 2008, 6–7 wk after the last round of IPTc." Pg 4.
- **Konaté et al. 2011** followed up 6 weeks after the last round of SMC.
  - "A cross-sectional survey of all children enrolled in the study was carried out 6 wk after the last course of IPTc had been given (November 2008). Fever within the last 24 h was documented, and axillary temperature, weight, and height were measured. Thick and thin blood films and filter paper blood spots were prepared and Hb concentration was measured." Pg 4.

- **Kweku et al. 2008** appears to have followed up for six months for six treatments delivered monthly.
  - “Children received study drugs every 28 days on six occasions.”
  - ”During the six months of the intervention period, the incidence of anaemia, the primary trial endpoint, was significantly lower in all IPTc groups compared to the placebo group.”
- **Sesay et al. 2011**: It is unclear from the text what the precise period of surveillance was. Our best guess is surveillance covered a period of 3.5 months, for three treatments delivered at monthly intervals.
  - “SP/AQ (person months at risk, 2248)” (Table 4); “SP/AQ (n = 639)” (Table 1). 2248/639=3.5 months.
  - “monthly IPTc with a single dose of sulphadoxine/pyrimethamine (SP) plus three doses of amodiaquine (AQ) or SP and AQ placebos given by village health workers (VHWs) on three occasions during the months of September, October and November”
- **Tagbor et al. 2016**: It is unclear from the text what the precise period of surveillance was. It reports results “during the SMC period” but we are uncertain whether this period extended beyond four weeks after the last treatment.
  - “The protective efficacy of SMC was lower than expected during the SMC period, at around 38%, with no significant protection over the whole study period” Pg 233.

**19.**

- "We inspected the forest plots to detect overlapping CIs, applied the Chi2 test and a P value of 0.10 was used as the cut-off value to determine statistical significance. We also estimated the I2 statistic with values of 30 to 59%, 60 to 89% , and 90 to 100% used to denote moderate, substantial and considerable levels of heterogeneity respectively." **Meremikwu et al. 2012**, Pg 8.
- "Heterogeneity: Tau2 = 0.20, Chi2 = 84.28, df = 5 (P < 0.00001); I2 = 94%” **Meremikwu et al. 2012**, Analysis 1, Pg 40.

**20.**

“The size of this effect varied from a 45% reduction in Mali (Dicko et al. 2008) to an 86% reduction in Senegal (Cissé et al. 2006). This variation could be explained by differences in efficacy between the antimalarial regimen used, by variation in local transmission or resistance patterns, or other factors related to the conduct of the trials. However there were insufficient trials to make meaningful conclusions from subgroup analyses exploring the effects of these factors (Analysis 2.1; Analysis 3.1).” **Meremikwu et al. 2012**, Pg 12.

**21.**

**Dicko et al. 2008** had (i) a longer follow-up (ii) fewer treatments, and (iii) longer time interval between treatments than the other trials.

- **Dicko et al. 2008** report reduction in incidence of malaria in the period 52 weeks after the start of the intervention. The other RCTs in the Cochrane review report incidence between 13 weeks and 6 months after the start of the intervention.
  - **Dicko et al. 2008**: “Cisse et al [12] in Senegal found a reduction of 86% in incidence of clinical malaria children less than five years of age over 13 weeks period. This higher efficacy can be explained by the shorter time interval between treatments (four weeks instead of eight weeks), the number of intermittent treatments (three instead of two) and the shorter duration of the follow up (13 instead 52 weeks) [12].” Pg 7.
  - **Cissé et al. 2006**: “During 13 weeks of follow-up, the intervention led to an 86% (95% CI 80–90) reduction in the occurrence of clinical episodes of malaria” Pg 663.
  - **Dicko et al. 2011**: “Incidence rate expressed as number of episodes/child/year. Note that this is based on the 3-mo surveillance period and does not correspond to an annual rate.” Pg 9.
  - **Konaté et al. 2011**: “From mid-September to the end of November 2008, 150 enrolled children were randomly selected and surveyed each week to monitor the prevalence of malaria infection.” Pg 4.
  - **Kweku et al. 2008**: “During the six months of the intervention period, the incidence of anaemia, the primary trial endpoint, was significantly lower in all IPTc groups compared to the placebo group”
  - **Sesay et al. 2011**: “SP/AQ (person months at risk, 2248)” (Table 4); “SP/AQ (n = 639)” (Table 1). 2248/639=3.5 months.

