Malaria rebound: does it need to be taken into account when evaluating the impact of malaria control interventions?

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WHO technical consultation on the malaria rebound phenomenon

- No standardized definition of rebound phenomenon
- An interesting immunological phenomenon, but public health importance unclear
- Need to better understand the phenomenon to
  - Guide evaluation of new products and other malaria control strategies
  - Evaluate if and when rebound may be of public health significance
- Conducted a literature review to inform discussion

Definition of rebound used in the review

"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."

Different from:

- **Age shift:** Change in the malaria age-pattern towards older children and in the clinical presentation of severe malaria cases resulting from a permanent reduction in transmission intensity.
- **Malaria resurgence:** an increasing trend in malaria incidence or prevalence following suppression achieved through implementation of control efforts, which does not necessarily lead to an increased risk compared to areas/individuals not receiving the intervention.

Review question and eligibility criteria

Primary objective: 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 **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 was >1 month in both the intervention and the comparison arm.

Randomised controlled trials and non-randomized studies were included, as well as modelling studies.

Review question and eligibility criteria

Studies were included if the the **types of interventions screened** were:

- antimalarial **drug-based strategies** (excluding studies that administered one single dose of chemoprevention)
  - chemoprophylaxis
  - intermittent preventive treatment in infants (IPTi)
  - seasonal malaria chemoprevention (SMC)
  - mass drug administration (MDA)
  - chemoprevention in school-aged children

- **vector control** strategies
  - insecticide-treated nets (ITNs)
  - indoor residual spraying (IRS)
- **RTS,S vaccine**

- **other strategies** such as combinations of different interventions or cotrimoxazole prophylaxis for HIV-positive patients

Review question and eligibility criteria

The following **outcomes** were assessed:

- clinical malaria cases
- severe malaria
- all-cause and malaria-specific mortality
- hospital admissions
- *P. falciparum* and/or *P. vivax* infection
- anaemia

*Immunological and entomological outcomes were not included

Included studies

50 studies (reported in 62 publications)

Drug-based strategies

Chemoprophylaxis

Dobrovolny 1953
Archibald 1956
Bradley-Moore 1985
Björkman 1986
Greenwood 1988
Menon 1990/Greenwood 1995 🔴
Saarinen 1988 🔴
Otoo 1988/Otoo 1989
Oyediran 1993 🟤
Hogh 1994
Menéndez 1997/Aponte 2007 🔴🟤🟣
Guinovart 2012
Bigira 2014
Kamya 2014
Prinsen-Geerligs 2003 (review)

IPTi

Aponte 2009 (pooled analysis)
Schellenberg 2001/Schellenberg 2005
Chandramohan 2005 🔴
Macete 2006
Kobbe 2007/Kobbe 2011
Grobusch 2007/Grobusch 2009
Mockenhaupt 2007 🟤🟣
Odhiambo 2010
Senn 2012

SMC

Cissé 2006
Dicko 2008
Kweku 2008 🔴
Dicko 2011/Dicko 2011b
Konaté 2011/Konaté 2011b 🔴
Tagbor 2011

MDA

Landier 2017 🔴 *(for Pv)*
Tripura 2018
Pongvongsa 2018
von Seidlein 2019
Morris 2018
McLean 2021

🔴 Rebound for clinical malaria; 🟤 Rebound for severe malaria;
🟣 Rebound for severe anaemia.

Vector-control

IRS

Okullo 2017 🔴

RTS,S

Olotu 2013/Olotu 2016 🔴 *(for year 5 in high exposure cohort)*
Sacarlal 2009
RTS,S Clinical Trials Partnership 2011/2012/2014/2015
Tinto 2019 🔴 *(for older children in Burkina Faso)*

Other strategies

Combination of strategies

Molineaux 1980 (Garki)

Cotrimoxazole discontinuation (as HIV intervention)

Homsy 2014

Modelling

Coleman 1999
Gurarie 2007
Ross 2008
Gosling 2008
Águas 2009
Okell 2011
Sallah 2021

Chemoprophylaxis studies evaluating incidence of clinical malaria (1/2)

