OPT-SMC
Optimizing Seasonal Malaria Chemoprevention in West and Central Africa

EDCTP
This project is part of the EDCTP2 programme supported by the European Union

UNIVERSITE DE THIES
L'HUMILITE MON CHOIX, L'EXCELLENCE MA VOIE

Optimising the use of the RTS,S/AS01 malaria vaccine in the control of seasonal malaria

Paul Milligan, LSHTM

OPT-SMC meeting, Dakar, Senegal

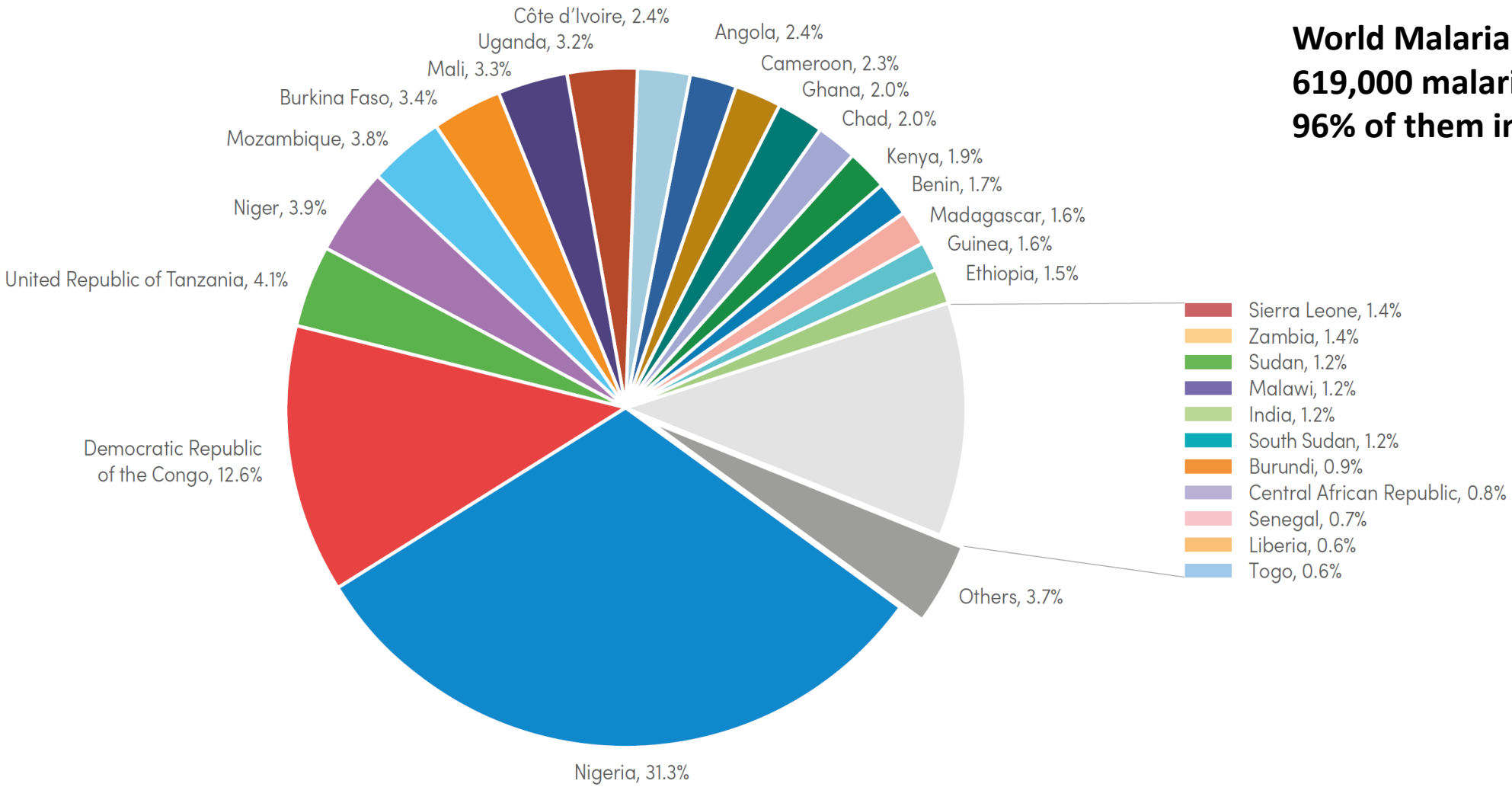
Jan 23 2023

World Health Organization

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

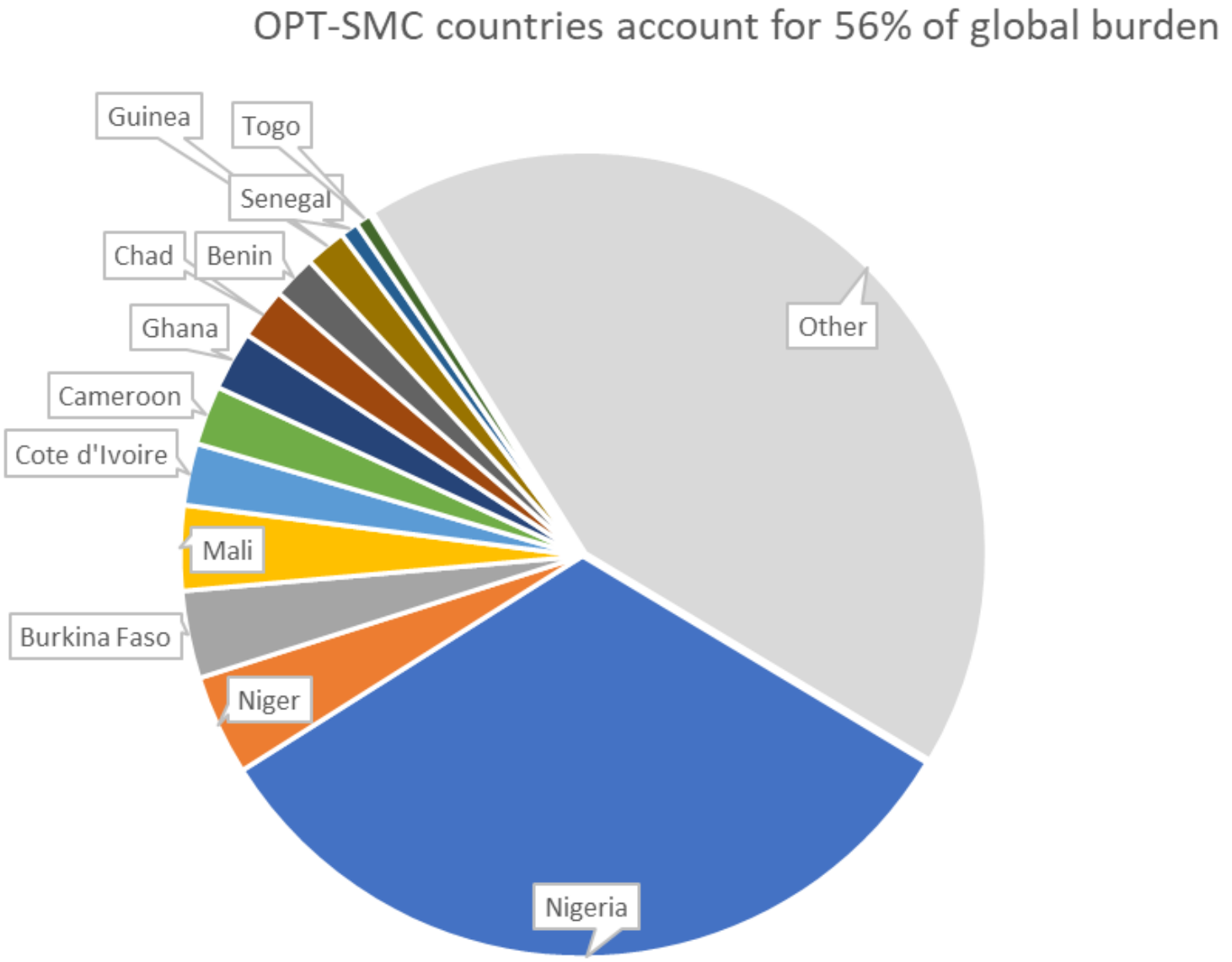
MMV Medicines for Malaria Venture

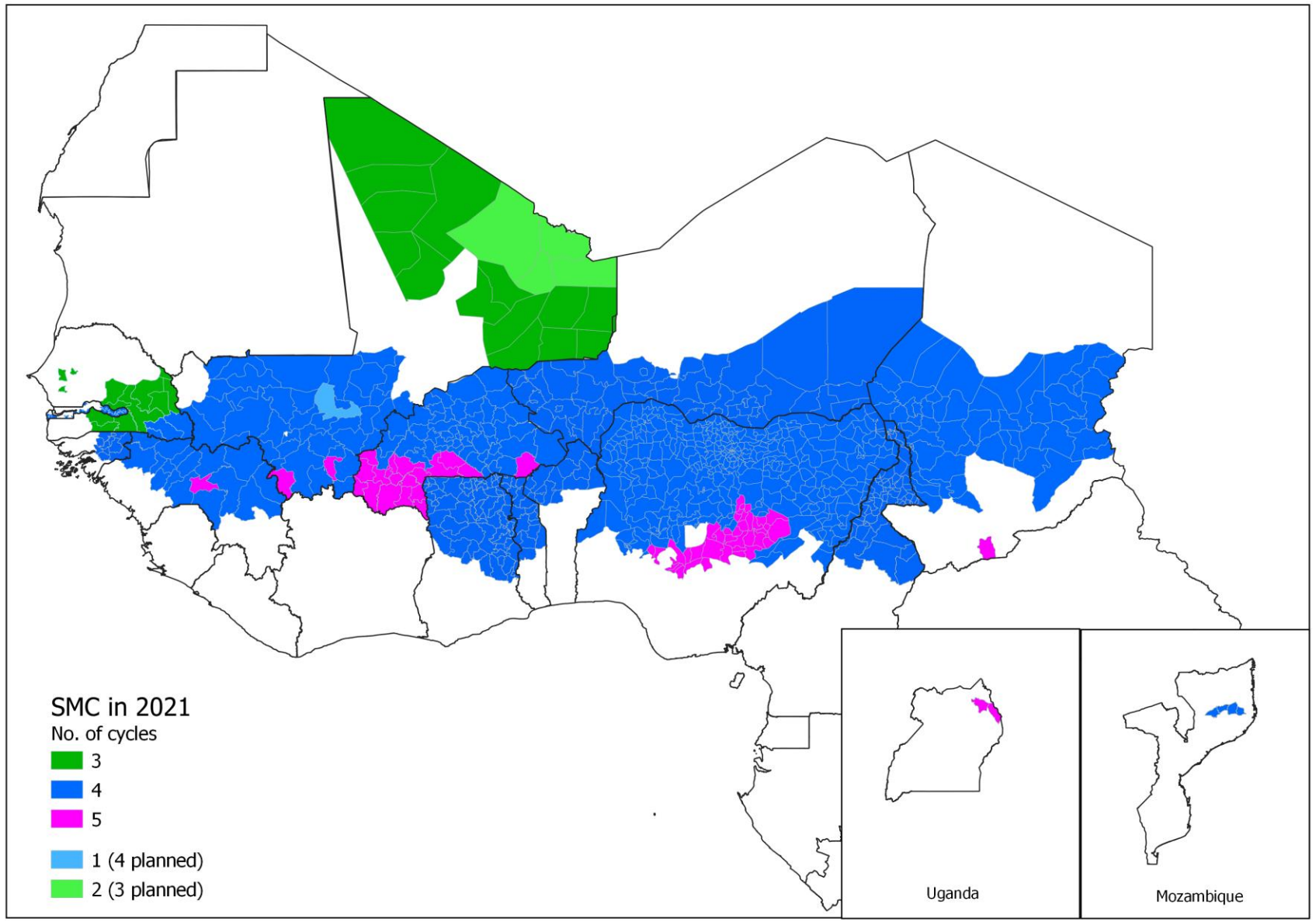
London School of Hygiene & Tropical Medicine



World Malaria Report 2022
619,000 malaria deaths in 2021
96% of them in 29 countries

56% of the global burden of malaria mortality occurs in 12 countries in W and C Africa with (areas of) highly seasonal malaria





SMC In 2021:

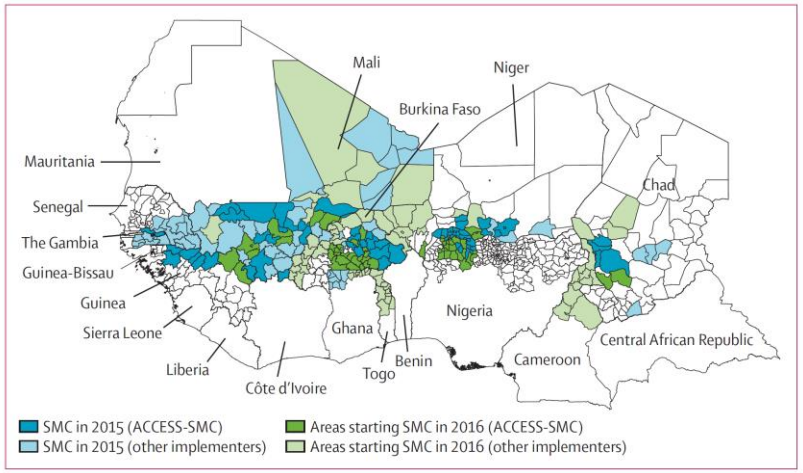
45 million children reached

180 million doses

SMC scale-up had been highly effective despite the challenges of delivery.