- **Dicko et al. 2008** included two treatments with eight weeks between each treatment. The other RCTs in the Cochrane review include three to six treatments, with one month between each treatment.
  - **Dicko et al. 2008**: "Cisse et al [12] in Senegal found a reduction of 86% in incidence of clinical malaria children less than five years of age over 13 weeks period. This higher efficacy can be explained by the shorter time interval between treatments (four weeks instead of eight weeks), the number of intermittent treatments (three instead of two) and the shorter duration of the follow up (13 instead 52 weeks) [12]." Pg 7.
  - **Dicko et al. 2011**: "Eligible children were treated with a course of SP+AQ or matching placebos on three occasions at monthly intervals during the malaria transmission season" Pg 4.
  - **Konaté et al. 2011**: "to receive three courses of IPTc with SP plus AQ or placebos given at monthly intervals during the peak malaria transmission season." Pg 14.
  - **Kweku et al. 2008**: "2451 children aged 3–59 months from 30 villages were individually randomised to receive placebo or artesunate plus amodiaquine (AS+AQ) monthly or bimonthly, or sulphadoxine-pyrimethamine (SP) bimonthly over a period of six months."
  - **Sesay et al. 2011**: "During the 2008 malaria transmission season, 1,277 children under five years of age resident in villages within the rural Farafenni demographic surveillance system (DSS) in North Bank Region, The Gambia were randomized to receive monthly IPTc with a single dose of sulphadoxine/pyrimethamine (SP) plus three doses of amodiaquine (AQ) or SP and AQ placebos given by village health workers (VHWs) on three occasions during the months of September, October and November, in a double-blind trial"
- **Tagbor et al. 2016** had (i) low coverage (ii) low malaria incidence prior to treatment (iii) unreliable adherence data, and (iv) the course did not start until the high transmission season was already in progress.
  - "The lower efficacy may partly be due to relatively low coverage of all five SMC cycles (36.4% in the SMC group), but even among children who received five cycles of SMC, protective efficacy was around 47% during the SMC period, lower than the efficacy of 70-80% seen in other studies of monthly SP-AQ [4, 6, 7], or monthly artesunate-amodiaquine" **Tagbor et al. 2016**, Pg 233.
  - "Overall efficacy might also be lower because incidence is relatively low in the study area as a whole: 7 of the 13 study communities have an annual incidence of malaria below 100 cases per 1000 child-years at risk, the lower limit suggested for SMC to be cost-effective [8]. In three small communities with a high prevalence of malaria at baseline and high incidence during the transmission season (Korase, Sarpeh and Timeabu) the protective efficacy of SMC (any number of cycles) was more consistent with earlier studies: 69.7% (95% CI: 22.7%, 88.1%). Potentially supporting this is the fact that there was no benefit of SMC on anaemia, in contrast to findings from SMC studies in high transmission areas [6, 7] but agreeing with areas of lower transmission [1]." **Tagbor et al. 2016**, Pg 233.
  - "This could be a chance finding, because malaria incidence was low and confidence intervals for the efficacy are wide. However, if correct, it could suggest failure to complete the 3-day course of SMC (SP plus AQ on day one, AQ only on days two and three): although SP alone retains reasonably high efficacy in most of West Africa, the efficacy of SP plus AQ is higher [5]. Adherence data were collected but implausibly high values of adherence were reported, as seen elsewhere [23]" **Tagbor et al. 2016**, Pg 233.
  - "Low efficacy may also be a consequence of the timing of administration of the first cycle of SMC. At the baseline survey in July, prevalence was around 26%, suggesting that the transmission season was well underway by this point. Although SP-AQ is likely to have very good curative efficacy in West Africa [24, 25], the benefit of SMC will likely be greater where children are protected prior to exposure each year. If SMC was started too late in 2012 relative to the start of the transmission season, this suggests that five cycles of SMC will be insufficient in this setting, as there was also some malaria incidence in January 2013. Seven or possibly eight cycles could cover the period between May and January, but this raises new questions of cost-effectiveness, and the safety and acceptability of a substantial additional number of SMC cycles." **Tagbor et al. 2016**, Pg 233.

