Safety and efficacy of seasonal malaria vaccination with RTS,S/AS01, with or without Seasonal Malaria Chemoprevention

D. Chandramohan, I. Zongo, I. Sagara, M. Cairns, R.-S. Yerbanga, M. Diarra, F. Nikiema, A. Tapily, F. Sompougdou, D. Issiaka, C. Zoungrana, K. Sanogo, A. Haro, M. Kaya, A.-A. Sienou, S. Traore, A. Mahamar, I. Thera, K. Diarra, A. Dolo, I. Kuepfer, P. Snell, P. Milligan, C. Ockenhouse, O. Ofori-Anyinam, H. Tinto, A. Djimde, JB. Ouedraogo, ***A. Dicko****, B. Greenwood*

WHO-TDR virtual workshops on the introduction of the RTS,S/AS01 (RTS,S) malaria vaccine
Feb 24th , 2022

MALARIA RESEARCH & TRAINING CENTER
BAMAKO, MALI

INSTITUT DE RECHERCHE EN SCIENCES DE LA SANTE
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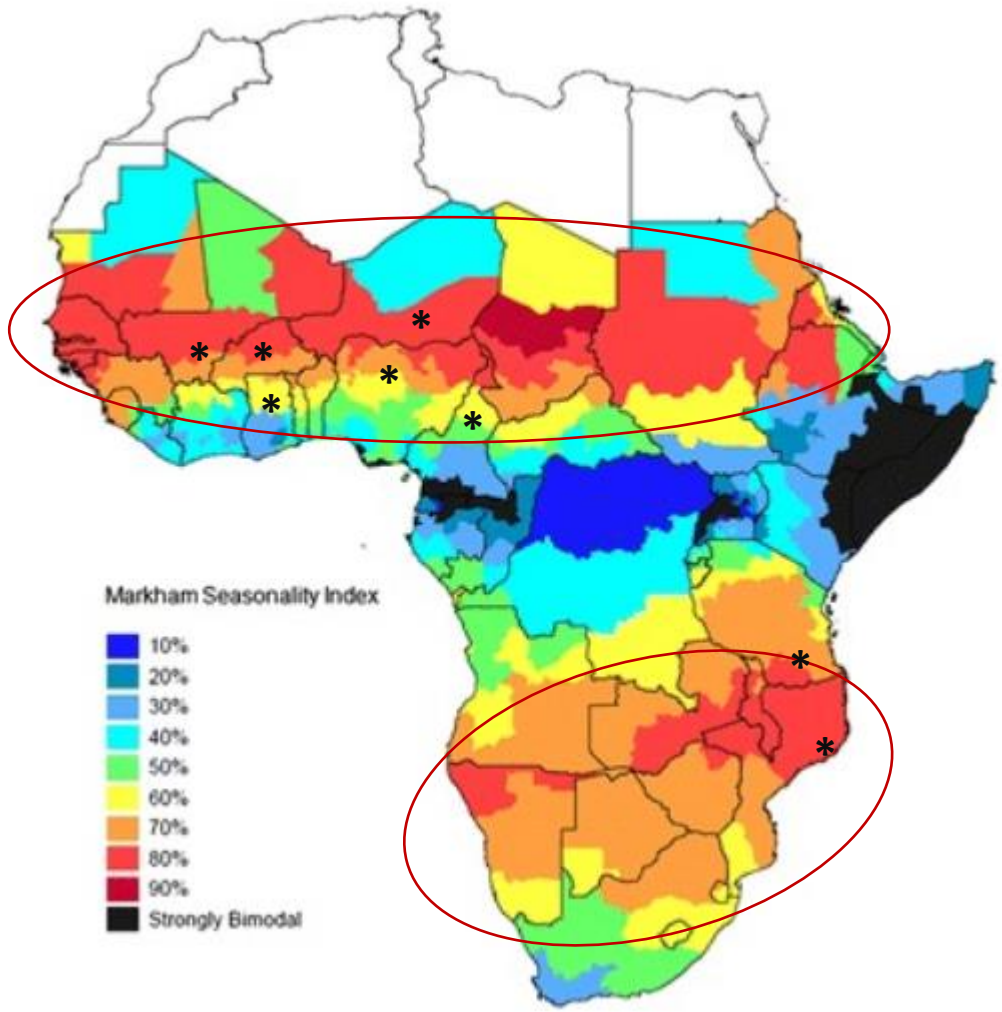
Seasonality of malaria in Africa