4 monthly cycles of SP+AQ
5 monthly cycles in areas with longer season

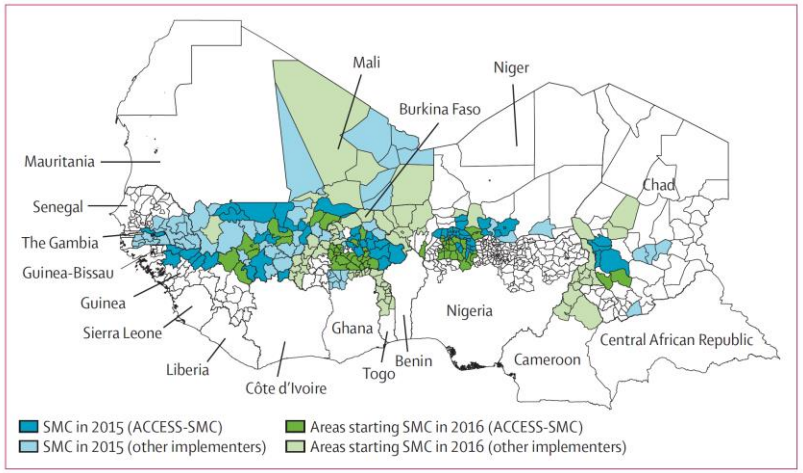
Source:
SMC Alliance and WHO (2022)



- **SMC is effective at scale** (ACCESS-SMC)
- 85% efficacy per month (case control studies in 5 countries)
- Low frequency of resistant parasite genotypes

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32227-3/fulltext

En francais: https://www.lshtm.ac.uk/media/46876



- **SMC is effective at scale** (ACCESS-SMC)
- 85% efficacy per month (case control studies in 5 countries)
- Low frequency of resistant parasite genotypes

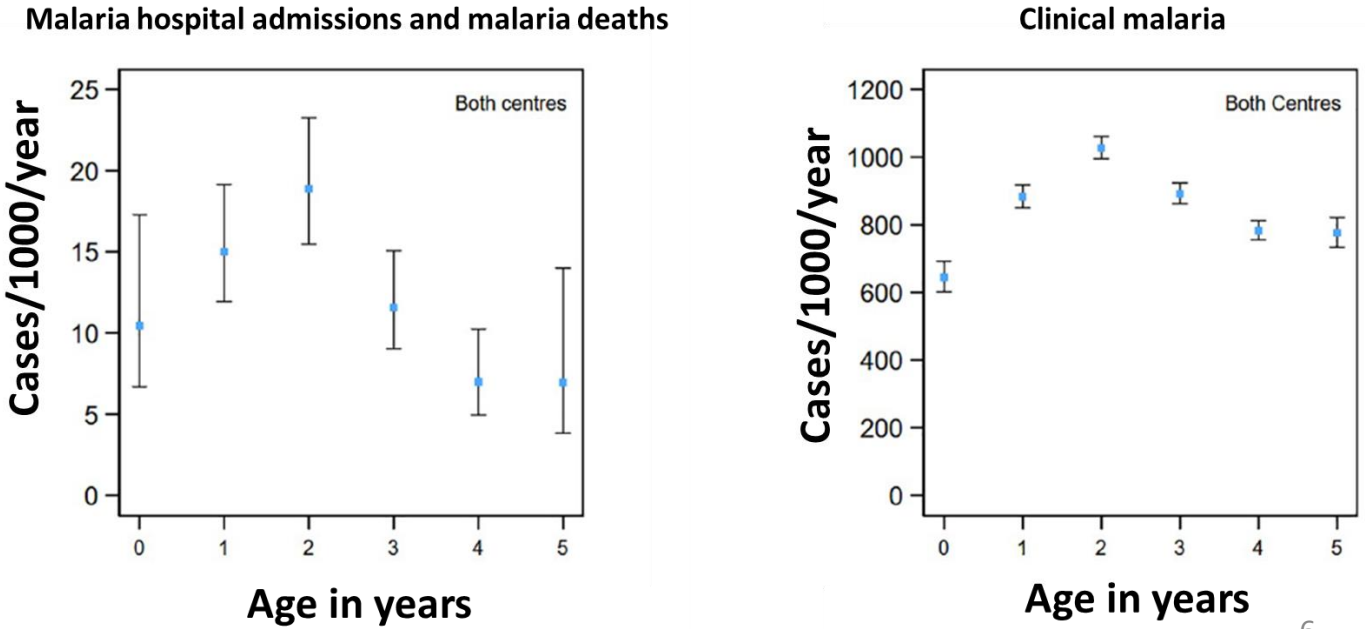
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32227-3/fulltext

En francais: https://www.lshtm.ac.uk/media/46876

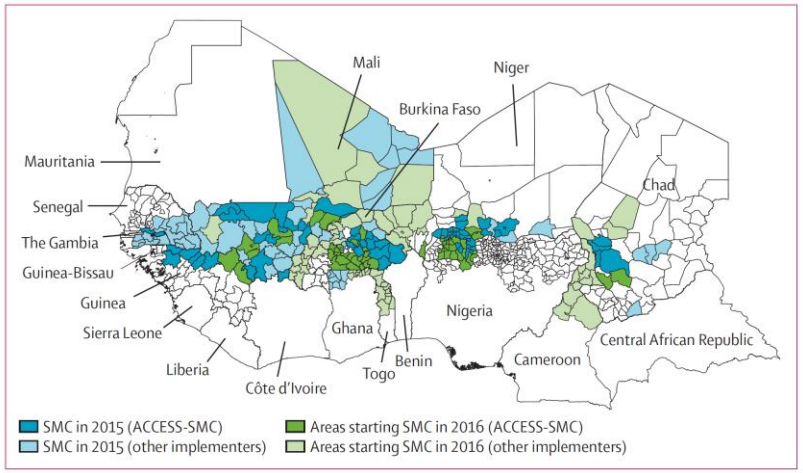
- **But a high burden remains**

https://www.nejm.org/doi/full/10.1056/nejmoa1811400

Incidence of malaria in cohorts of children with high SMC coverage in the AZ-SMC trial, Burkina Faso and Mali, 2014-2016



Chandramohan et al., NEJM, 2019



- **SMC is effective at scale** (ACCESS-SMC)
- 85% efficacy per month (case control studies in 5 countries)
- Low frequency of resistant parasite genotypes

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32227-3/fulltext

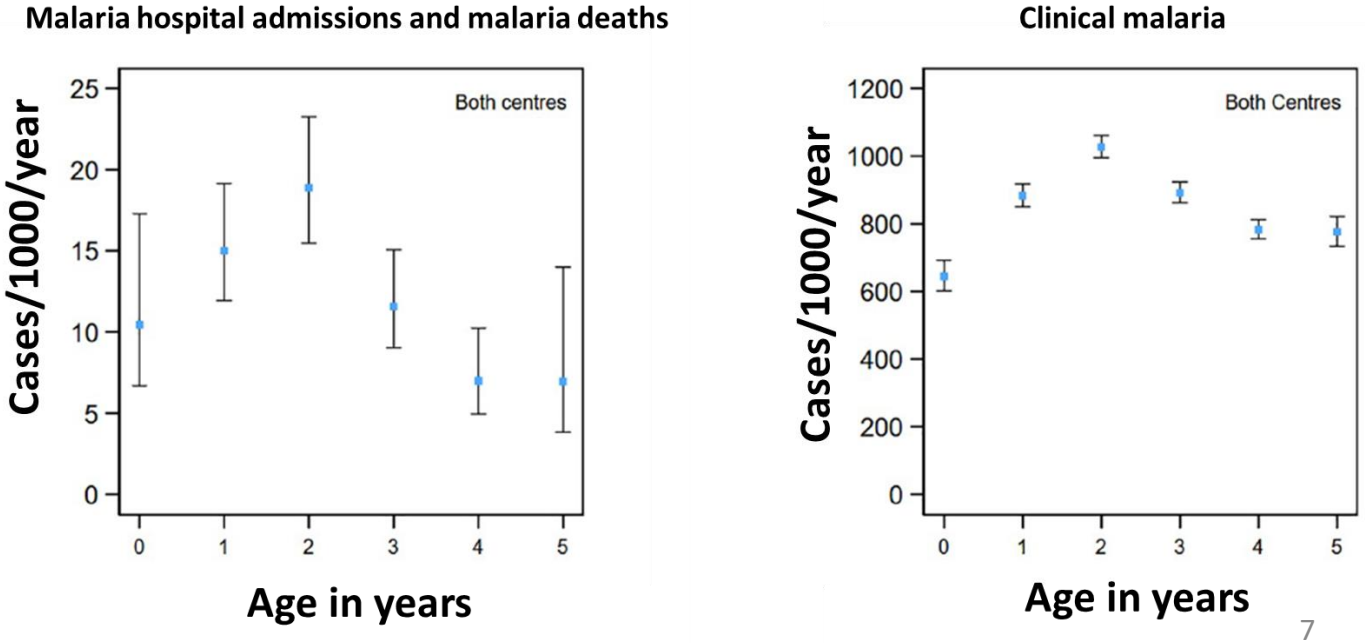
En francais: https://www.lshtm.ac.uk/media/46876

- **But a high burden remains**

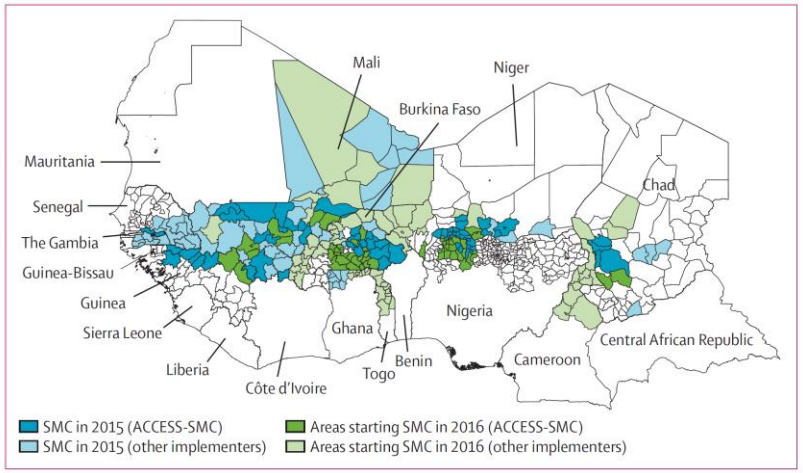
https://www.nejm.org/doi/full/10.1056/nejmoa1811400

and is not confined to very young children

Incidence of malaria in cohorts of children with high SMC coverage in the AZ-SMC trial, Burkina Faso and Mali, 2014-2016



Chandramohan et al., NEJM, 2019



- **SMC is effective at scale** (ACCESS-SMC)
- 85% efficacy per month (case control studies in 5 countries)
- Low frequency of resistant parasite genotypes

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32227-3/fulltext

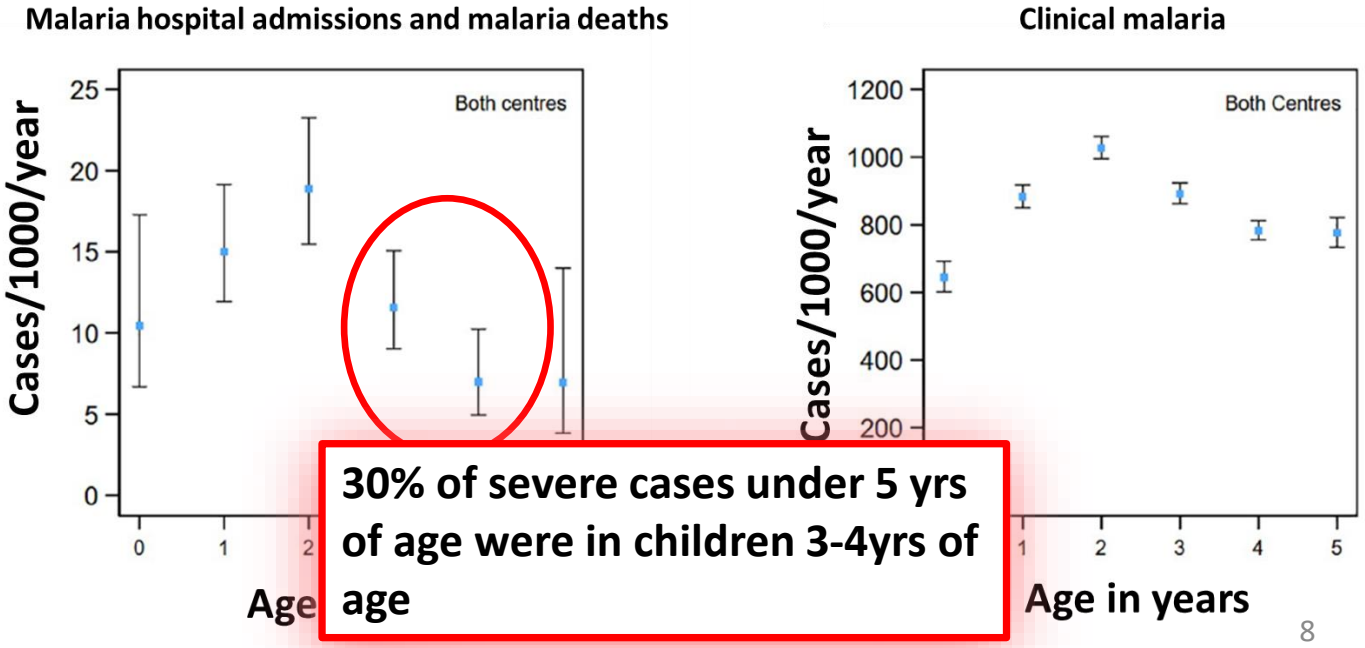
En francais: https://www.lshtm.ac.uk/media/46876

- **But a high burden remains**

https://www.nejm.org/doi/full/10.1056/nejmoa1811400

and is not confined to very young children

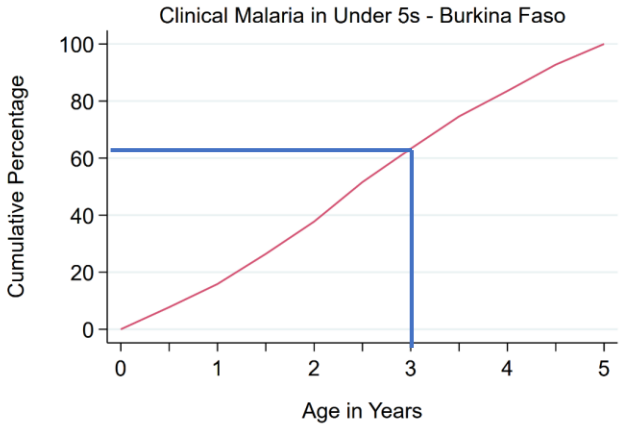
Incidence of malaria in cohorts of children with high SMC coverage in the AZ-SMC trial, Burkina Faso and Mali, 2014-2016