**22.**

- **Cissé et al. 2006**:"Intermittent treatment: IPTi with sulfadoxine-pyrimethamine plus artesunate given once monthly" **Meremikwu et al. 2012**, Pg 23.
- **Dicko et al. 2008**:"262 children 6 months-10 years in Kambila, Mali were randomized to receive either IPT with SP twice at eight weeks interval or no IPT during the transmission season of 2002 and were followed up for 12 months." **Dicko et al. 2008**, Pg 1.
- **Dicko et al. 2011**:"Sulphadoxine Pyrimethamine (SP) SP + Amodiaquiune AQ or Placebo tablets were given during the peak malaria transmission season, with one month intervals between treatments." **Meremikwu et al. 2012**, Pg 25.
- **Konaté et al. 2011**:"Sulphadoxine Pyrimethamine (SP) SP + Amodiaquiune AQ or Placebo tablets were given in August, September, and October during the peak malaria transmission season, with one month intervals between treatments" **Meremikwu et al. 2012**, Pg 27.
- **Kweku et al. 2008**:"Monthly artesunate plus amodiaquine reduced the incidence of malaria by 69% (95% CI: 63%, 74%) and anaemia by 45% (95% CI: 25%,60%)" **Kweku et al. 2008**
- **Sesay et al. 2011**:"During the 2008 malaria transmission season, 1,277 children under five years of age resident in villages within the rural Farafenni demographic surveillance system (DSS) in North Bank Region, The Gambia were randomized to receive monthly IPTc with a single dose of sulphadoxine/pyrimethamine (SP) plus three doses of amodiaquine (AQ) or SP and AQ placebos given by village health workers (VHWs) on three occasions during the months of September, October and November, in a double-blind trial"
- **Tagbor et al. 2016**:"SMC involves monthly administration of the long-acting antimalarial drugs sulfadoxine-pyrimethamine and amodiaquine (SP-AQ) to all children under five years of age" **Tagbor et al. 2016**, Pg 224.
- For more information on Malaria Consortium's program, see our **review**.

**23.**

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- **Sesay et al. 2011**:"During the 2008 malaria transmission season, 1,277 children under five years of age resident in villages within the rural Farafenni demographic surveillance system (DSS) in North Bank Region, The Gambia were randomized to receive monthly IPTc with a single dose of sulphadoxine/pyrimethamine (SP) plus three doses of amodiaquine (AQ) or SP and AQ placebos given by village health workers (VHWs) on three occasions during the months of September, October and November, in a double-blind trial" **Sesay et al. 2011**
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**24.**

- "Seven trials (12,589 participants), including one cluster-randomized trial, met the inclusion criteria. All were conducted in West Africa, and six of seven trials were restricted to children aged less than 5 years." **Meremikwu et al. 2012**, Pg 2.

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**25.**

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**26.**

- **Cissé et al. 2006**:"1136 children aged 2–59 months received either one dose of artesunate plus one dose of sulfadoxine-pyrimethamine or two placebos on three occasions during the malaria transmission season." **Cissé et al. 2006**, Pg 659.
- **Dicko et al. 2008**:"262 children 6 months-10 years in Kambila, Mali were randomized to receive either IPT with SP twice at eight weeks interval or no IPT during the transmission season of 2002 and were followed up for 12 months." **Dicko et al. 2008**, Pg 1.
- **Dicko et al. 2011**:"After screening, eligible children aged 3–59 mo were given a long-lasting insecticide-treated net (LLIN) and randomised to receive three rounds of active drugs or placebos" **Dicko et al. 2011**, Pg 1.
- **Konaté et al. 2011**:"Sulphadoxine Pyrimethamine (SP) SP + Amodiaquiune AQ or Placebo tablets were given in August, September, and October during the peak malaria transmission season, with one month intervals between treatments" **Meremikwu et al. 2012**, Pg 27.
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- **Tagbor et al. 2016**:"SMC or placebo was delivered on five occasions during the rainy season" **Tagbor et al. 2016**, Pg 224.
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**27.**

