JTEG's Summary of RTS,S/ AS01 Clinical Trial Data

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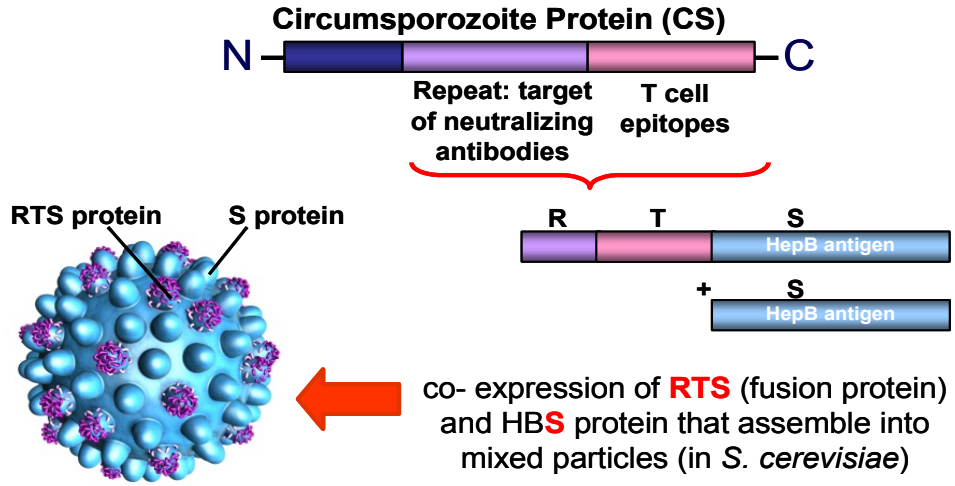
On behalf of the Joint Technical Expert Group (JTEG)

RTS,S/AS01 Malaria Vaccine

- Based on large segment of *P. falciparum* circumsporozoite protein and hepatitis B viral surface protein (as carrier matrix) expressed in yeast cells and includes adjuvant (AS01)
- Phase 2 trials shown consistent evidence of partial protection against clinical malaria
- Pivotal Phase 3 multicentre trial started in 2009

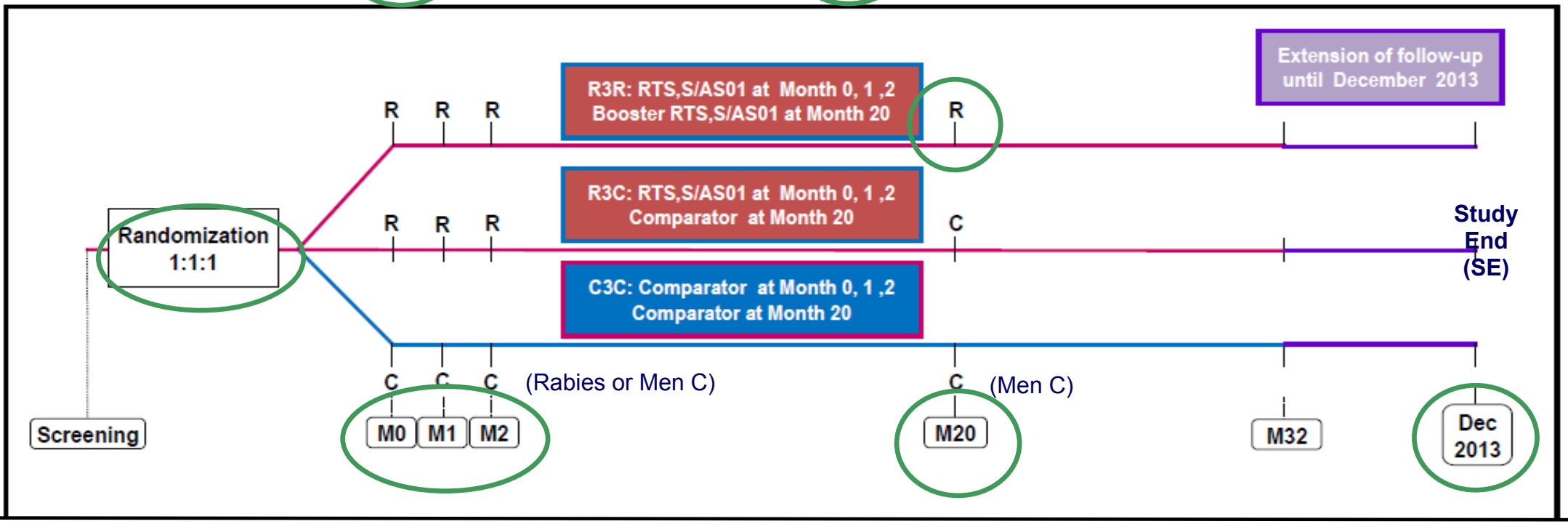


RTS,S/AS01: 25ug of RTS,S adjuvanted with AS01, which is composed of liposomes and the immunomodulatory molecules 3-O-desacyl-f4-monophosphoryl lipid A (MPL) and QS21