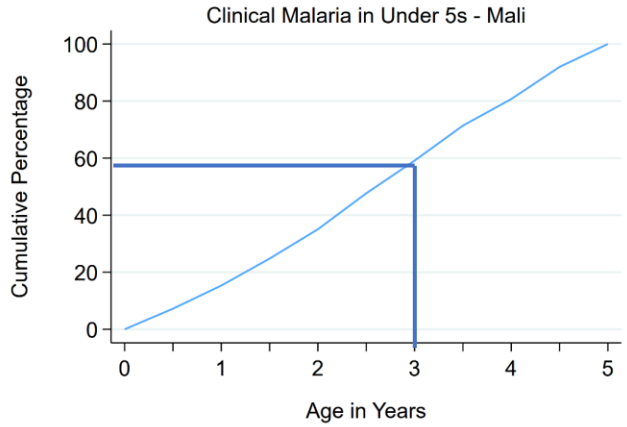


Chandramohan et al., NEJM, 2019

Burden distribution among the under-5s

~40% of clinical cases above 3 years of age

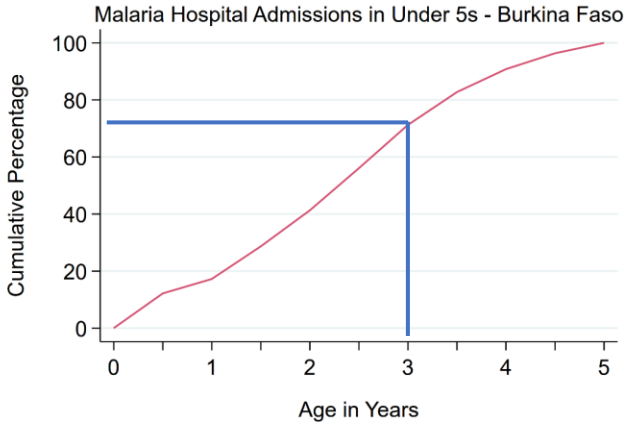


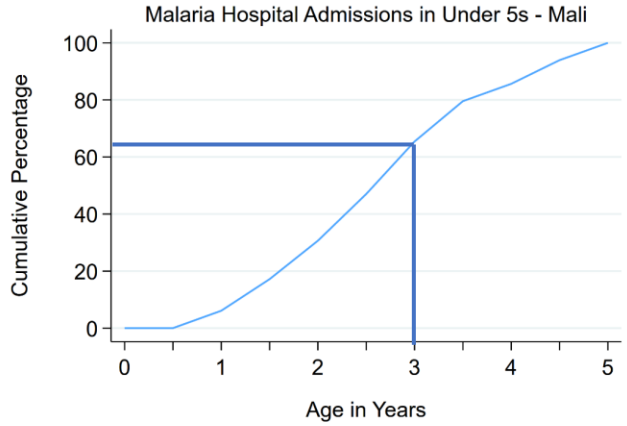


AZ-SMC trial, Burkina Faso and Mali 2014-2016, (*Chandramohan et al., NEJM, 2019*)

https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003214

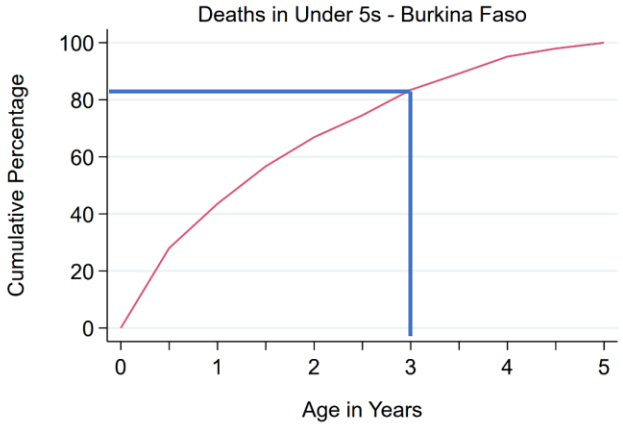
~30% of malaria hospital admissions above 3 years of age

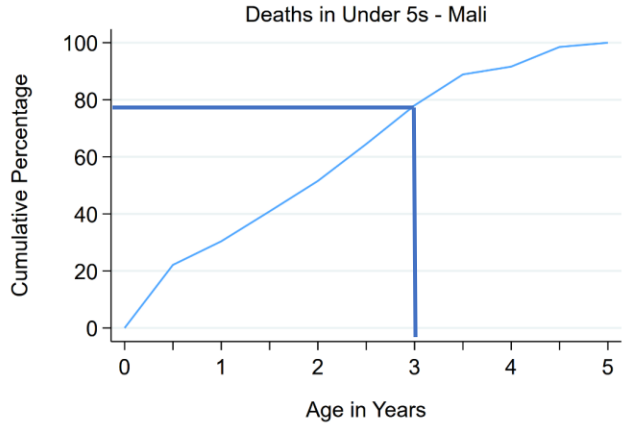




MVIP: Areas without RTSS. Severe malaria under 5 yrs, % aged 3-4yrs:
Ghana 31%
Malawi 22%
Western Kenya 29%

~20% of malaria deaths above 3 years of age

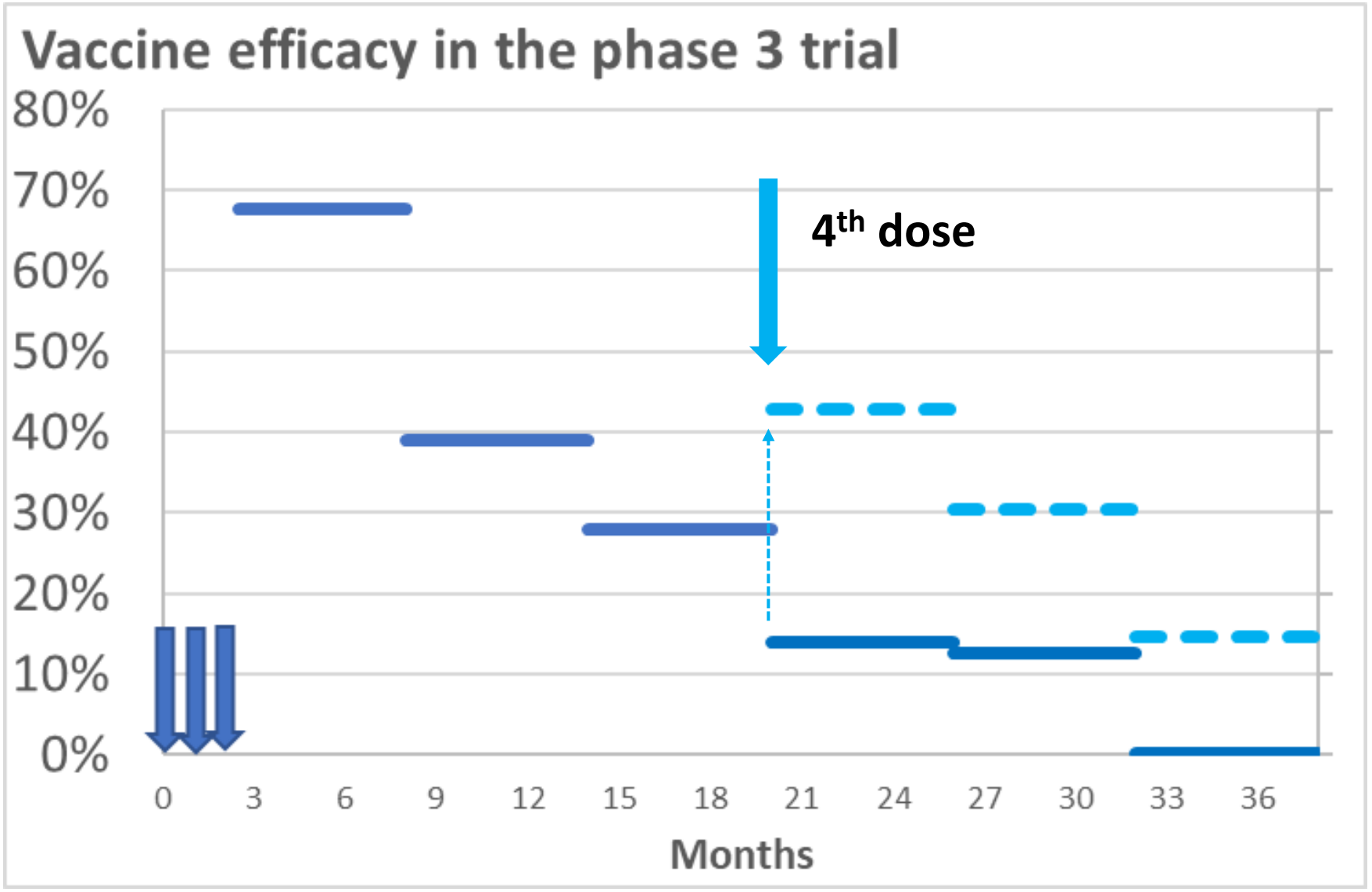




Age pattern depends on: transmission intensity and seasonality

RTS,S/AS01 efficacy and impact

The trajectory of vaccine efficacy



https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Oct2015/7_session_malaria/Oct2015_session7_malaria%20vaccines.pdf

Vaccine impact depends on the **trajectory** of vaccine efficacy, and the context in which the vaccine is used

MVIP pilot implementation (in areas with year-round malaria)

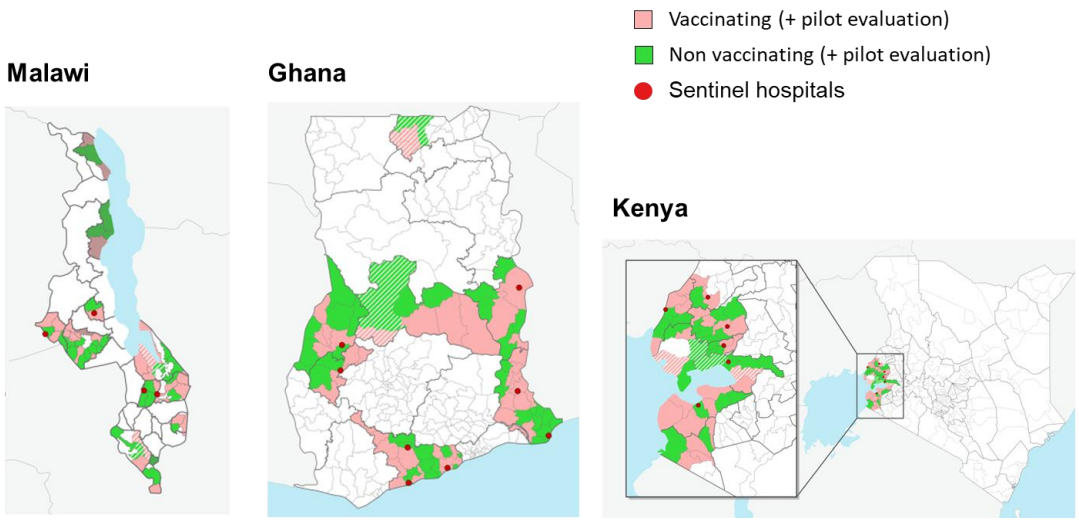
During first 24 months:

- Coverage of 3 doses RTS,S: 62%,66%,62%

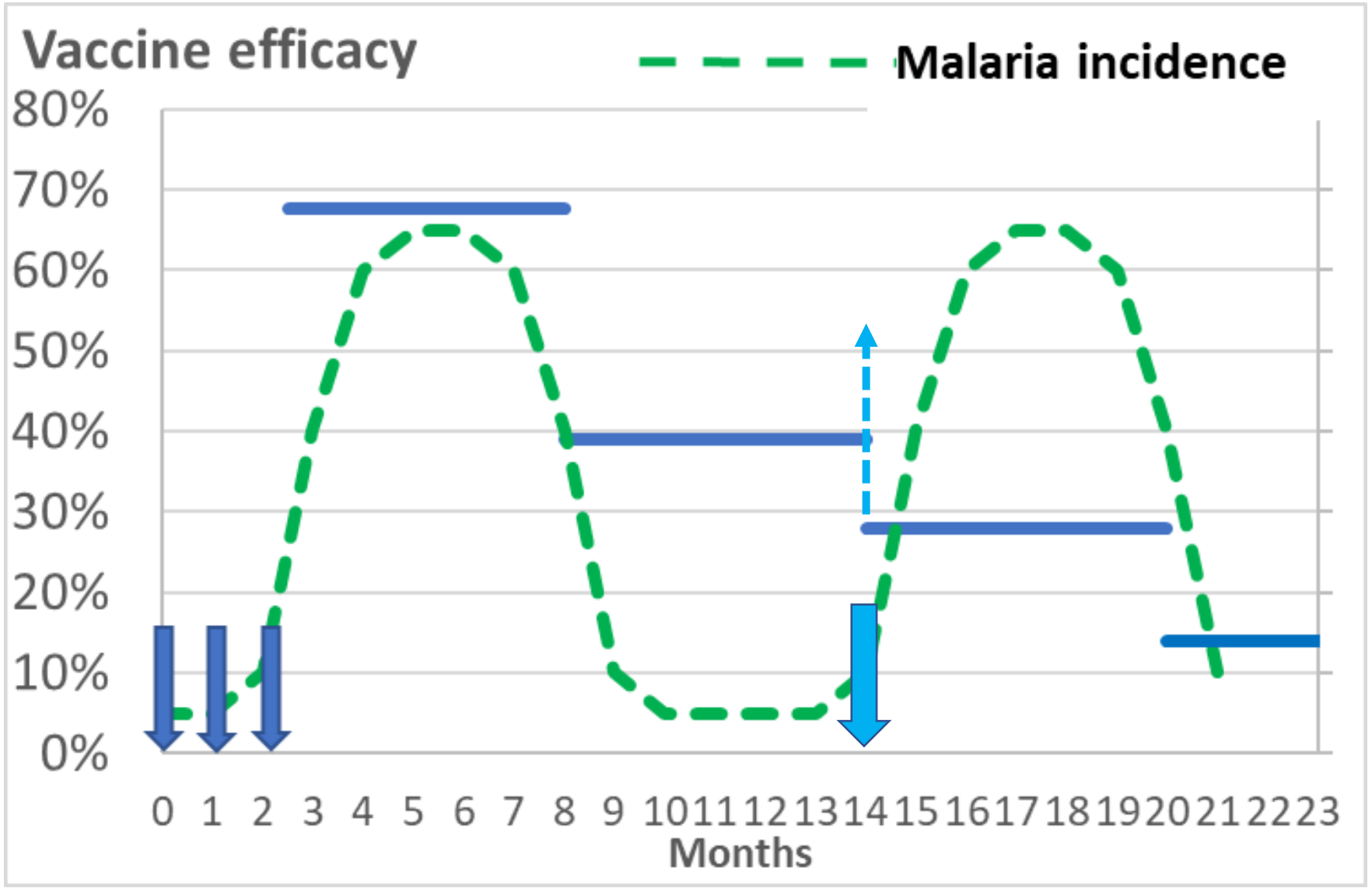
  Coverage of measles-1: 85%, 90%, 85%
- 32% reduction in severe malaria admissions
- 9% reduction in all-cause admissions
- 9% reduction in all-cause deaths
- No evidence of the safety signals that had been observed in the phase 3 trial

Consistent with about 50% average efficacy over the 2 years
Consistent with about 28% of deaths being caused by malaria in these children

WHO (2021) RTSS Full Evidence Review



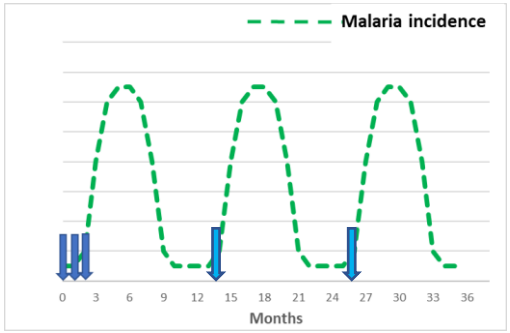
Child Age / Vaccine/1	Birth	6 wks	10 wks	14 wks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22 mo	24 mo
BCG	1											
Oral polio	0	1	2	3								
DTP-HepB-Hib (penta)		1	2	3								
Pneumococcal conj.		1	2	3								
Rotavirus		1	2									
Inactivated Polio				1								
Meningococcal A conj.										1		
Measles-Rubella								1		2		
Yellow Fever								1				
RTS,S in Ghana						1	2	3				4
RTS,S in Kenya						1	2	3				4
RTS,S in Malawi					1	2	3				4	
Vitamin A						1			2	3		4
Growth Monitoring												
Deworming												



In areas of highly seasonal malaria, impact can be optimized by timing doses before the onset of the malaria season

with annual booster doses

Seasonal vaccination: results over 3 years (primary vaccination and 2 annual boosters)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention

D. Chandramohan, I. Zongo, I. Sagara, M. Cairns, R.-S. Yerbanga, M. Diarra, F. Nikièma, 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, J.-B. Ouédraogo, A. Dicko, and B. Greenwood

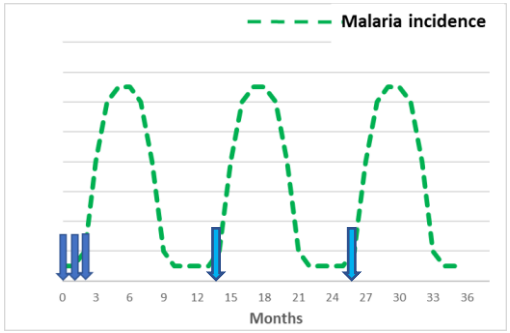
https://www.nejm.org/doi/full/10.1056/NEJMoa2026330

Efficacy of RTS,S (in children receiving SMC):

	Efficacy against clinical malaria
• Year 1 (after primary 3 doses)	71.7%
• Year 2 (after 4th dose)	63.2%
• Year 3 (after 5th dose)	58.6%
Average efficacy over 3 years:	**62.8%**

Chandramohan et al. (2021) N Engl J Med 385:1005-1017

Seasonal vaccination: results over 3 years (primary vaccination and 2 annual boosters)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention

D. Chandramohan, I. Zongo, I. Sagara, M. Cairns, R.-S. Yerbanga, M. Diarra, F. Nikièma, 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, J.-B. Ouédraogo, A. Dicko, and B. Greenwood

https://www.nejm.org/doi/full/10.1056/NEJMoa2026330

Efficacy of RTS,S (in children receiving SMC):

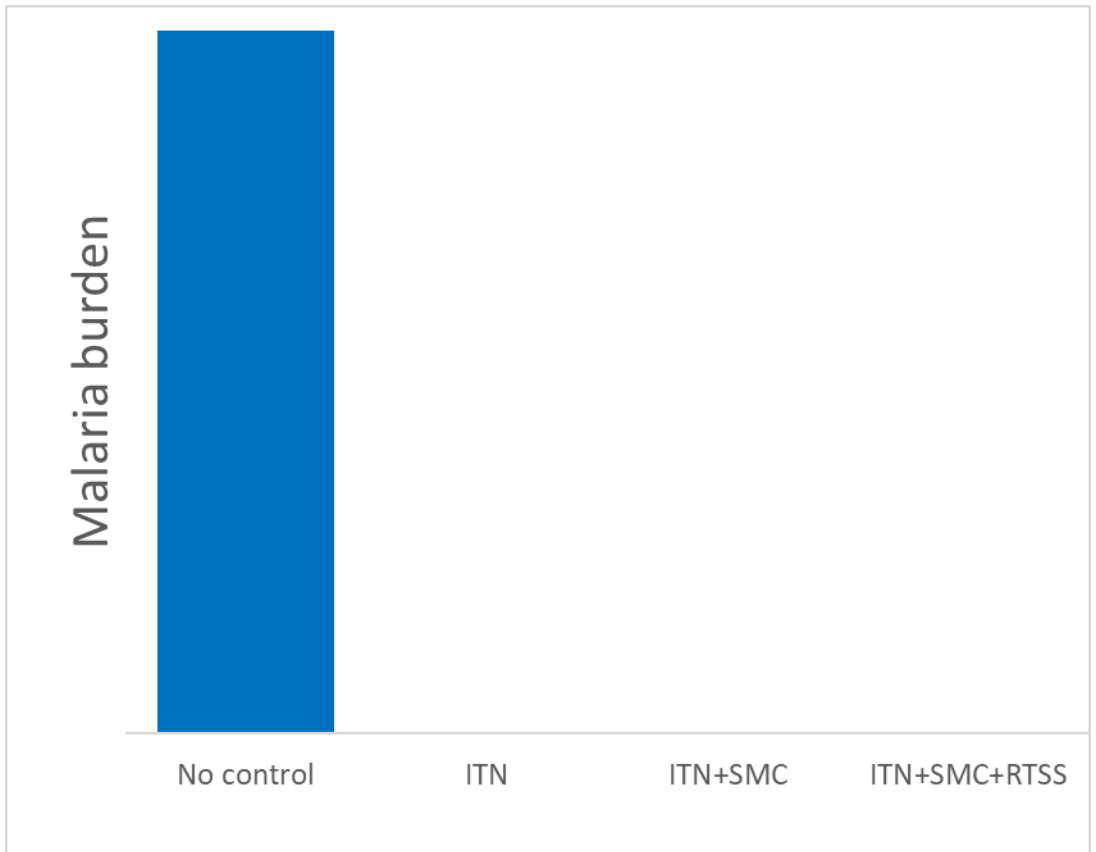
	Efficacy against clinical malaria
• Year 1 (after primary 3 doses)	71.7%
• Year 2 (after 4th dose)	63.2%
• Year 3 (after 5th dose)	58.6%
Average efficacy over 3 years:	**62.8%**

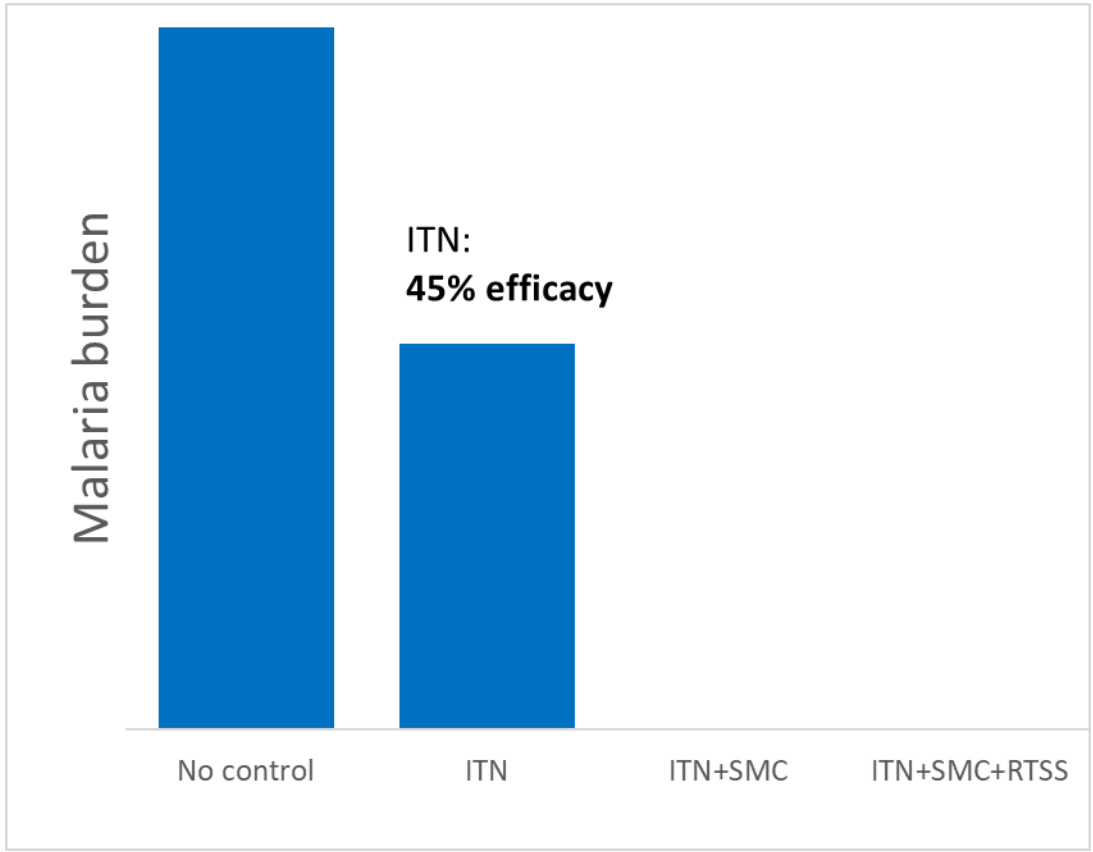
Efficacy against hospital admission with severe malaria: **70.5%**

Efficacy against malaria deaths: **72.9%**

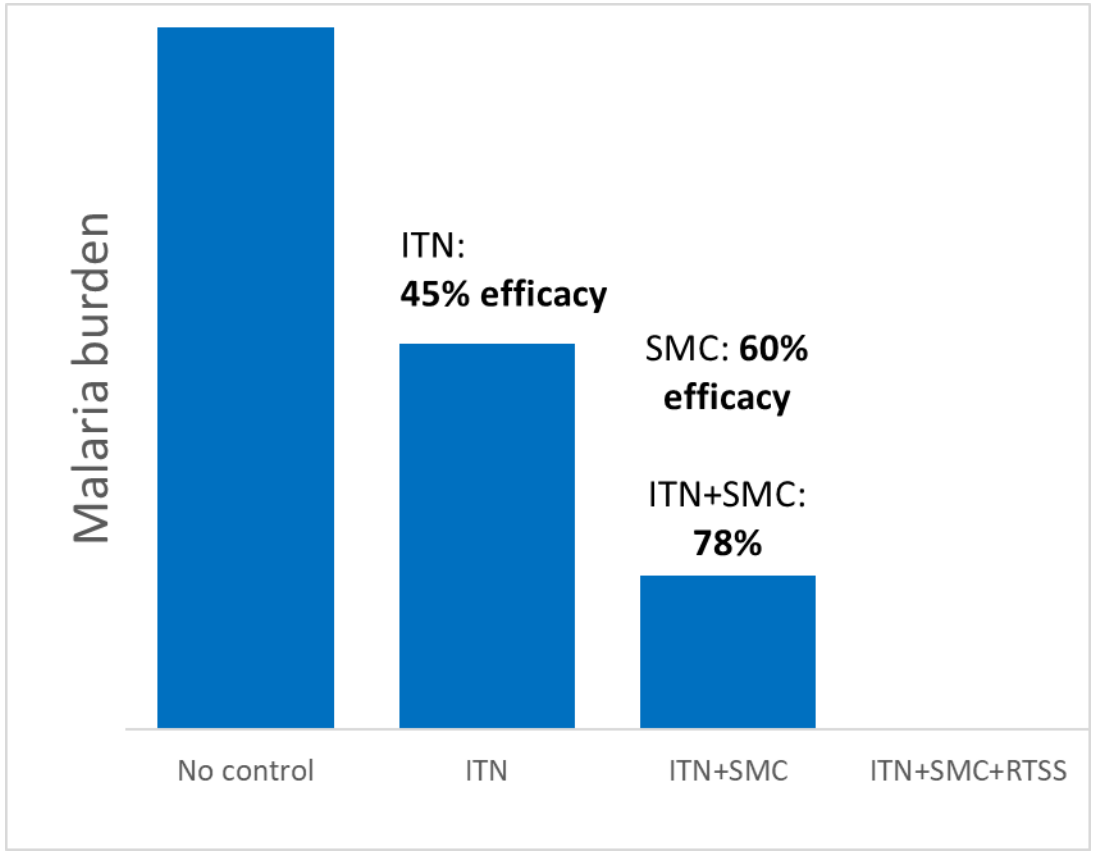
Reduction in deaths of all causes: **53.4%**

Chandramohan et al. (2021) N Engl J Med 385:1005-1017


Malaria burden
No control
ITN
ITN+SMC
ITN+SMC+RTSS

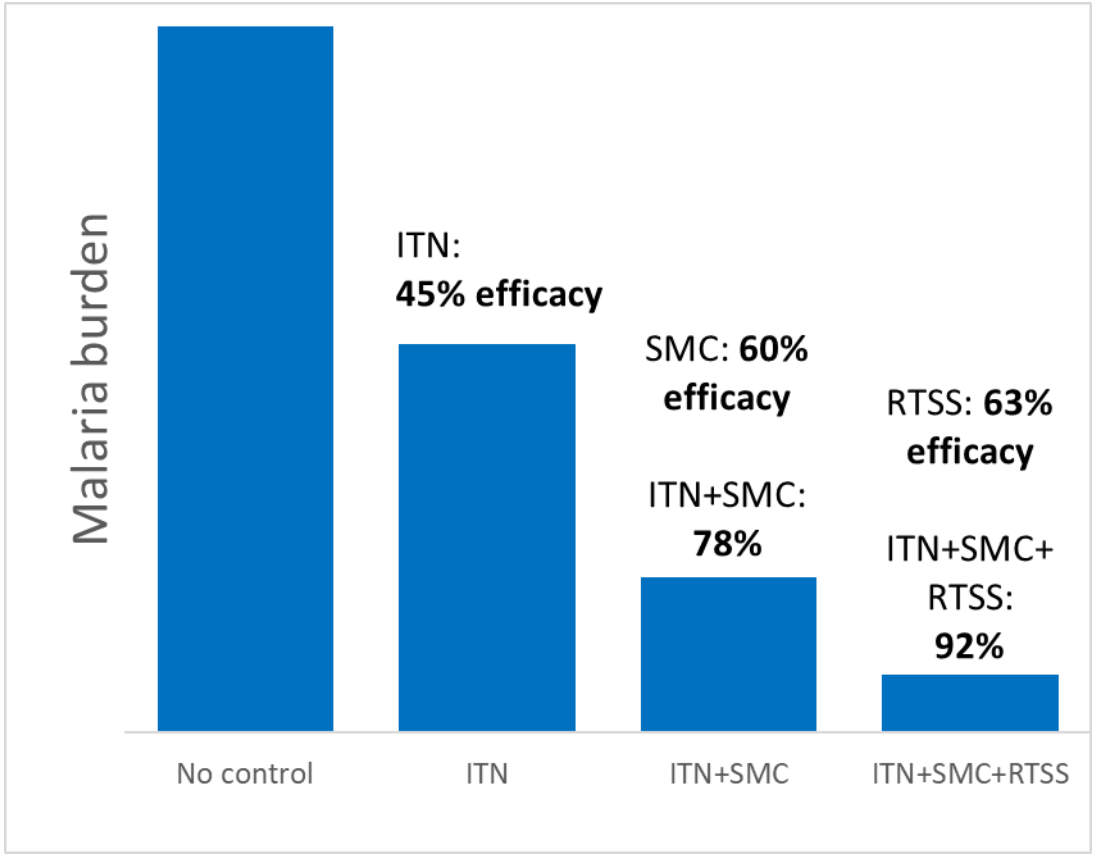


ITN efficacy:
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000363.pub3/full



ITN efficacy: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000363.pub3/full