- **Cissé et al. 2006**:"Use of bednets was limited in the study population. In the control group, 128 children (23%) slept under a bednet, compared with 116 (21%) in the active treatment group" **Cissé et al. 2006**, Pg 662.
- **Dicko et al. 2008**:"The bed net coverage in the area at the time of the survey was less than 5%." **Dicko et al. 2008**, Pg 2.
- **Dicko et al. 2011**:"The coverage of ITNs at baseline was 33.4% (312/935) in Siby, 84.7% (563/665) in Djoliba, and 89.8% (2,207/2,458) in Ouelessebougou." **Dicko et al. 2011**, Pg 3.
- **Konaté et al. 2011**:"the proportions of children who used an ITN before the intervention were also similar (less than 0.5%)." **Konaté et al. 2011**, Pg 5.
- **Kweku et al. 2008**: 20.1%-21.7%. **Kweku et al. 2008**, Figure 1.
- **Sesay et al. 2011**:"93% of the study subjects slept under an ITN" **Sesay et al. 2011**
- **Tagbor et al. 2016**:"Firstly, due to a recent distribution campaign, around 80% of children were regularly sleeping under an insecticide-treated net." **Tagbor et al. 2016**, Pg 231.

**28.**

See **GiveWell's analysis of SMC coverage in RCTs**

**29.**

See **GiveWell's SMC cost-effectiveness analysis** (go to most recent version of published cost-effectiveness analysis file, sheet “SMC”, section labelled “Coverage adjustment”).

30. "IPTc probably produces a small reduction in all-cause mortality consistent with the effect on severe malaria, but the trials were
underpowered to reach statistical significance (risk ratio 0.66, 95% CI 0.31 to 1.39, moderate quality evidence)." **Meremikwu et al. 2012**, Pg 2.

31. "IPTc prevents approximately three quarters of all clinical malaria episodes (rate ratio 0.26; 95% CI 0.17 to 0.38; 9321 participants, six trials, high quality evidence), and a similar proportion of severe malaria episodes (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials, high quality evidence)." **Meremikwu et al. 2012**, Pg 2.

32. **Meremikwu et al. 2012**, Pg 13.

33. See **GiveWell's SMC cost-effectiveness analysis** (go to most recent version of published cost-effectiveness analysis file, sheet "SMC", row labelled "Ratio of the reduction in malaria mortality to the reduction in malaria incidence").

34.
- "Recently, the median time for resistance to a given drug to develop has been roughly 10 to 15 years; for instance, resistance to sulfadoxine-pyrimethamine (SP) resistance took roughly 10 years to emerge in Southeast Asia (where SP was being used as a mainline treatment for malaria)." **GiveWell's non-verbatim summary of a conversation with Professor Sir Brian Greenwood, January 4 2017**
- "Professor Greenwood's best guess is that SP/AQ will still be working, at least partially, in 5-10 years' time, but this is quite uncertain (it is possible, though unlikely, that an unanticipated type of resistance mutation could appear at any time)." **GiveWell's non-verbatim summary of a conversation with Professor Sir Brian Greenwood, January 4 2017**

35. "SP has been used alone for intermittent preventive treatment in pregnancy (IPTp) for roughly 20 years. This is likely to have contributed to resistance to SP developing in Tanzania and East Africa, and SP is no longer very effective in those places for IPTp. However, it is still effective in much of the rest of Africa. A mutation associated with a particularly high level of SP resistance that appeared in Southeast Asia (the DHFR 164 mutation) also appeared in Uganda but has not spread in Africa." **GiveWell's non-verbatim summary of a conversation with Professor Sir Brian Greenwood, January 4 2017**