Study	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Bradley- Moore 1985	1-6 months	Data not shown	No
Saarinen 1988	**1-4 months**	**RR 1.30 (95% CI 1.07-1.57)**	**Yes**
Greenwood 1988	1-12 months	4.8/1000 (2/417) vs 8.5/1000 (5/585)	No
Menon 1990 Greenwood 1995	**1-12 months**	*Children who had received the intervention for 1-4 years:* 212 vs 206 attacks/1000	Not significant
		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)**	**Yes**
Otoo 1988 Otoo 1989	1-6 months 1-12 months	4/48 vs 5/47 No increase observed in the intervention arm	No
Menéndez 1997	**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	**2 months-3 years**	**0.99 vs 0.72 events/PYAR** **IRR 1.38 (95% CI 1.21-1.59)**	**Yes**
	0-3 years	CR 3.22 vs 3.02 episodes CR difference 0.20 (95% CI -0.21-0.59)	Not significant

*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.

Chemoprophylaxis studies evaluating incidence of clinical malaria (2/2)

Study	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Bradley- Moore 1985	1-6 months	Data not shown	No
Guinovart 2012	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% 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	Not significant No or not significant
Bigira 2014	1-12 months	All episodes: *SP:* 11.98, *TS:* 10.90, *DP:* 10.77 vs 10.85 episodes/PYAR	Not significant
Kamya 2014	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.

Rebound in chemoprophylaxis studies evaluating incidence of clinical malaria

Saarinen 1988, Angola
Year(s): 1986
Study design: Non-randomised trial
Age group: Children 5-59 months
Drug: Proguanil
Frequency of intervention: Daily
Duration of intervention: 4 months
Duration of follow-up post-intervention: 4 months

- A rebound effect in the incidence of clinical malaria was observed among Namibian refugees in Angola four months after chemoprophylaxis was stopped.

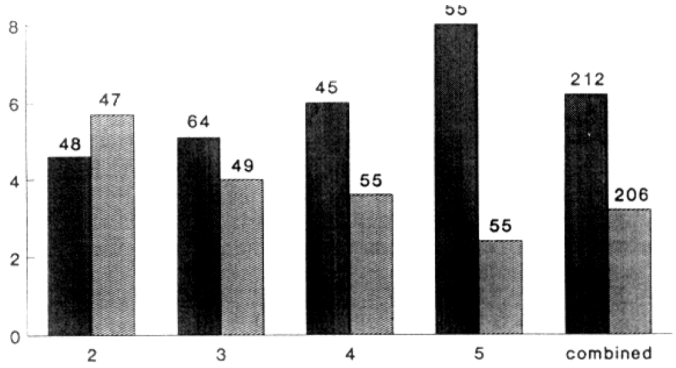
Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Saarinen 1988	NR	1-4 months	RR 1.30 (95% CI 1.07-1.57)	**Yes**

*Month/year 1 is considered the first month/year post-intervention; ^Adjusted measures when available; NR: not reported; RR: relative risk.

Rebound in chemoprophylaxis studies evaluating incidence of clinical malaria

Menon 1990/Greenwood 1995, The Gambia
Year(s): 1983-1989
Study design: Non-randomised controlled trial
Age group: Children 3-59 months
Drug: Pyrimethamine-dapsone
Frequency of intervention: Fortnightly
Duration of intervention: 2-5 years
Duration of follow-up post-intervention: 2-7 years

Attacks per 1000 observations, intervention (dark bars) or placebo (light bars) in children aged 5 to 6 years of age (1 year after CP discontinuation)



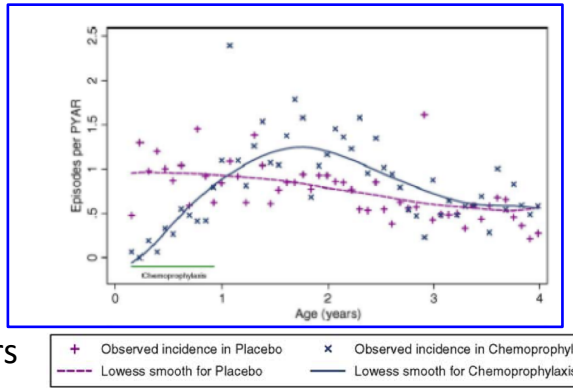
- Rebound in clinical malaria during the year post-intervention in children who had received chemoprophylaxis for five years (from 3 months to 5 years of age), but not in those who had received it for 1-4 years.