Malaria transmission is highly seasonal in many part of Africa

- Sahel and sub-Sahel region
- Southern and Eastern region

* high burden countries in Africa



Seasonality of malaria using the Markham seasonality index by first administrative area in Africa

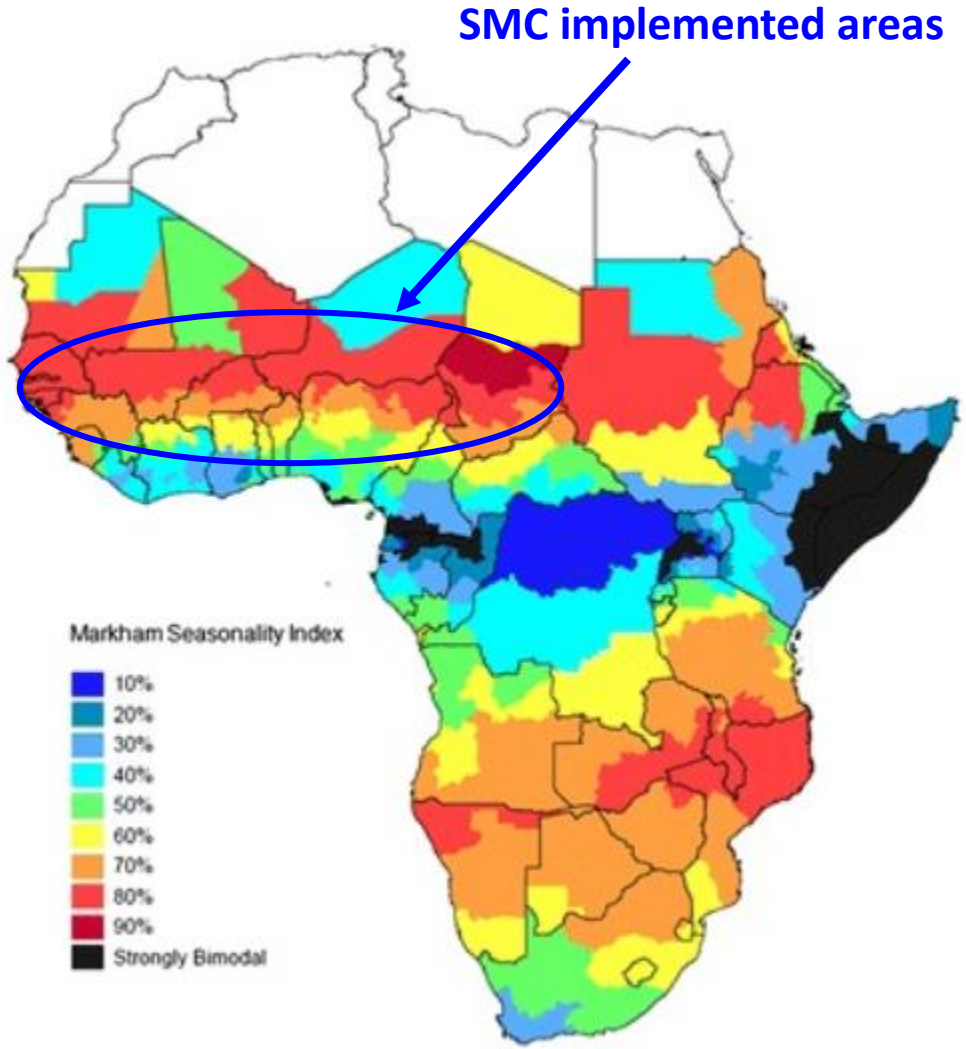
Cairns et al. Malar J (2015) 14:321

Seasonal Malaria Chemoprevention

- Recommended by WHO in 2012
- Widely deployed in the Sahel and sub-Sahel region
- 33.5 million children received treatment in 2020

Effectiveness: 88·2% (95% CI 78·7–93·4) over 0-28 days

***Lancet* 2020; 396: 1829–40**



Seasonality of malaria using the Markham seasonality index by first administrative area in Africa

Cairns et al. Malar J (2015) 14:321

THE CONTINUING BURDEN OF MALARIA DESPITE SMC

Hospital admissions in children < 5 years Bougouni, Mali and Hounde, Burkina Faso 2014-2016

Aetiology	Hospital admissions		Deaths	
	Houndé	Bougouni	Houndé	Bougouni
Malaria	**165 (87%)**	**103(52%)**	**27 (50%)**	**25 (33%)**
ALRI	10	50	3	8
Gastroenteritis	2	3	0	7
Other infections	7	1	3	5
Malnutrition	2	23	4	13
Others	3	19	17	18
TOTAL	189	199	54	76