36. "AQ has relatively little history of resistance, compared to SP. Some resistance has been reported, but overall efficacy has remained high despite extensive use in West Africa for 40 years." **GiveWell's non-verbatim summary of a conversation with Professor Sir Brian Greenwood, January 4 2017**

37.
- "While Professor Greenwood thinks it is likely that SP/AQ will maintain its effectiveness for up to 10 years, if resistance to SP/AQ does develop, dihydroartemisinin-piperaquine (DHAPQ) could be used to replace its role in prevention. However, there is some risk that broad use of an artemisinin-based drug like DHAPQ for prevention could encourage artemisinin resistance, e.g., by encouraging an artemisinin-resistant parasite that already exists in Cambodia to emerge in Africa. While Professor Greenwood would be concerned about using artemisinin in prevention, he would not rule it out as an option, and other experts might disagree about the level of risk." **GiveWell's non-verbatim summary of a conversation with Professor Sir Brian Greenwood, January 4 2017**
- "The WHO recommends that children living in areas of highly seasonal malaria transmission in the Sahel subregion should receive seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine plus amodiaquine (SPAQ). We evaluated the use of dihydroartemisinin-piperaquine (DHAPQ) as an alternative drug that could be used if SPAQ starts to lose efficacy. A total of 1,499 children 3 to 59 months old were randomized to receive SMC with SPAQ or DHAPQ over 3 months. The primary outcome measure was the risk of clinical malaria (fever or a history of fever with a parasite density of at least

3,000/µl). A cohort of 250 children outside the trial was followed up as a control group. Molecular markers of drug resistance were assessed. The risk of a malaria attack was 0.19 in the DHAPQ group and 0.15 in the SPAQ group, an odds ratio of 1.33 (95% confidence interval [CI], 1.02 to 1.72). Efficacy of SMC compared to the control group was 77% (67% to 84%) for DHAPQ and 83% (74% to 89%) for SPAQ. pfdhfr and pfdhps mutations associated with antifolate resistance were more prevalent in parasites from children who received SPAQ than in children who received DHAPQ. Both regimens were highly efficacious and well tolerated. DHAPQ is a potential alternative drug for SMC. (This trial is registered at ClinicalTrials.gov under registration no. NCT00941785.)." **Zongo et al. 2015**, Abstract.

**38.**

- "Post-intervention (rebound) events: Data on post-intervention assessment of trial outcomes were included in meta-analysis if they were adequate; only a few trials provided adequate post-intervention data for meta-analysis. Three trials provided adequate information on incidence of clinical malaria post-intervention (Cissé 2006; Dicko et al. 2008; Kweku 2008)." **Meremikwu et al. 2012**, Pg 9.
- "Three studies continued to monitor children for a full transmission season after IPTc was stopped. There was no observed rebound increase in malaria in children who had received the intervention compared to controls (2299 participants, three trials; Analysis 1.1)." **Meremikwu et al. 2012**, Pg 12.

**39.**

"Since delivery of drugs for up to 5 years will be necessary to achieve sustained protection in young children, assessment of rebound morbidity after several years of intervention will be important. Such assessment will require a trial that lasts for several years, and some
form of phased intervention study will probably be needed." **Cissé et al. 2006**, Pg 666.

**40.**

"Two trials distributed and promoted the use of ITNs to both the intervention and control groups (Dicko 2011 and Konate 2011)." **Meremikwu et al. 2012**, Pg 13.

**41.**

"Two trials distributed and promoted the use of ITNs to both the intervention and control groups (Dicko 2011 and Konate 2011). Despite ITN use being reported as >90% in both treatment arms, IPTc had high protective efficacy against both clinical malaria (rate ratio 0.22, 95% CI 0.13 to 0.38; 5964 participants, two trials; Analysis 2.1) and severe malaria (rate ratio 0.27, 95% CI 0.10 to 0.76; 5964 participants, two trials; Analysis 1.2)." **Meremikwu et al. 2012**, Pg 13.

**42.**

See **GiveWell's SMC cost-effectiveness analysis** (go to most recent version of published cost-effectiveness analysis file, "SMC" and "Results" sheets).