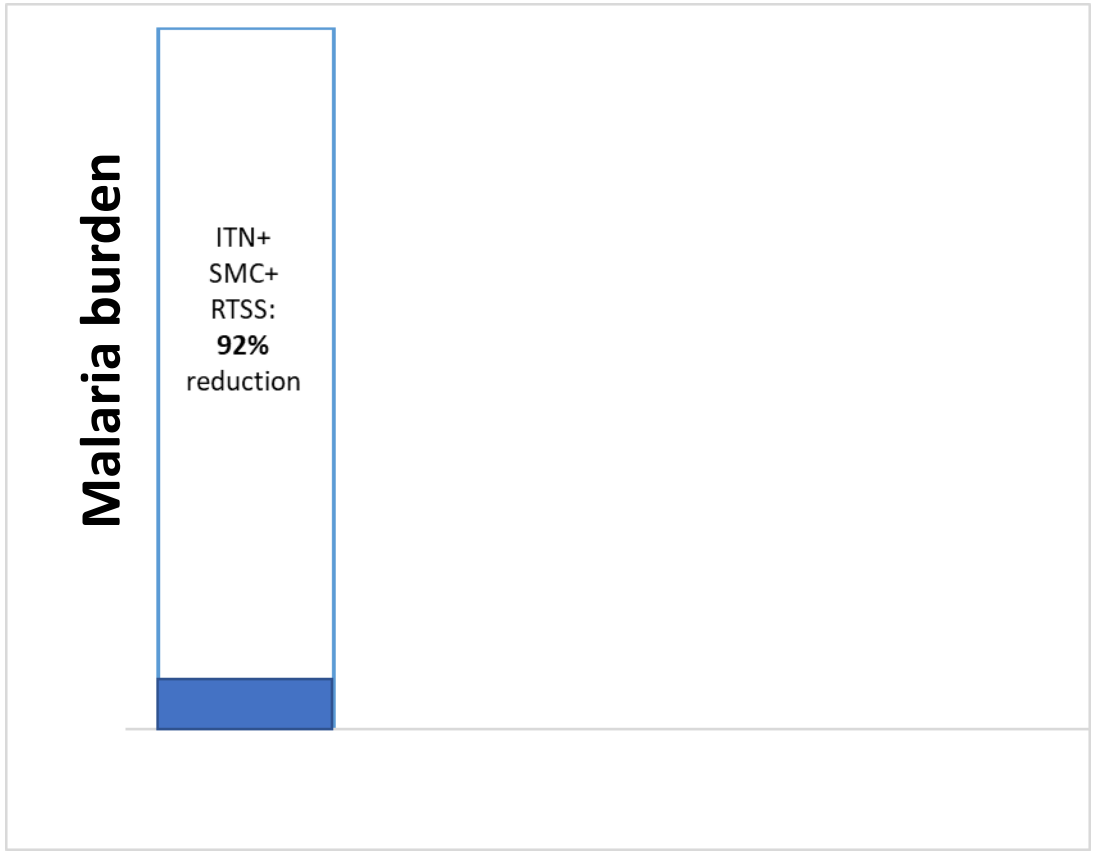
SMC efficacy: 85% per month, case control studies in 5 countries, https://journals.plos.org/plosmedicine/article/authors?id=10.1371/journal.pmed.1003727 (SMC for 5 months covering 70% of annual burden)



ITN efficacy: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000363.pub3/full

SMC efficacy: 85% per month, case control studies in 5 countries, https://journals.plos.org/plosmedicine/article/authors?id=10.1371/journal.pmed.1003727 (SMC for 5 months covering 70% of annual burden)

RTS,S efficacy of seasonal vaccination over 3 years https://www.nejm.org/doi/full/10.1056/NEJMoa2026330



A very high level of protection from malaria is possible even in the highest burden areas, if the core interventions now available are combined

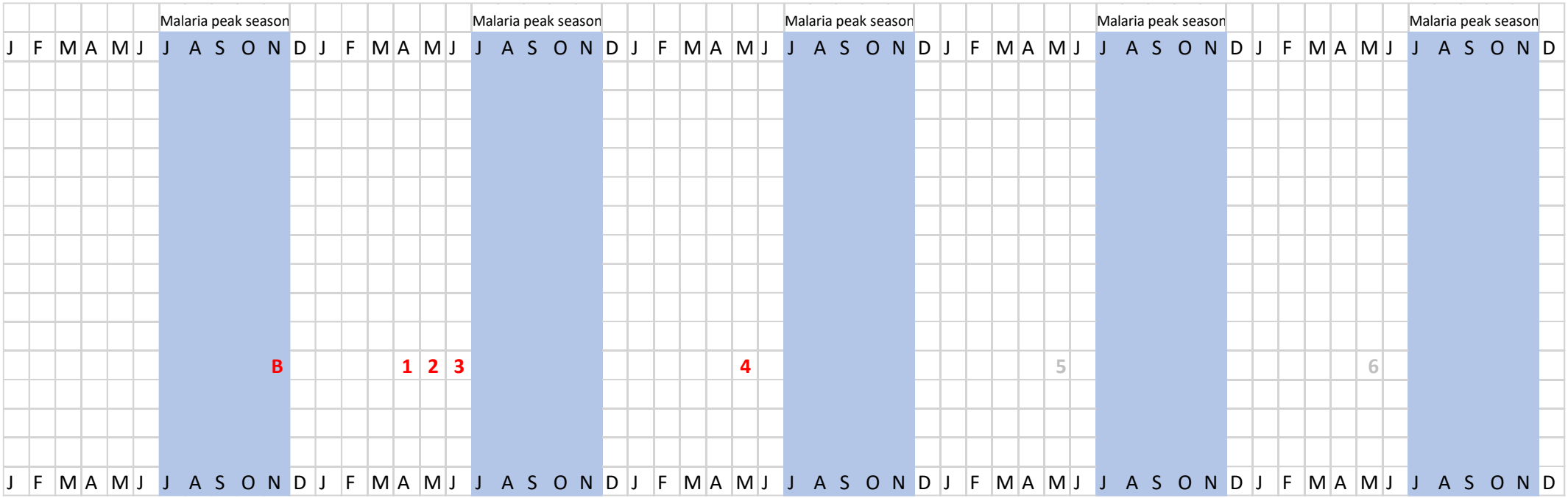
How might the vaccine be delivered in seasonal areas to optimize impact?

Dose 1 is not recommended before 5 months of age

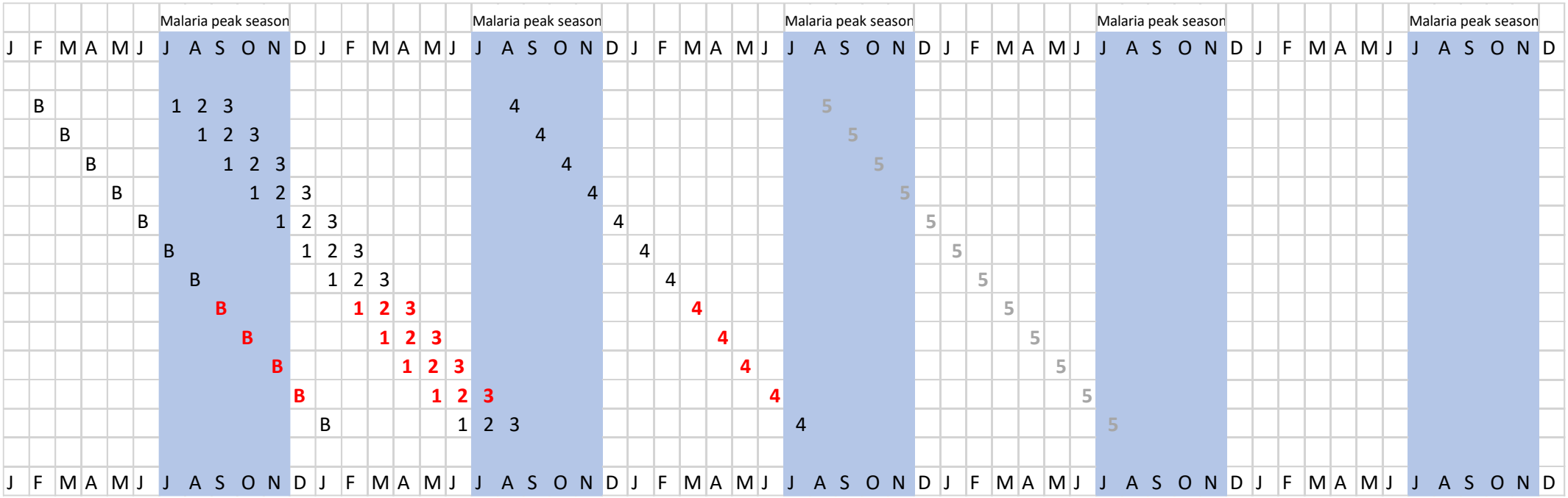
Ideally children receive the first 3 doses just before the malaria season, and the 4th dose just before the next season, (and 5th dose a year later)

- Option 1: through EPI, at 5,6,7 and 18-22 months
- Option 2: seasonal delivery of all doses (e.g. via campaigns)
- Option 3: give first 3 doses as early as possible (at 5,6,7 months via EPI), and 4th (and subsequent) doses delivered before the malaria season

Option 1: through EPI, at 5,6,7 and 18-22 months

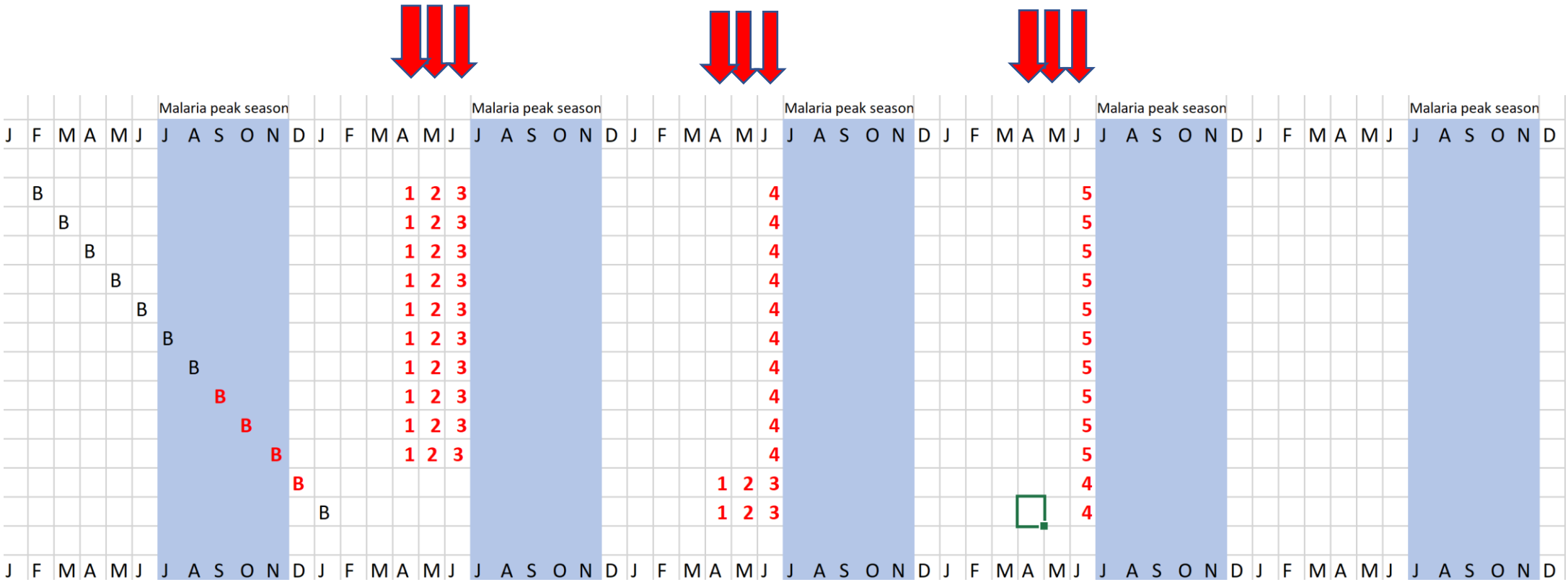


Option 1: through EPI, at 5,6,7 and 18-22 months



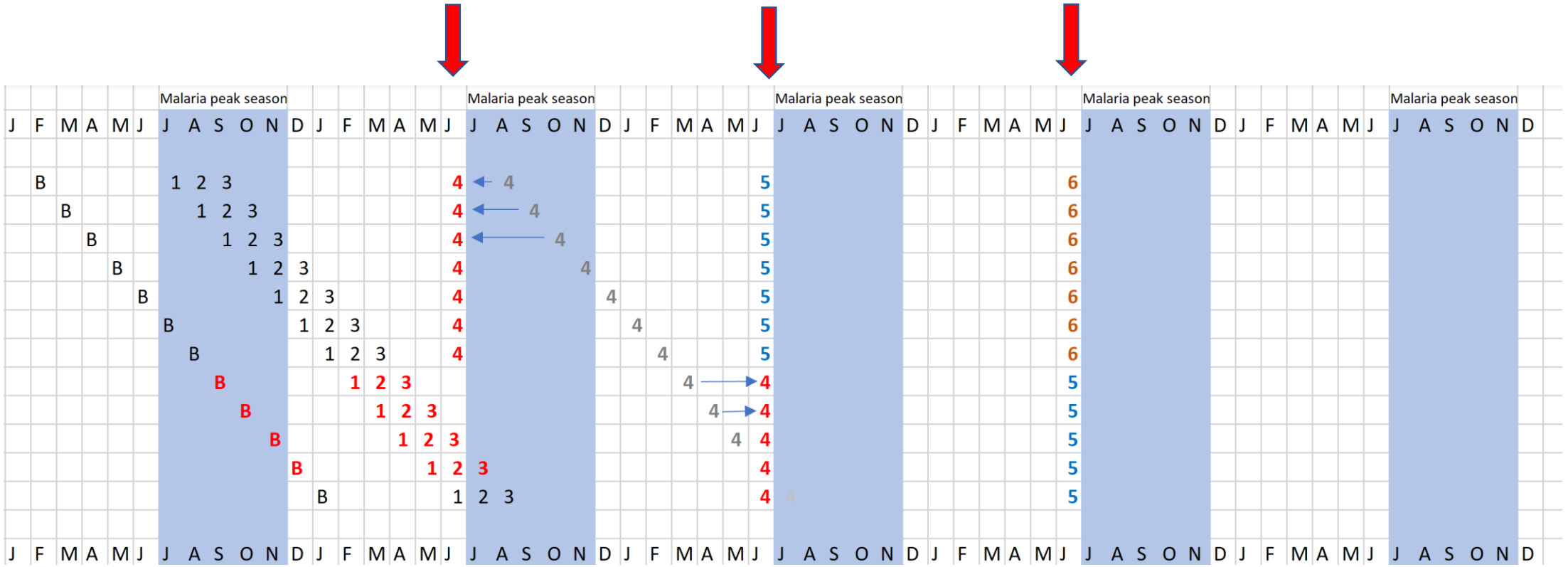
doses not optimally timed (unless born in the right month!)

Option 2: All doses delivered seasonally



Optimal timing, but children less than 5months old at the time of the campaign, have to wait to next year to get their first dose (and costly)

Option 3: primary doses when eligible, 4th and subsequent doses delivered seasonally



The first 3 doses as early as possible (5,6,7 months of age via EPI outreach),
The 4th (and subsequent) doses seasonally
(e.g. via campaigns, during which, a 5th, 6th … dose could also be delivered)

How might the vaccine be delivered in seasonal areas to optimize impact?