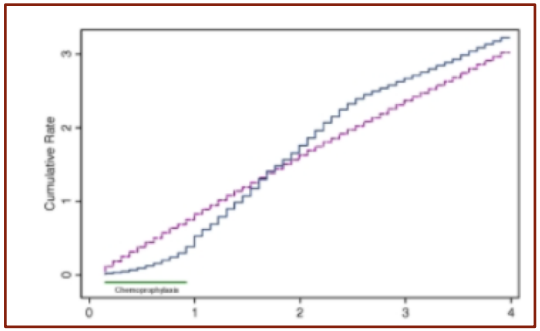
Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Menon 1990 Greenwood 1995	Active case detection	1-12 months	*Children who had received the intervention for 1-4 years:* 212 vs 206 attacks/1000 *Children who had 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**

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

Rebound in chemoprophylaxis studies evaluating incidence of clinical malaria

Menéndez 1997/Aponte 2007, Tanzania
Year(s): 1995-1999
Study design: Randomised controlled trial
Age group: Children 2-12 months
Drug: Pyrimethamine-dapsone
Frequency of intervention: Weekly
Duration of intervention: 10 months
Duration of follow-up post-intervention: 12 months/3 years





- 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 higher in the treated group (3.22 vs 3.02 episodes), were not statistically significant in terms of differences.

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	*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 months-3 years	0.99 vs 0.72 events/PYAR IRR 1.38 (95% CI 1.21-1.59)	**Yes**
		0-3 years	CR 3.22 vs 3.02 episodes CR difference 0.20 (95% CI -0.21-0.59)	Not significant

*Month/year 1 is considered the first month/year post-intervention; ^Adjusted measures when available; CR: cumulative rate; IRR: incidence rate ratio.

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	**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**	**1 month-3 years**	**0.15 vs 0.10 events/PYAR** **IRR 1.54 (95% CI 1.07-2.2)**	**Yes**
		0-3 years	CR 0.47 vs 0.59 episodes CR difference -0.12 (95% CI -0.27-0.03)	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.

Rebound in chemoprophylaxis studies evaluating incidence of severe malaria

Oyediran 1993, Nigeria
Year(s): 1976-1982
Study design: Non-randomised trial
Age group: Children 6 weeks-4 years
Drug: Chloroquine or pyrimethamine
Frequency of intervention: Weekly
Duration of intervention: 1-5 years
Duration of follow-up post-intervention: 5 months

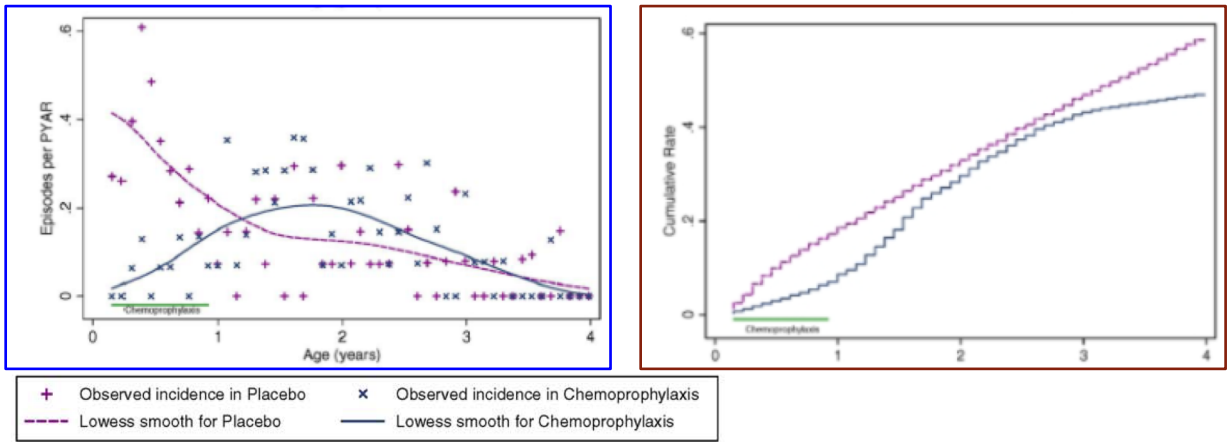
- Rebound for severe malaria in the group treated with chloroquine but not in the group treated with pyrimethamine.