Need for additional tools such as malaria vaccine

Greenwood *et al. Malar J (2017) 16:182*
DOI 10.1186/s12936-017-1841-9

Malaria Journal

REVIEW

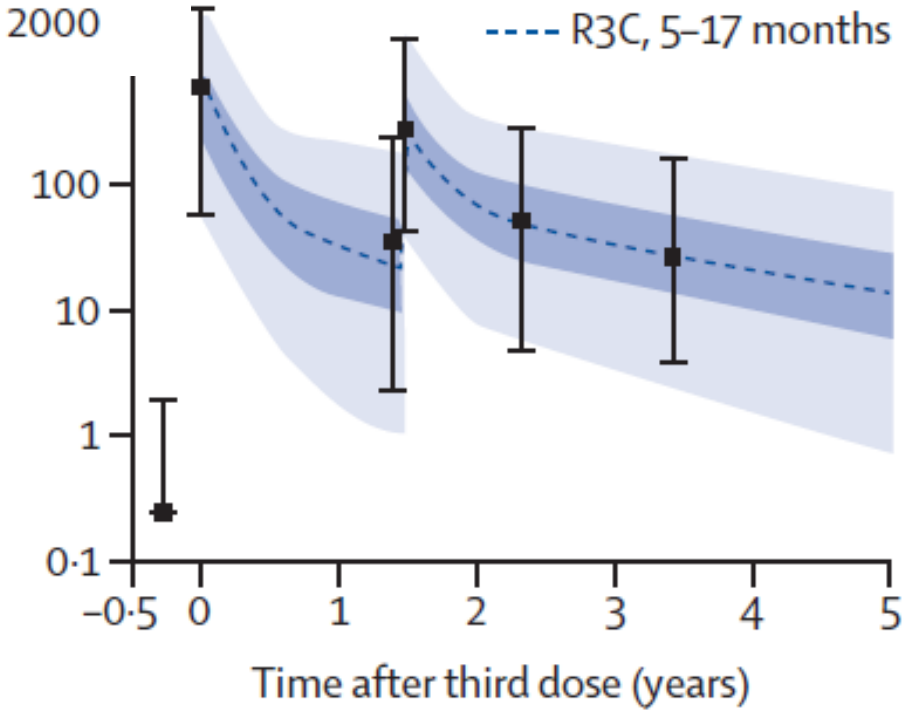
Open Access

Seasonal vaccination against malaria: a potential use for an imperfect malaria vaccine

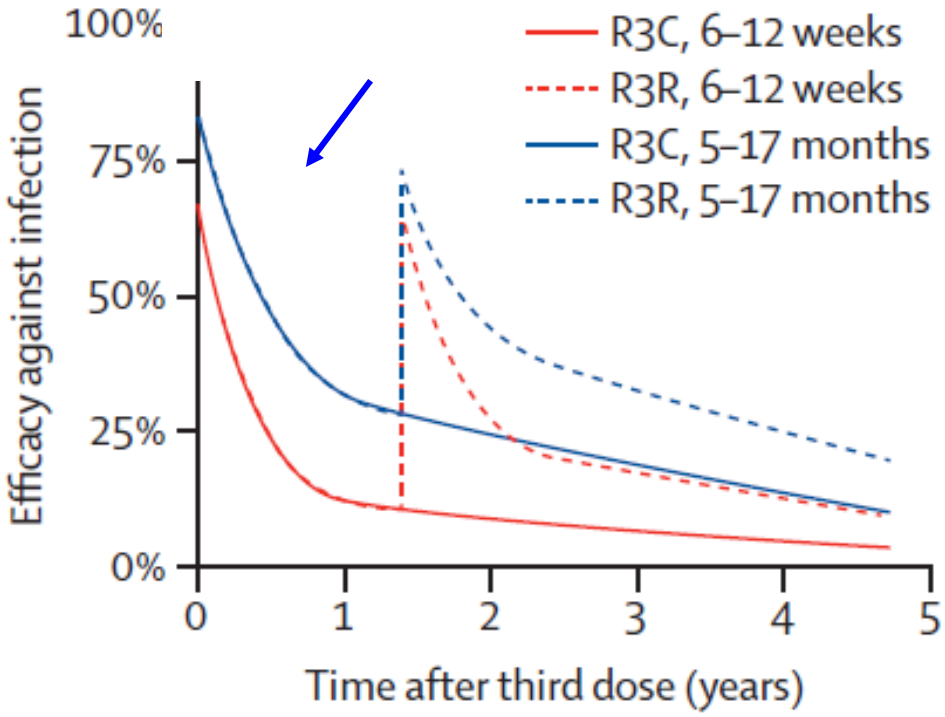
Brian Greenwood[1*], Alassane Dicko[2], Issaka Sagara[2], Issaka Zongo[3], Halidou Tinto[3], Matthew Cairns[4], Irene Kuepfer[1], Paul Milligan[4], Jean-Bosco Ouedraogo[3], Ogobara Doumbo[2] and Daniel Chandramohan[1]