Dose 1 not recommended before 5 months of age

Ideally children receive the first 3 doses just before the malaria season, and the 4th dose just before the next season

- Option 1: through EPI, at 5,6,7 and 18-22 months
  - doses not optimally timed (unless born in the right month!)
- Option 2: seasonal campaigns:
  - but children <5months have to wait to next year, and costly
- Option 3: give first 3 doses as early as possible (via EPI), and 4th (and subsequent) doses seasonally
  - e.g. through seasonal campaigns (which could also deliver 5th, 6th … doses)

How might the vaccine be delivered in seasonal areas to optimize impact?

Dose 1 not recommended before 5 months of age

Ideally children receive the first 3 doses just before the malaria season, and the 4th dose just before the next season

- Option 1: through EPI, at 5,6,7 and 18-22 months
  - doses not optimally timed (unless born in the right month!)
- Option 2: seasonal campaigns:
  - but children <5months have to wait to next year, and costly
- Option 3: give first 3 doses as early as possible (via EPI), and 4th (and subsequent) doses seasonally
  - e.g. through seasonal campaigns (which could also deliver 5th, 6th … doses)

Questions not yet answered:

- Effect of parasitaemia at time of vaccine dose?
- Optimal interval between dose3 and dose 4?
- Feasibility and impact of different models of seasonal delivery?

Extra slides

Synergy between vaccine and chemoprevention?

Known advantages:

- Fewer children with malaria at time of SMC visits, so more get SPAQ rather than AL
- Dose 4 given earlier in seasonal areas: efficacy post D4 greater if closer to D3
- SMC can strengthen vaccine uptake – check vaccine status during SMC visits and refer under-vaccinated children

Potential advantages:

- Less parasitaemia at time of vaccination? (not known)
- Possible synergy due to reduced parasite load entering bloodstream? (not known)

Key issues

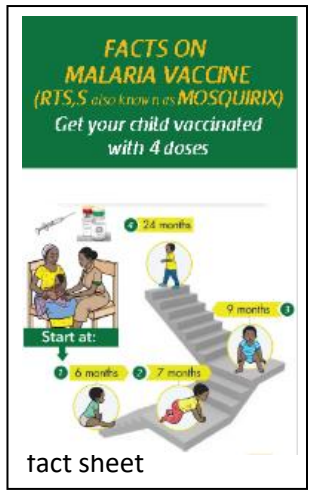
1. Careful evaluation in first countries to implement is needed, for learning and to demonstrate impact

2. This should include piloting of alternative delivery methods to optimize impact, strategies to promote uptake esp. in older children

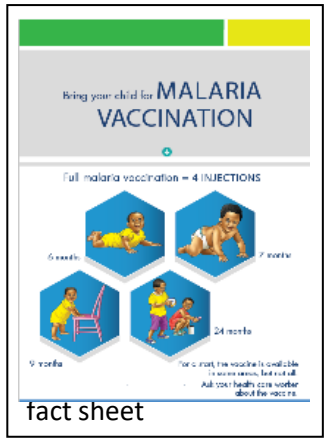
3. Potential synergies with SMC

4. Need for effective communication. Possibility that recognition of the importance of malaria could help acceptability of the malaria vaccine and may be opportunity to strengthen EPI

Extracts from countries' information, education and communication materials

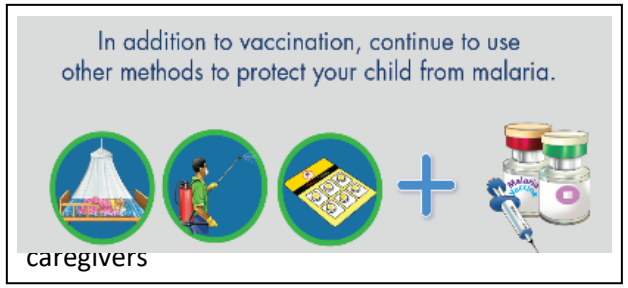


fact sheet

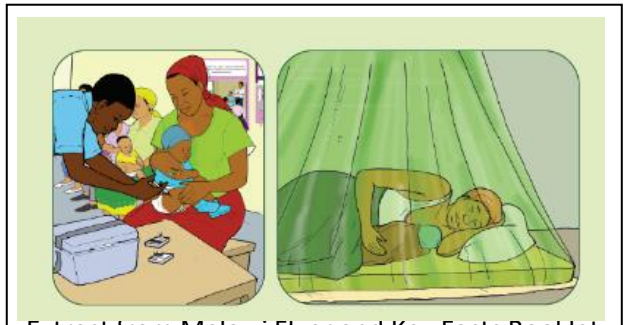


fact sheet

workers

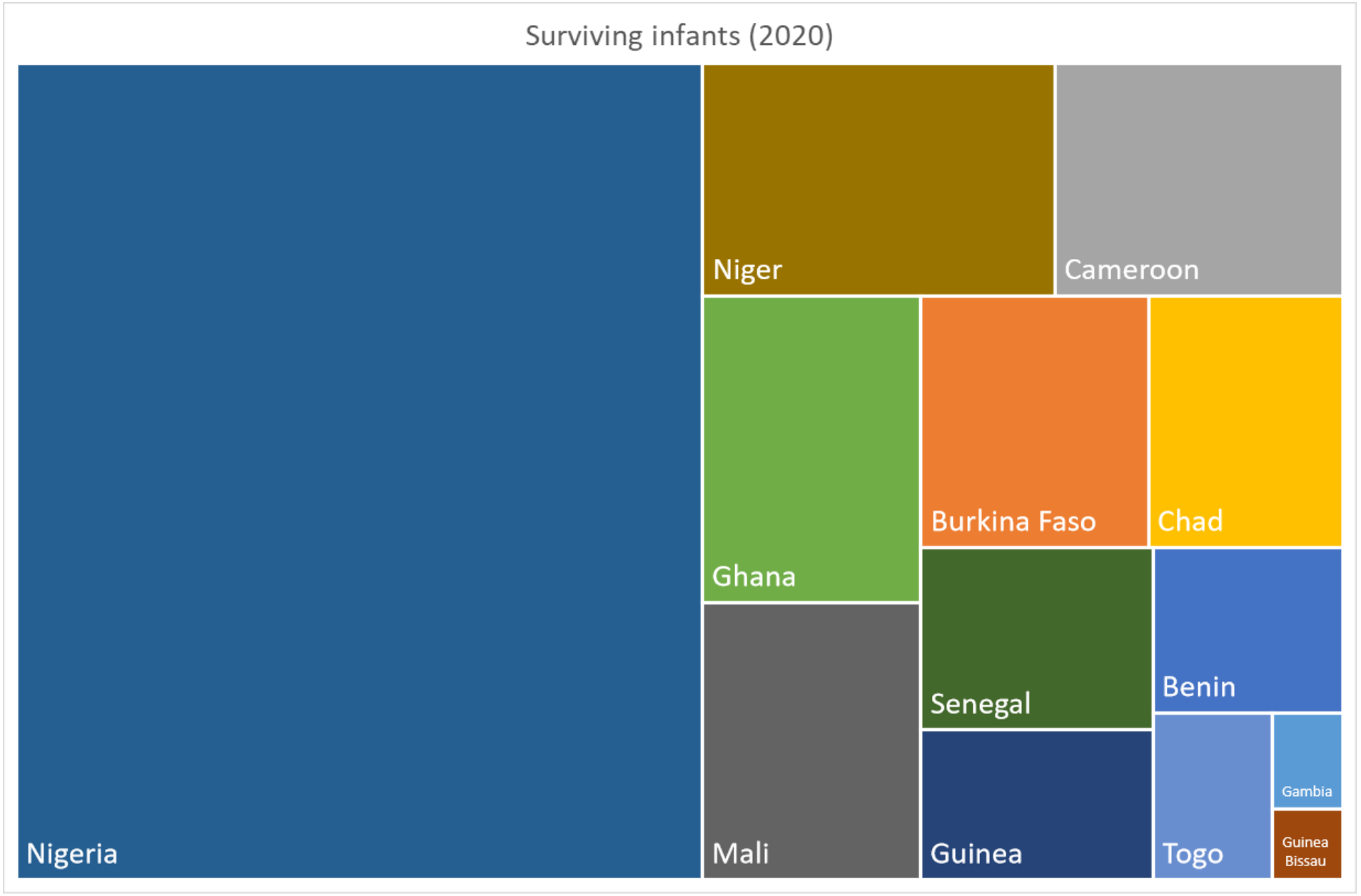


caregivers


Extract from Malawi Flyer and Key Facts Booklet

Extracts: WHO MVIP

Implementation challenges: 1



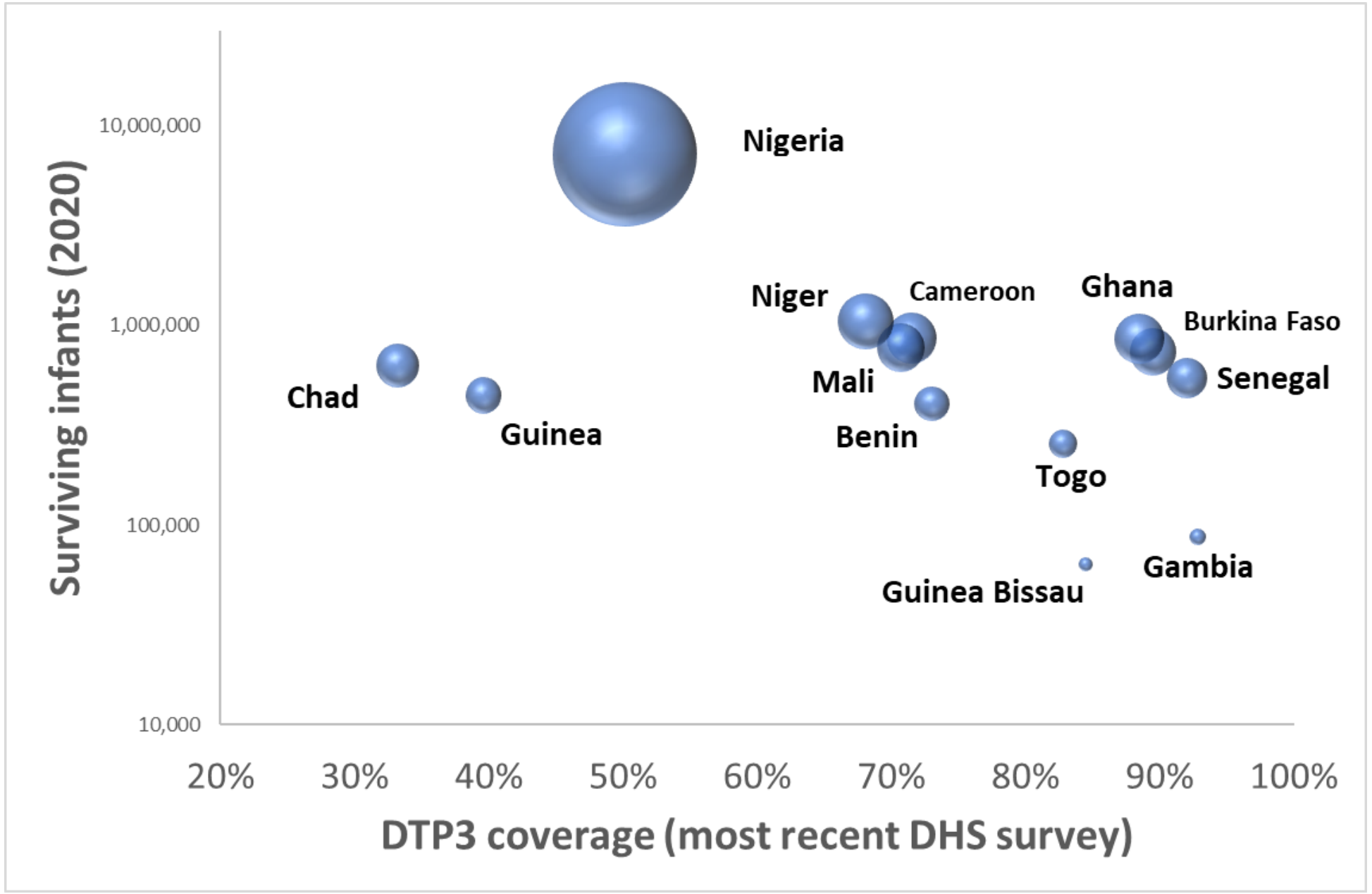
14million surviving infants 2020

UN World Population Prospects

https://population.un.org/wpp/

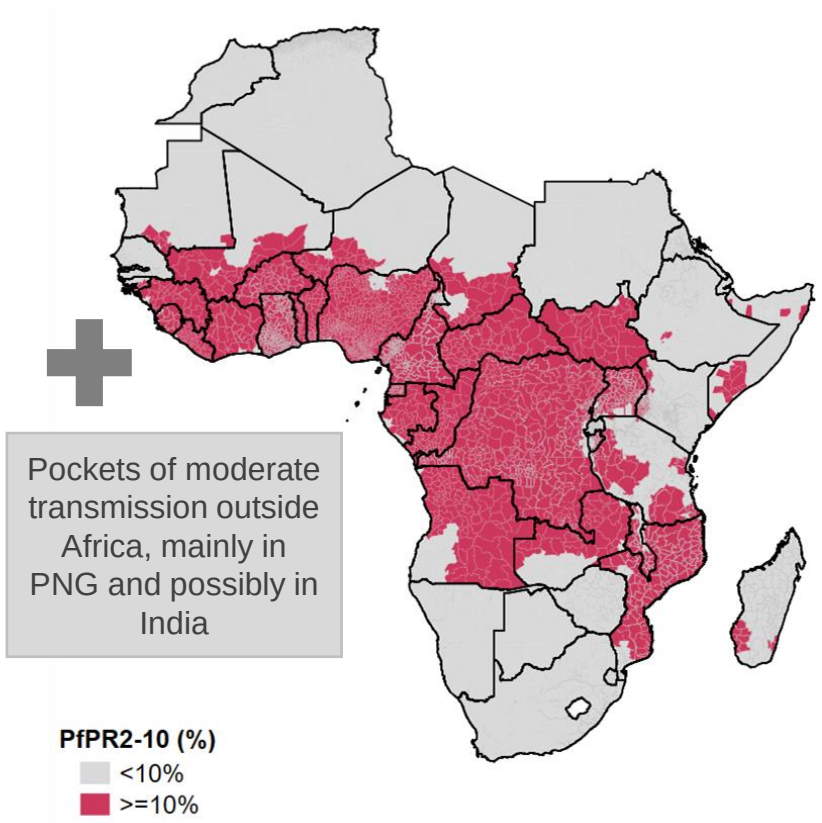
Adapted after Wariri et al. BMJ Global Health 2019;4:e001713