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Oyediran 1993	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**

*Month/year 1 is considered the first month/year post-intervention; ^Adjusted measures when available; RR: risk ratio.

Rebound in chemoprophylaxis studies evaluating incidence of severe malaria

Menéndez 1997/Aponte 2007, Tanzania
Year(s): 1995-1999
Study design: Randomised controlled trial
Age group: Children 2-12 months
Drug: Pyrimethamine-dapsone
Frequency of intervention: Weekly
Duration of intervention: 10 months
Duration of follow-up post-intervention: 3 years



- Rebound in the risk of severe malaria, which decreased over time.
- 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.

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Aponte 2007	Passive case detection	2 months-3 years	0.15 vs 0.10 events/PYAR IRR 1.54 (95% CI 1.07-2.2)	**Yes**
		0-3 years	CR 0.47 vs 0.59 episodes CR difference -0.12 (95% CI -0.27-0.03)	No

*Month/year 1 is considered the first month/year post-intervention; ^Adjusted measures when available; CR: cumulative rate; IRR: incidence rate ratio.

Chemoprophylaxis 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?
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 years)	*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 years)	*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 years)	Probability of death identical for the 2 groups (0.008 for both)	No
		12 months (ages 5-6 years)	*Children recruited at trial start or over the following 6 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 years)	Probability of dying 0.040 vs 0.052, RR 0.87 (95% CI 0.50-1.60), p=0.37	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/year 1 is considered the first month/year post-intervention; ^Adjusted measures when available; CP: chemoprophylaxis; RR: rate ratio.

Chemoprophylaxis studies evaluating all-cause mortality

Menon 1990/Greenwood 1995, The Gambia
Year(s): 1983-1989
Study design: Non-randomised controlled trial
Age group: Children 3-59 months
Drug: Pyrimethamine-dapsone
Frequency of intervention: Fortnightly
Duration of intervention: 2-5 years
Duration of follow-up post-intervention: 2-7 years

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.

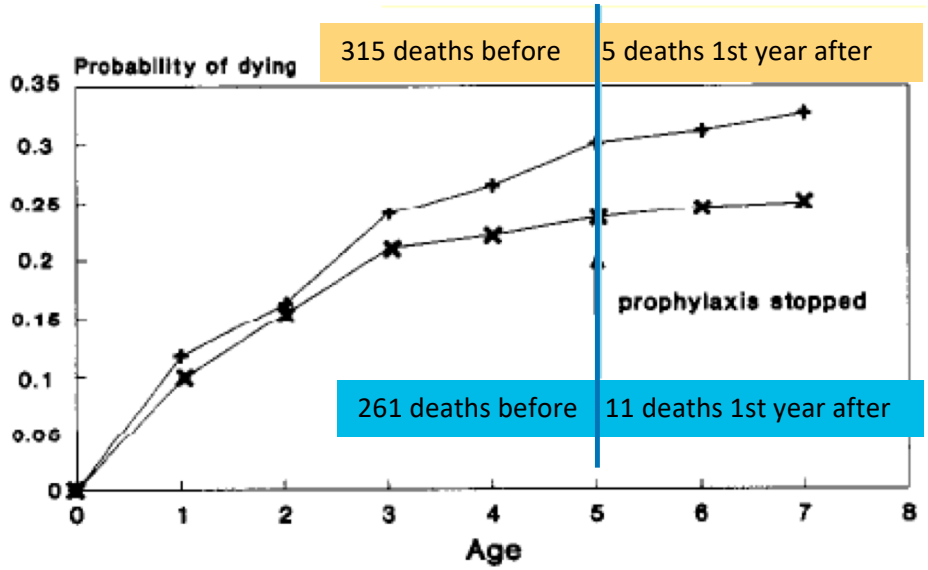


Fig. 1. The probability of dying from birth to the age of 7 years in a cohort of children who received chemoprophylaxis with Maloprim® (×) or placebo (+) from the age of 3 months to 5 years.