RATIONALE FOR SEASONALLY-TARGETED VACCINATION

Anti-CSP antibody



Efficacy against clinical malaria



(White et al., LID, 2015; 15:1450)

STUDY OBJECTIVES AND PRIMARY OUTCOME MEASURES

Objectives: To determine whether

- Seasonal vaccination with RTS,S/AS01 is **non-inferior** to four monthly courses of seasonal malaria chemoprevention (SMC).
- The combination of seasonal vaccination with RTS,S/AS01 and SMC with SP+AQ is **superior** to RTS,S/AS01 alone or SMC alone.

Primary outcome: Uncomplicated clinical malaria defined as

- Fever (measured temperature ≥ 37.5°C, or a history of fever within 48h), plus *P. falciparum* parasite density ≥5,000 per µl.

Number of secondary outcomes including:

- Severe malaria
- Malaria death

STUDY AREAS

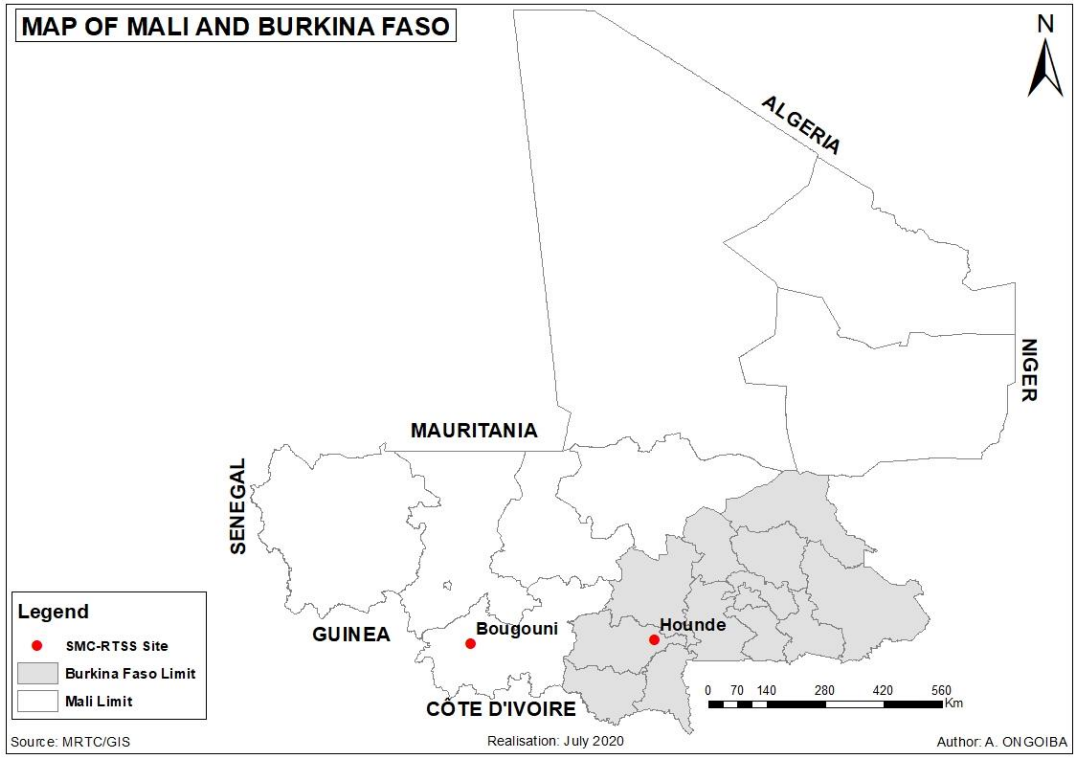
Sites of the previous AZ-SMC trial
(N Engl J Med 2019; 380:2197-2206)