Implementation challenges: 2



Adapted after Wariri et al. BMJ Global Health 2019;4:e001713

WHO recommendation: Oct 2021



P. falciparum parasite prevalence ($PfPR_{2-10}$) estimates, 2019. Source: MAP 2019

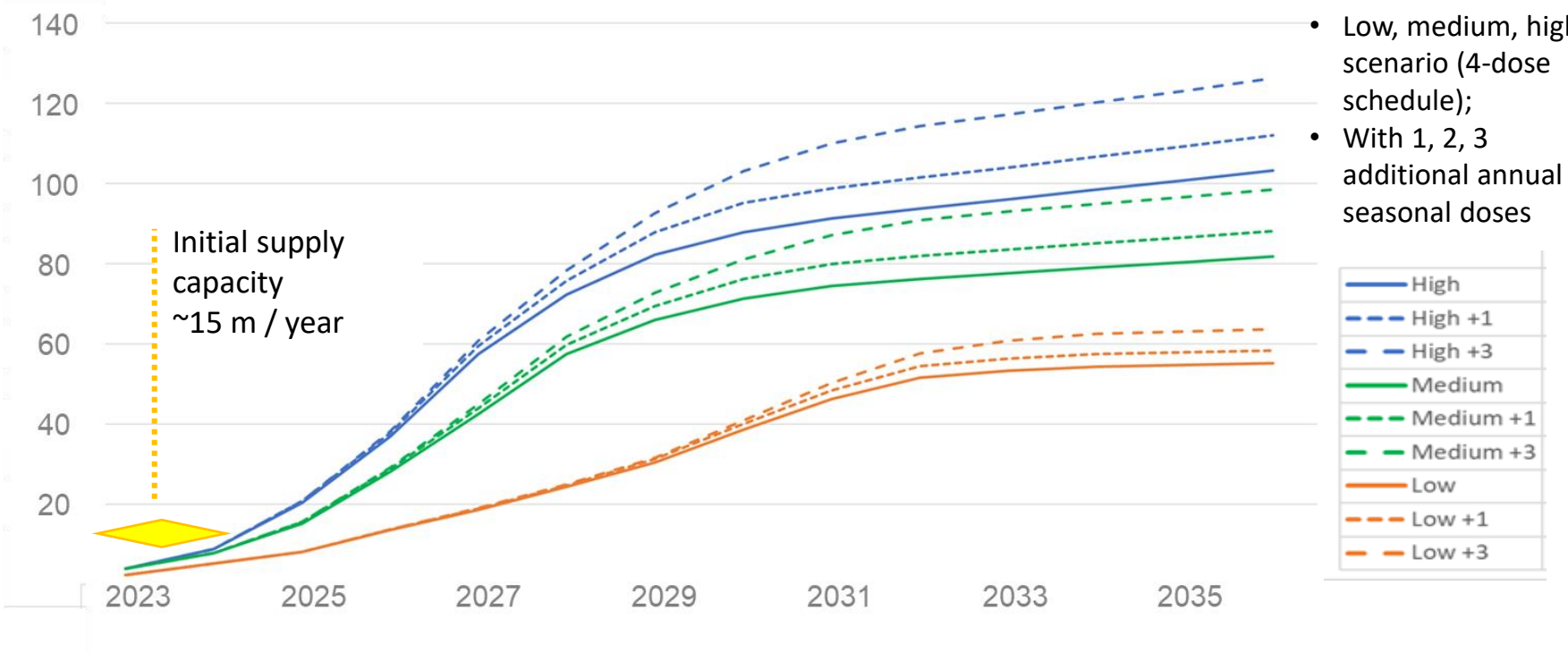
- **WHO recommends the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO**

Over 25 million children are born each year in regions with medium to high malaria transmission

Demand may exceed 100 million doses per year at peak

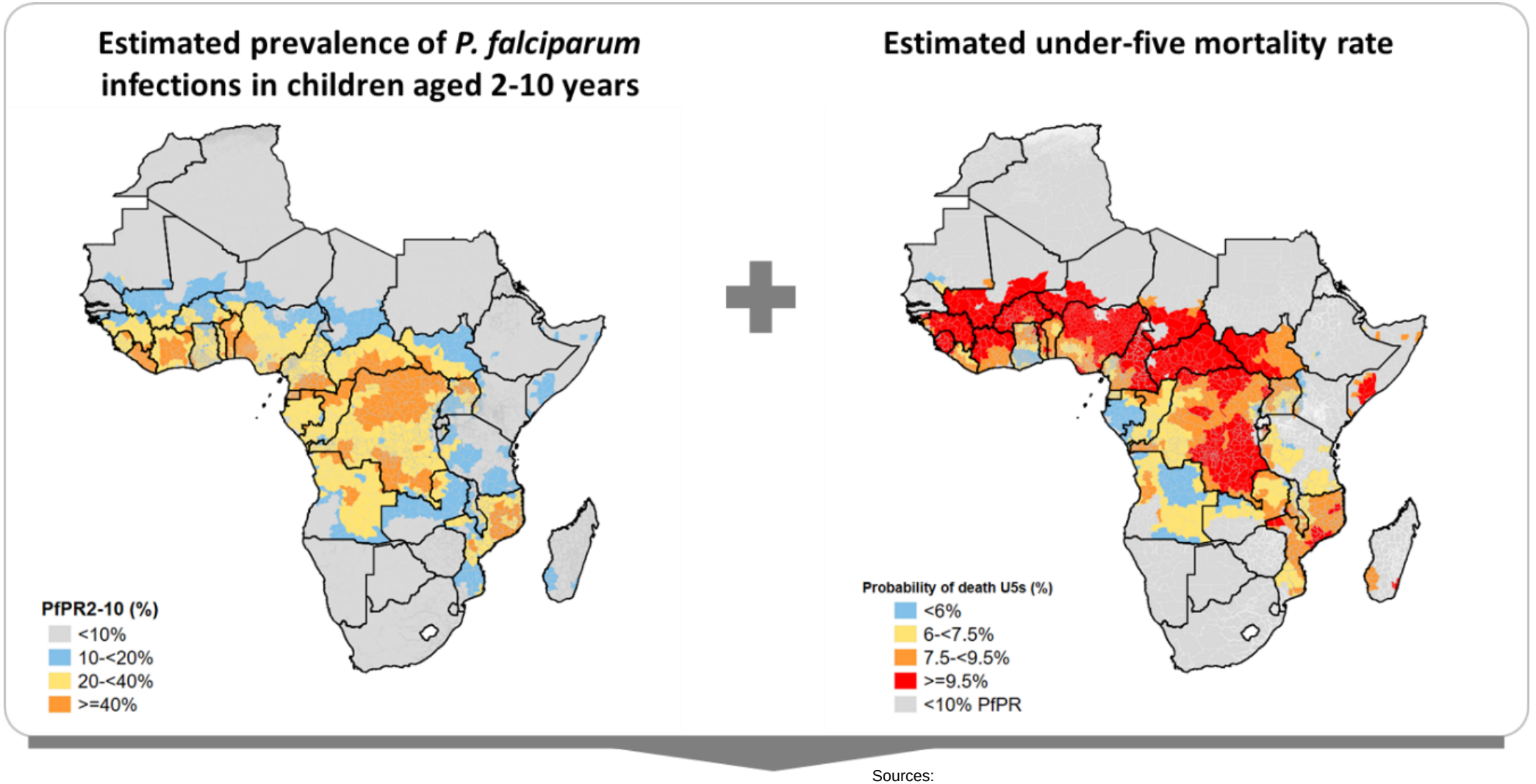
Demand for a malaria vaccine expected to be high

Depending on the forecast scenario, 55 – 120 million doses per year by 2035
(preliminary draft forecast)



- Low, medium, high scenario (4-dose schedule);
- With 1, 2, 3 additional annual seasonal doses

Illustration of “need” classification

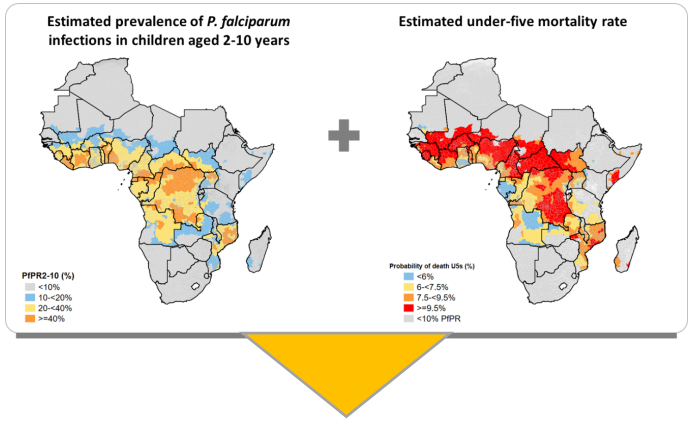


Sources:
District level mean estimates of *Pf*PR in 2-10 year old children in 2019 (Malaria Atlas Project)
District level mean estimates probabilities of death from all-causes before the age of 5 in 2015 (IHME)

Illustration of “need” classification

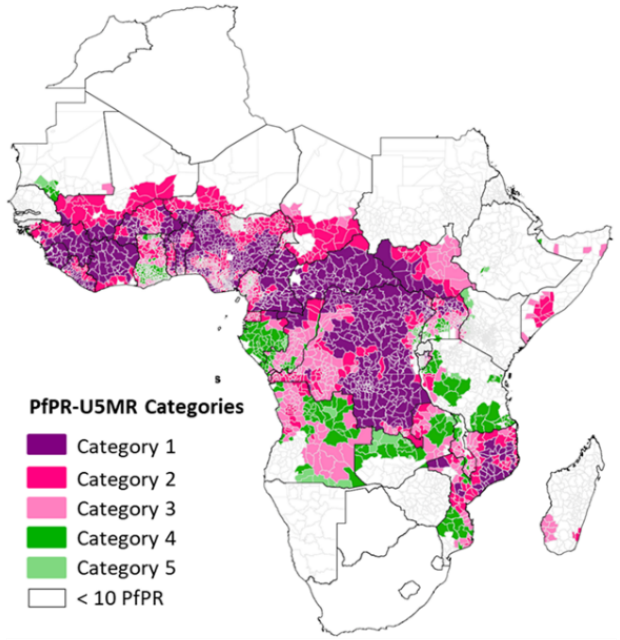
Composite classification of malaria prevalence and all-cause under-five mortality as proxy for “need”

Maps are illustrative based on global estimates. Countries will identify areas of highest burden and need within its own borders based on best available local evidence and the broader context of sub-national tailoring of malaria interventions

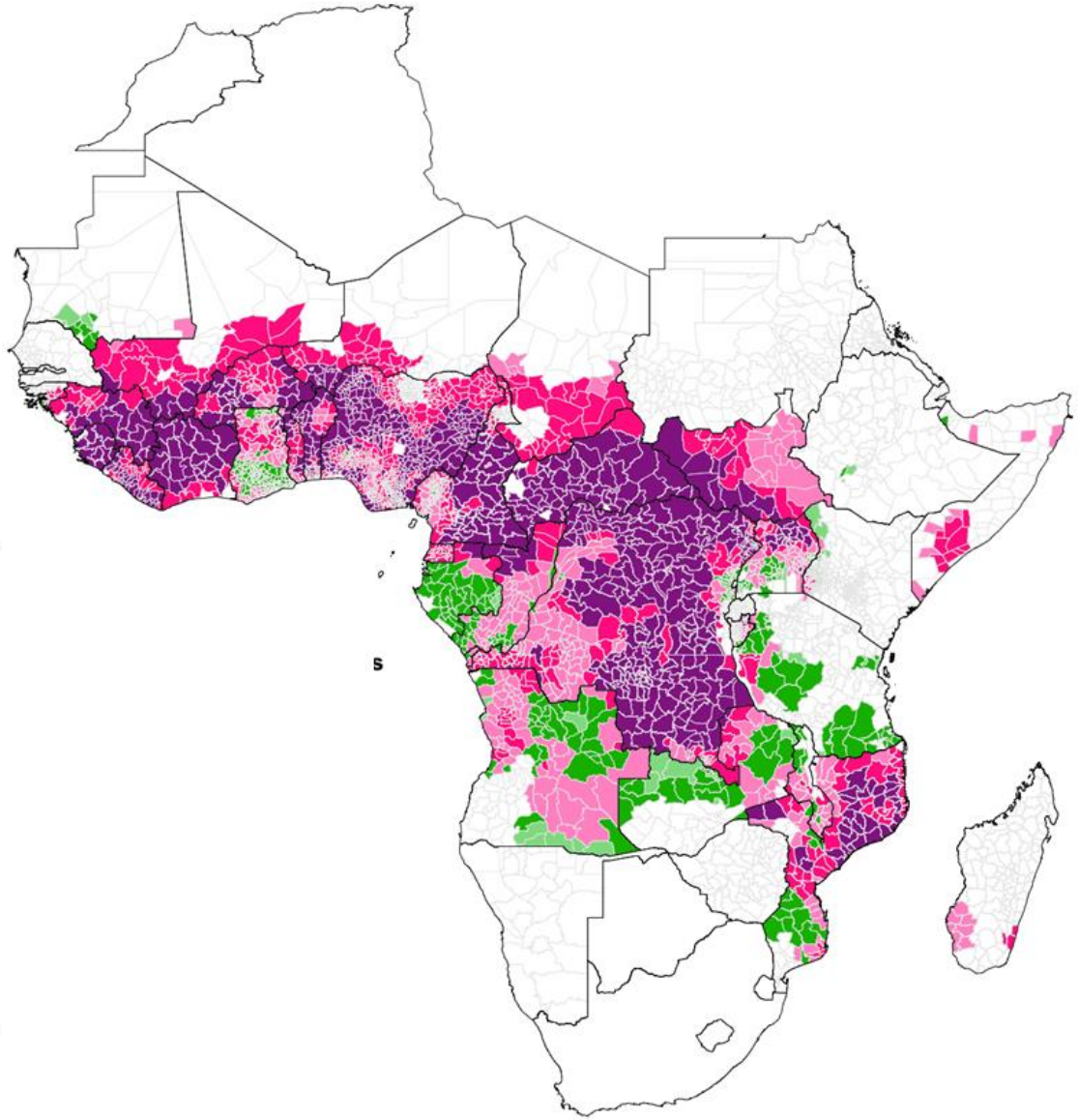


Composite classification of malaria prevalence and all-cause under-five mortality as proxy for “need”

Category	Possible combinations	
	Malaria prevalence	All-cause under-five mortality
1 Greatest need	PfPR 20-<40%	& U5MR >=9.5%
	PfPR >=40%	& U5MR >=9.5%
	PfPR >=40%	& U5MR 7.5-<9.5%
2	PfPR 10-<20%	& U5MR >=9.5%
	PfPR 20-<40%	& U5MR 7.5-<9.5%
	PfPR >=40%	& U5MR 6-<7.5%
3	PfPR 10-<20%	& U5MR 7.5-<9.5%
	PfPR 20-<40%	& U5MR 6-<7.5%
	PfPR >=40%	& U5MR <6%
4	PfPR 10-<20%	& U5MR 6-<7.5%
	PfPR 20-<40%	& U5MR <6%
5	PfPR 10-<20%	& U5MR <6%



Categories of need:
Composite classification of malaria prevalence and under-five mortality



PfPR-U5MR Categories

- Category 1 → **Highest need**
- Category 2
- Category 3
- Category 4
- Category 5
- < 10 PfPR