IPTi studies evaluating incidence of clinical malaria (1/2)

Study	Type of follow-up	Follow-up period post- intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Aponte 2009 (meta-analysis of 6 trials)	*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:*** **558.4 vs 460.3 events/1000 PYAR** **IRR 1.19 (95% CI 1.02-1.39)**	Not significant **Yes**
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

*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.

IPTi studies evaluating incidence of clinical malaria (2/2)

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
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 vs 0.75 events/PYAR; PE 1.5% (95% CI -23.1-21.2), p=0.89 *AQ+AS:* 0.77 vs 0.75 events/PYAR; PE -1.1% (95% CI -26.3-19.0), p=0.92 *CPG+D:* 0.82 vs 0.75 events/PYAR; 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.

Rebound in IPTi studies evaluating incidence of clinical malaria

Chandramohan 2005, Ghana
Year(s): 2000-2004
Study design: Cluster randomised controlled trial
Age at which IPTi was administered: 2, 3, 4, 9, 12 months
Drug: Sulfadoxine-pyrimethamine
Duration of follow-up post-intervention: 8 months

- Rebound only for high-density parasitaemia clinical malaria (parasitaemia ≥5000 parasites/µl) over 4 to 12 months post-intervention.
- When accounting for all malaria episodes, the incidence was still higher in the intervention arm but the effect was not statistically significant.

Study	**Type of follow-up**	**Follow-up period post-intervention***	**Effect (intervention vs control) during the post-intervention follow-up^**	**Rebound?**
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)	Not significant
			≥5000 parasites/µl: 558.4 vs 460.3 events/1000 PYAR IRR 1.19 (95% CI 1.02-1.39)	**Yes**

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

Rebound in IPTi studies evaluating incidence of severe malaria

Mockenhaupt 2007, Ghana
Year(s): 2003-2005
Study design: Randomised controlled trial
Age at which IPTi was administered: 3, 9, 15 months
Drug: Sulfadoxine-pyrimethamine
Duration of follow-up post-intervention: 9 months

- Rebound for severe malaria over the period 1-9 months post-intervention only statistically significant when accounting for first or only episodes but not significant when considering all episodes.

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Mockenhaupt 2007		1-9 months	*First or only episode:* 0.05 vs 0.02 events/PYAR Protective effect -101.5 (95% CI -298.9-(-1.8)), p=0.04 *All episodes:* 0.07 vs 0.04 events/PYAR Protective effect -97.2%, 95% CI -296.6–2.0, p=0.06).	**Yes** Not significant

*Month/year 1 is considered the first month/year post-intervention; ^Adjusted measures when available; PYAR: person-years-at-risk.

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 *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	Not significant
		6-12 months (rainy season)	***15–23 months age group (SMC at 3–11 months of age):*** *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** *24–71 months age group (SMC at 12–59 months of age):* *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	**Yes, for AQ+ASm** 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/year 1 is considered the first month/year 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..

Rebound in SMC studies evaluating incidence of clinical malaria

Konaté 2011/Konaté 2011b, Burkina Faso
Year(s): 2008-2009
Study design: Randomised controlled trial
Age group: Children 3-59 months
Drug: Sulfadoxine-pyrimethamine + amodiaquine
Frequency of intervention: 3 rounds, monthly for 1 year
Duration of intervention: SMC for 3 months
Duration of follow-up post-intervention: 12 months

- Rebound in the incidence of clinical malaria during the year after the intervention.

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
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; IR: incidence rate; IRR: incidence rate ratio; PYAR: person-years-at-risk.

RTS,S vaccine included studies (summary)

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.

Rebound in RTS,S vaccine studies evaluating incidence of clinical malaria

Olotu 2013/Olotu 2016, Kenya
Year(s): 2007-2014
Study design: Extension study of a randomised controlled trial
Age group: Children 5-17 months at the time of the first vaccine dose
Frequency of intervention: 3 monthly doses
Duration of follow-up after last dose of the vaccine: 4/7 years

- Rebound in the incidence of clinical malaria during the **fifth year** for the group of children that had a higher-than-average exposure to malaria.