Bougouni area, Mali

Houndé area, Burkina Faso

Intense malaria transmission July-Nov each year

NMCP currently delivers 4 X SMC July-October



STUDY DESIGN

Double blind randomised control trial

~6000 children 5-17 months of age
~3000 per country

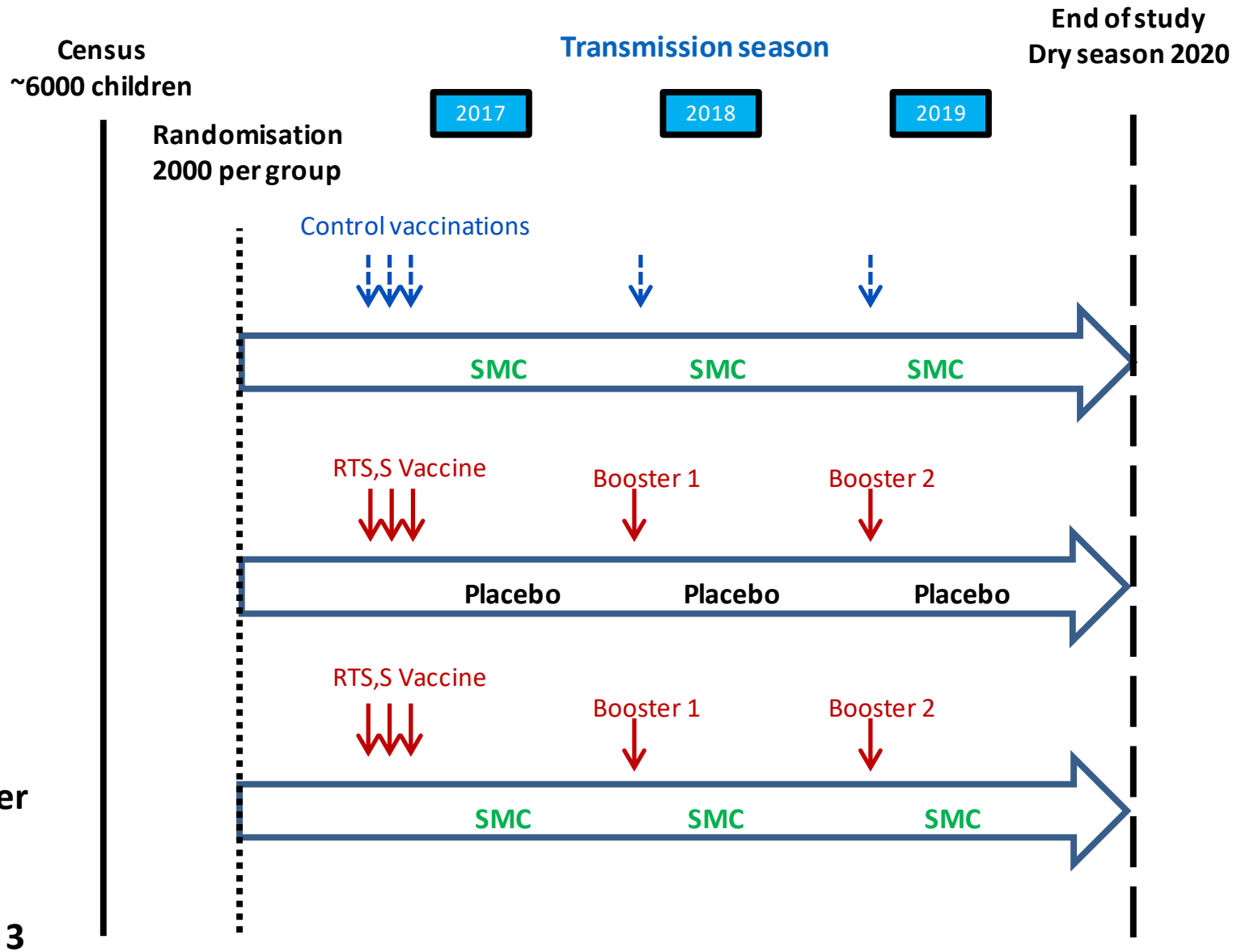
3 study groups
~1000 children per group per country

RTS,S/AS01 or rabies vaccine given in April/May/June 2017

RTS,S/AS01 booster or Hep A given in June 2018 and June 2019

4 SMC courses or 4 SMC placebo courses per year in 2017-2019

Morbidity data collected continuously over 3 years through passive surveillance



VACCINE COVERAGE

	SMC alone	RTS,S alone	Combined	Total
Study Year 1	N=1965	N=1988	N=1967	N=5920
Received Dose 1 (%)	100	100	100	100
Received Dose 2 (%)	96.4	96.1	96.9	96.5
Received Dose 3 (%)	**93.0**	**93.6**	**93.8**	**93.4**
Study Year 2	N=1904	N=1927	N=1919	N=5750
Received Booster 1 (%)	**94.4**	**95.2**	**95.6**	**95.1**
Study Year 3	N=1847	N=1882	N=1873	N=5602
Received Booster 2 (%)	**94.6**	**94.4**	**95.0**	**94.7**