Map production: Global Malaria Programme (GMP), World Health Organization (WHO)
Disclaimer: The designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Table 2: New births estimated for 2023 by need category in sub-Saharan African countries with moderate to high malaria transmission

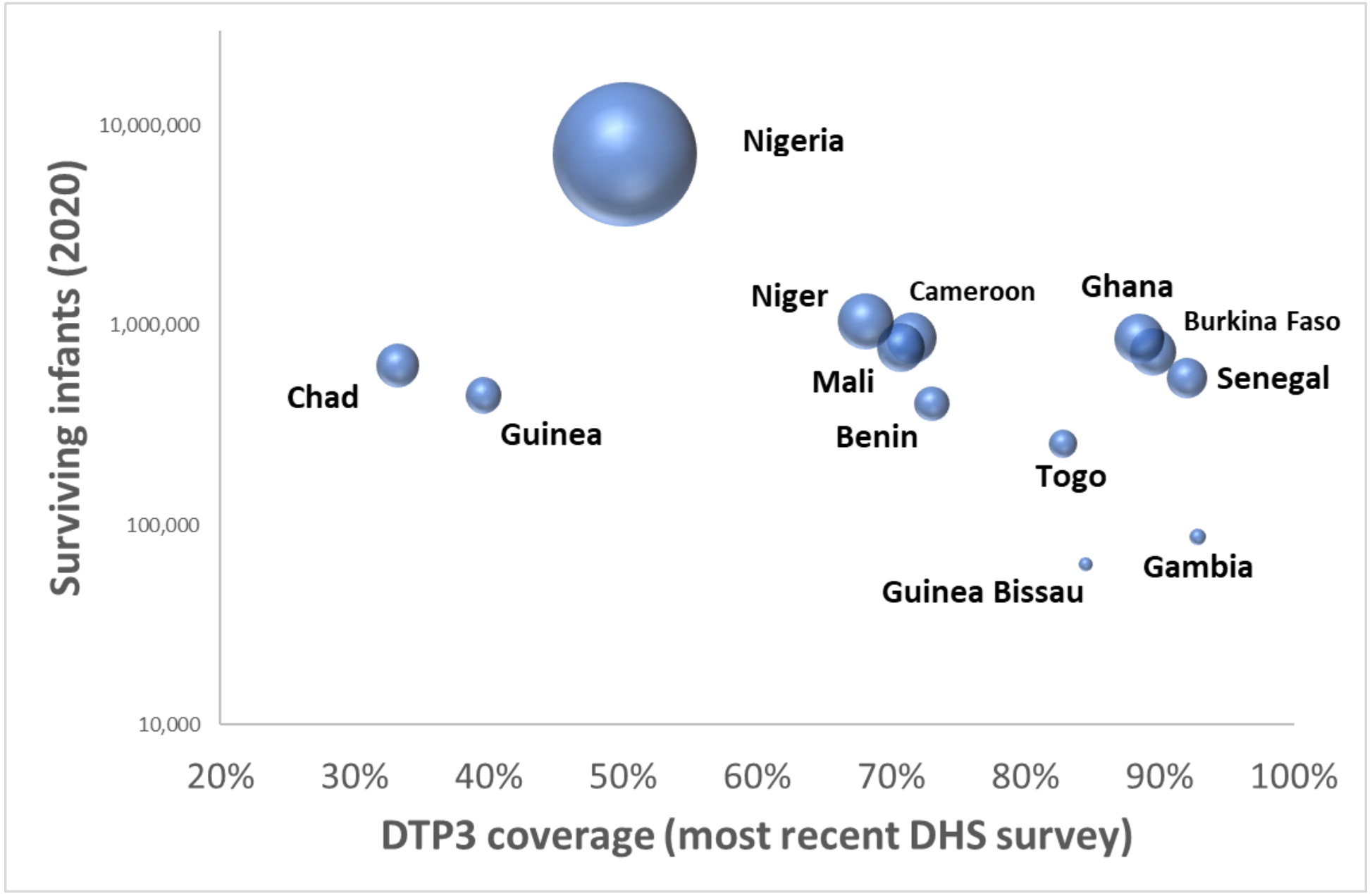
Highest need

	Cat 1	Cat 2	Cat 3	Cat 4	Cat 5	Total Cat 1-5	<10% PfPR
Angola	-	86,000	255,000	224,000	351,000	916,000	297,000
Benin	205,000	102,000	108,000	43,000	-	458,000	-
Burkina Faso	266,000	385,000	163,000	-	-	814,000	-
Burundi	111,000	80,000	100,000	24,000	-	315,000	208,000
Cameroon	190,000	213,000	318,000	104,000	32,000	857,000	91,000
Central African Republic	168,000	11,000	-	-	-	179,000	-
Chad	-	376,000	78,000	-	-	454,000	263,000
Congo	4,000	4,000	48,000	66,000	55,000	177,000	-
Côte d'Ivoire	567,000	328,000	-	-	-	895,000	-
Democratic Republic of the Congo	1,987,000	535,000	641,000	130,000	369,000	3,662,000	180,000
Equatorial Guinea	-	20,000	5,000	-	-	25,000	-
Ethiopia	-	-	-	7,000	19,000	26,000	3,620,000
Gabon	1,000	5,000	2,000	49,000	1,000	58,000	-
Ghana	10,000	75,000	70,000	247,000	147,000	549,000	96,000
Guinea	291,000	141,000	17,000	-	77,000	526,000	-
Guinea-Bissau	-	9,000	5,000	3,000	-	17,000	54,000
Kenya	-	4,000	4,000	11,000	93,000	112,000	1,097,000
Liberia	48,000	75,000	49,000	-	-	172,000	-
Madagascar	-	32,000	32,000	12,000	-	76,000	827,000
Malawi	-	19,000	240,000	136,000	-	395,000	13,000
Mali	171,000	458,000	11,000	-	-	640,000	244,000
Mauritania	-	-	3,000	26,000	44,000	73,000	86,000
Mozambique	337,000	406,000	183,000	77,000	-	1,003,000	237,000
Niger	192,000	628,000	100,000	-	-	920,000	281,000
Nigeria	2,830,000	3,188,000	890,000	301,000	-	7,209,000	788,000
Sierra Leone	178,000	-	37,000	-	-	215,000	-
Somalia	-	80,000	30,000	16,000	-	126,000	412,000
South Sudan	129,000	199,000	164,000	-	-	492,000	13,000
Togo	61,000	73,000	78,000	-	67,000	279,000	-
Uganda	181,000	192,000	650,000	327,000	243,000	1,593,000	163,000
United Republic of Tanzania	-	33,000	77,000	385,000	41,000	536,000	1,783,000
Zambia	15,000	33,000	113,000	160,000	88,000	409,000	312,000
TOTAL	**7,942,000**	**7,790,000**	**4,471,000**	**2,348,000**	**1,627,000**	**24,178,000**	**11,065,000**

Indicative
Countries will present their own data

Numbers in the table reflect indicative estimates based on globally available modelled estimates. Countries are encouraged to use their best available local evidence to assess the annual target population falling into the different categories of need in line with the definitions provided above. Estimates of new births by need category using country level data are likely to differ from global estimates.

Implementation challenges: 2

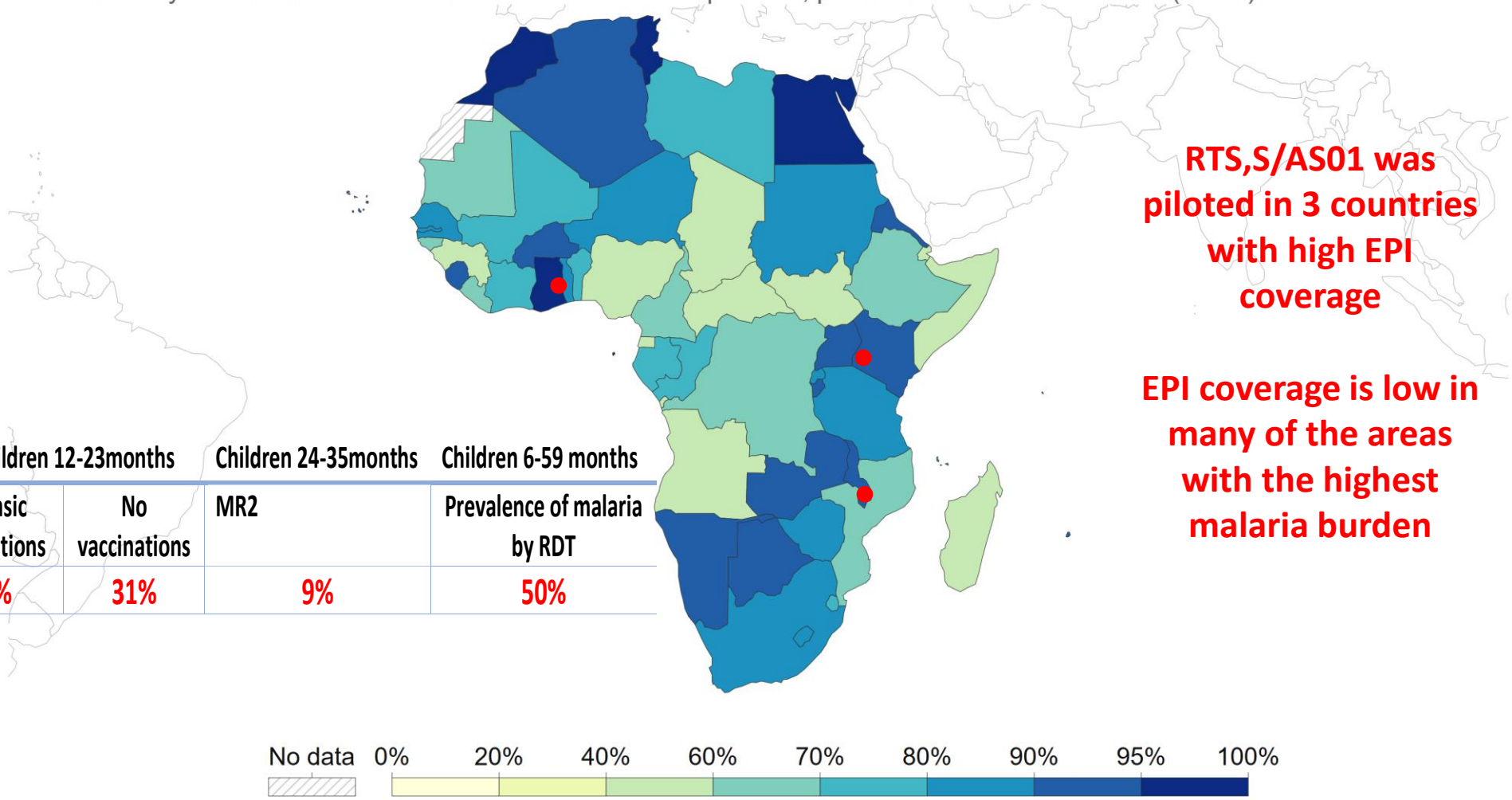


Adapted after Wariri et al. BMJ Global Health 2019;4:e001713

Share of one-year-olds vaccinated against diphtheria, pertussis, and tetanus, 2021

Share of one-year-olds who received the third dose of the diphtheria, pertussis and tetanus vaccine (DTP3).

Our World in Data



RTS,S/AS01 was piloted in 3 countries with high EPI coverage

EPI coverage is low in many of the areas with the highest malaria burden

	Vaccine uptake in children 12-23months				Children 24-35months	Children 6-59 months
	DTP3	MR1	All basic vaccinations	No vaccinations	MR2	Prevalence of malaria by RDT
North West zone Nigeria	29%	39%	20%	31%	9%	50%

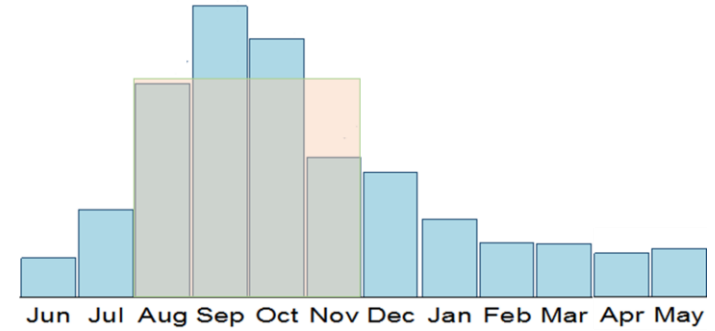
Source: WHO; UNICEF (2022)

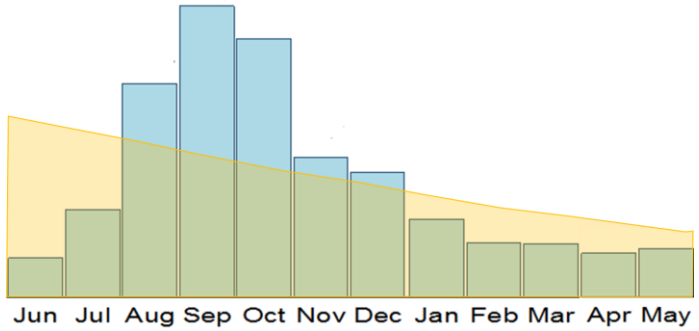
OurWorldInData.org/vaccination/ • CC BY

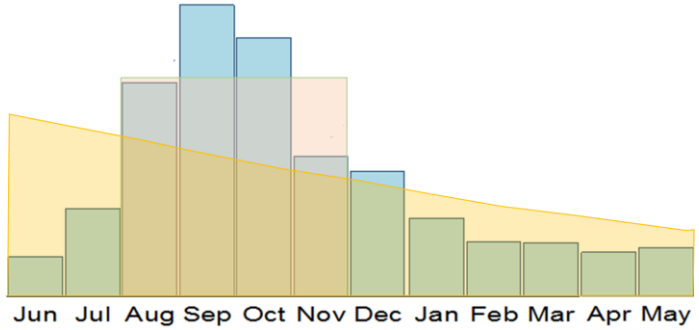
Note: Diphtheria and pertussis are infectious respiratory diseases caused by bacteria in the throat and airways. Tetanus is a bacterial infection that leads to severe muscle spasms, fever, headache, and can be fatal.

Seasonal vaccination: results over 3 years (primary vaccination and 2 annual boosters)

Chandramohan et al. (2021) N Engl J Med 385:1005-1017







Efficacy of seasonal RTS,S and of SMC

against clinical malaria

		Efficacy against hospital admission with severe malaria:	Efficacy against malaria deaths:	Reduction in deaths of all causes:
Efficacy of RTS,S (in children receiving SMC)				
• Year 1 (after primary 3 doses)	71.7%			
• Year 2 (after 4th dose)	63.2%			
• Year 3 (after 5th dose)	58.6%			
Average efficacy over 3 years:	**62.8%**	**70.5%**	**72.9%**	**53.4%**
Efficacy of SMC (in children receiving RTSS)				
• Year 1	72.1%			
• Year 2	59.1%			
• Year 3	52.6%			
Average efficacy over 3 years:	**59.6%**	**70.6%**	**75.3%**	**44.6%**

Chandramohan et al. (2021) N Engl J Med 385:1005-1017 https://www.nejm.org/doi/full/10.1056/NEJMoa2026330