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
Olotu 2016	Active and passive case detection	R-7 years§	*>2500 parasites/mm³*: *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/mm³*: *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	*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	**Yes, for year 5 in high exposure cohort**
		Year 6	VE -29.9% (95% CI -91.9-12.1), p=0.19	
		Year 7	VE 4.9% (95% CI -27.0-28.9), p=0.73	

*Duration of follow-up after last dose of the vaccine; ^Adjusted measures when available; ◤: per protocol cohort; §: intention-to-treat population; PYAR: person-years-at-risk; PE: protective efficacy; R: randomization; VE: vaccine efficacy.

Rebound in RTS,S vaccine studies evaluating incidence of clinical malaria

Tinto 2019, Tanzania, Kenya, Burkina Faso
Year(s): 2014-2016
Study design: Extension study of a randomised controlled trial
Age group: Infants 6-12 weeks and children 5-17 months at the time of the first vaccine dose
Frequency of intervention: 3 monthly doses with or without a 4th booster dose around month 20
Duration of follow-up after last dose of the vaccine: 6-7 years

- In **Burkina Faso**, a rebound in incidence of clinical malaria was observed in the older children group during the three-years extension period, but a benefit was still observed when accounting for the entire seven-year follow-up (VE 23.7%, 95% CI 15.93-30.71 (4-dose group); VE 19.1%, 95% CI 10.8-26.7 (3-dose group)).

Study	Type of follow-up	Follow-up period post- intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
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 VE -30.26% (95% CI -59.5-(-6.35)) *(4-dose group)*§ 2.411 vs 1.998 episodes/PYAR VE -26·04% (95% CI -56·0-(-1·84)) *(3-dose group)*§	**Yes, only for older children in Burkina Faso site**
		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)*§	No

*Duration of follow-up after last dose of the vaccine; ^Adjusted measures when available; ◤: per protocol cohort; §: intention-to-treat population; PYAR: person-years-at-risk; PE: protective efficacy; R: randomization; VE: vaccine efficacy.

RTS,S vaccine studies evaluating incidence of severe malaria

RTS,S Clinical Trials Partnership 2015, Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Tanzania
Year(s): 2010-2013
Study design: Randomised controlled trial, phase 3
Age group: Infants 6-12 weeks and children 5-17 months at the time of the first vaccine dose
Frequency of intervention: 3 monthly doses with or without a 4th booster dose around month 20
Duration of follow-up after last dose of the vaccine: 2-3 years

- Negative vaccine efficacies, but not statistically significant, in the group of children who received the vaccine at 5-17 months of age.
- **Mendoza 2019** presented in-depth safety results and concluded that these severe malaria signals could be considered likely chance findings.

Study	Type of follow-up	Follow-up period post-intervention*	Effect (intervention vs control) during the post-intervention follow-up^	Rebound?
RTS,S Clinical Trials Partnership 2015	Passive case detection	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)§**	**Not significant**
		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)*§	

*Duration of follow-up after last dose of the vaccine; ^Adjusted measures when available; §: intention-to-treat population; VE: vaccine efficacy.

Discussion

- **Difficult to compare across studies and draw general conclusions**, due to differences in study designs, target age groups, type, duration and efficacies of interventions, duration of follow-up, outcomes, methods to measure the outcomes, etc.
- **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**.
- **Low power to evaluate rebound for severe malaria or mortality**
  - non-significant increase in the risk of severe malaria or mortality might be due to chance, but we cannot rule out a rebound.
- Overall, rebound seems to be associated with **interventions that provided 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**
  - 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.

Methodological recommendations

- **Standardise the definition of rebound** and differentiate this phenomenon from similar concepts such as malaria resurgence and age shift.
- **Risks should 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/rates**.
- The evaluation of rebound should **use the same methods and outcomes** as the evaluation of the intervention efficacy.
- **Plan for ≥1 year of follow-up after intervention cessation**
    - if 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 sizes needed to be able to detect a rebound will be higher** during the post-intervention follow-up, as malaria risk decreases as children grow older.
- The most frequent clinical presentations of severe malaria in children will change over time as children grow older (severe anaemia vs cerebral malaria) → **sample size needs to be powered accordingly.**

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**, the studies 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, providing a positive "net benefit"**.
- 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**.
- There is a **need to define a standardised approach and methodology to assess the rebound phenomenon**.

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