SMC COVERAGE

No. SMC contacts attended	SMC alone	RTS,S alone	Combined	Total
2017	(N=1965)	(N=1988)	(N=1967)	(N=5920)
3 or 4	92.5	92.7	92.2	92.5
4	81.9	83.1	83.3	82.8
2018	(N=1904)	(N=1927)	(N=1919)	(N=5750)
3 or 4	90.5	92.0	91.4	91.3
4	83.7	84.2	84.3	84.1
2019	(N=1847)	(N=1882)	(N=1873)	(N=5602)
3 or 4	92.3	92.9	93.0	92.7
4	88.0	87.9	87.1	87.7

INCIDENCE OF THE PRIMARY OUTCOME BY STUDY GROUP OVERALL

Analyses by modified intention to treat (mITT)

Arm	PYAR	Events	Rate per 1000 PYAR (95% CI)	PE vs SMC alone (95% CI)	PE vs RTS,S alone (95%CI)
SMC alone	5449.9	1661	304.8 (290.5, 319.8)	[Reference]	
RTS,S alone	5535.7	1540	278.2 (264.6, 292.4)	**7.87** (-1.01, 16.0)	[Reference]
Combined	5508.0	624	113.3 (104.7, 122.5)	**62.8** (58.4, 66.8)	**59.6** (54.7, 64.0)

PYAR= person years at risk

INCIDENCE OF SEVERE MALARIA OUTCOMES

Outcome	Arm	Events	Rate per 1000 PYAR (95% CI)	PE vs SMC alone (95% CI)	PE vs RTS,S alone (95%CI)
Blood Transfusion	SMC alone	23	4.2 (2.8, 6.4)	[Reference]	
	RTS,S alone	21	3.8 (2.5, 5.8)	8.3 (-67.6, 49.8)	[Reference]
	Combined	8	1.5 (0.7, 2.9)	**65.4 (22.9, 84.5)**	**62.3 (14.1, 83.4)**
WHO Severe Malaria	SMC alone	37	6.79 (4.92, 9.37)	[Reference]	
	RTS,S alone	37	6.7(4.8, 9.2)	-0.4 (-60.2, 37.1)	[Reference]
	Combined	11	2.0 (1.1, 3.6)	**70.5** (41.9, 85.0)	**70.6** (42.3, 85.0)
Malaria Deaths	SMC alone	11	2.0 (1.1, 3.6)	[Reference]	
	RTS,S alone	12	2.2 (1.2, 3.8)	-9.5 (-148.3, 51.7)	[Reference]
	Combined	3	0.6 (0.2, 1.7)	**72.9 (2.9, 92.4)**	**75.3 (12.5, 93.0)**

PYAR= person years at risk

SAFETY

FEBRILE CONVULSIONS - 5 after approximately 20,000 doses (3 RTS,S alone, 2 combined).
- occurred the day after the vaccination.
- rapid recovery and no sequelae.

MENINGITIS - 8 suspected (4 SMC alone, 3 RTS,S alone, 1 Combined) – none proven.

MORTALITY BY GENDER - males: rate per 1,000 PYAR: 3.66 (2.39,5.62)
females: rate per 1,000 PYAR: 2.45 (1.42, 4.22)

SUMMARY

- **The protection provided by seasonal RTS,S vaccination against clinical malaria was shown to be non-inferior to the protection provided by 4 cycles of SMC per year.**

- **The addition of RTS,S on top of SMC resulted in superior protection compared to the protection provided by SMC alone**
  - **~63% additional reduction in primary outcome of clinical malaria**
  - **~ 65% additional reduction in blood transfusion**
  - **~70% additional reduction in WHO-defined severe malaria hospitalisations**
  - **~73% additional reduction in deaths from malaria**

- **No major safety issue**

More information: N Engl J Med. 2021 Sep 9;385(11):1005-1017

ACKNOWLEDGEMENTS

- *Study participants and Populations of the study areas*
- *District health officers and health staff in the study areas*
- *National Malaria Control Programs and MoH in Mali and Burkina Faso*

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