based on Cohen et al 2010

Design of RTS,S/AS01 Phase 3 trial

In both 5-17 months and 6-12 weeks at enrolment



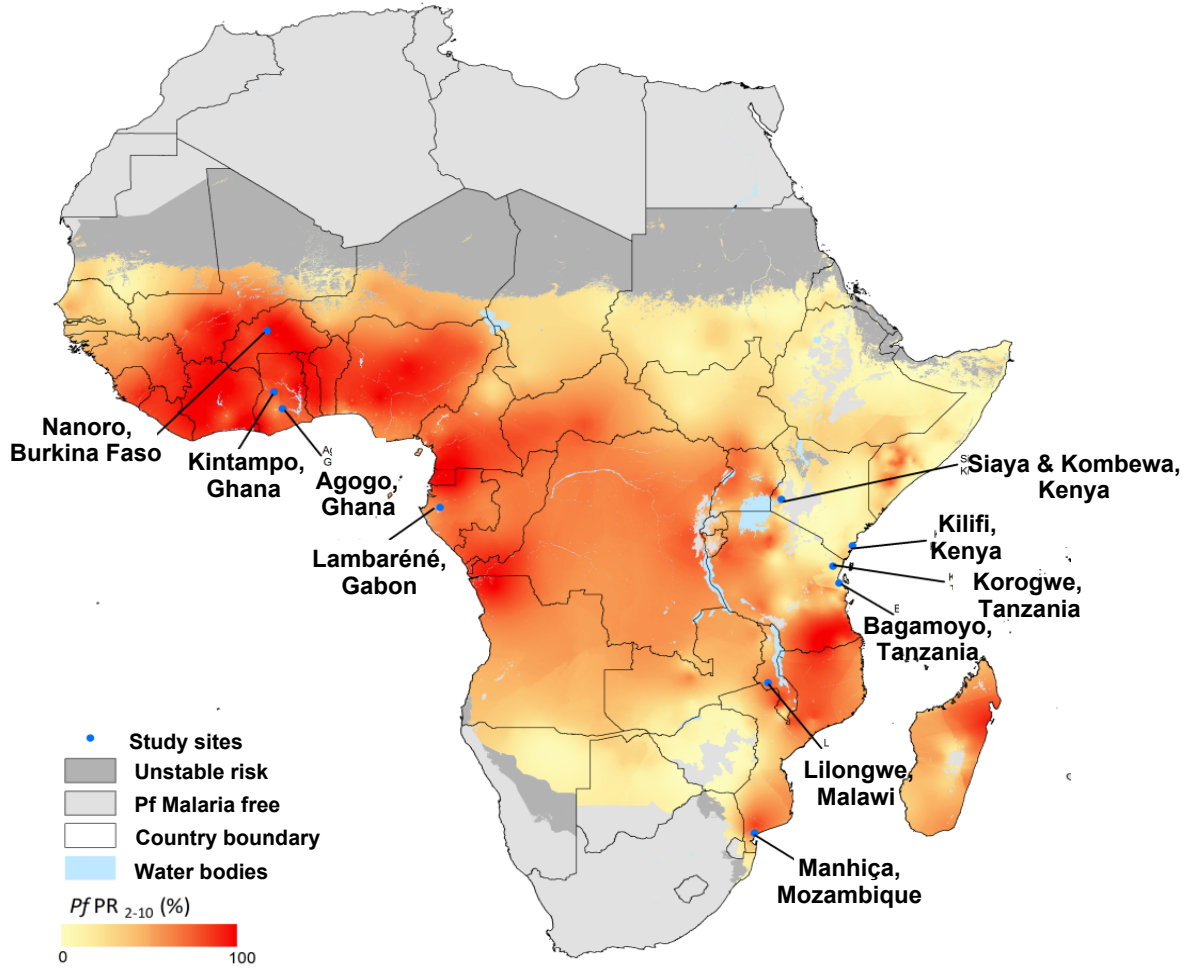
Median follow up to SE:

48 months for 5-17 mo

38 months for 6-12 wks

Pivotal Phase III RTS,S/AS01 malaria vaccine efficacy trial

- Randomized, controlled, double-blind trial conducted in 11 centres in 7 countries
- Over 15,000 children enrolled
- **Wide range of malaria transmission intensities (0.01 to >2.0 clinical episodes per child per year)**
- **Efficacy measured in presence of other malaria control interventions: ITN coverage 86% in 6-12 weeks and 75% in 5-17 months**



RTS,S/AS01 Trial Objectives

- **Co-primary objectives:** efficacy over one year post-dose 3 against clinical malaria* when administered in each of the two age groups

- **Secondary objectives:**
  - Vaccine efficacy against **severe malaria, anaemia, malaria hospitalization, fatal malaria, all-cause mortality**
  - Vaccine efficacy against clinical malaria by transmission setting
  - Vaccine efficacy over time
  - Effect of a fourth dose given at 18 months

** primary case definition for clinical malaria was >5,000 parasites/uL with an axillary temperature of >37.5°C or a case that met the primary case definition for severe malaria*

European Medicines Agency assessment

The European Medicines Agency (EMA), under a process known as article 58, performed a scientific evaluation of this vaccine and has now issued what is called "a European scientific opinion". EMA's opinion was positive indicating that in their assessment the quality of the vaccine and the risk/ benefit is favourable from a regulatory perspective.

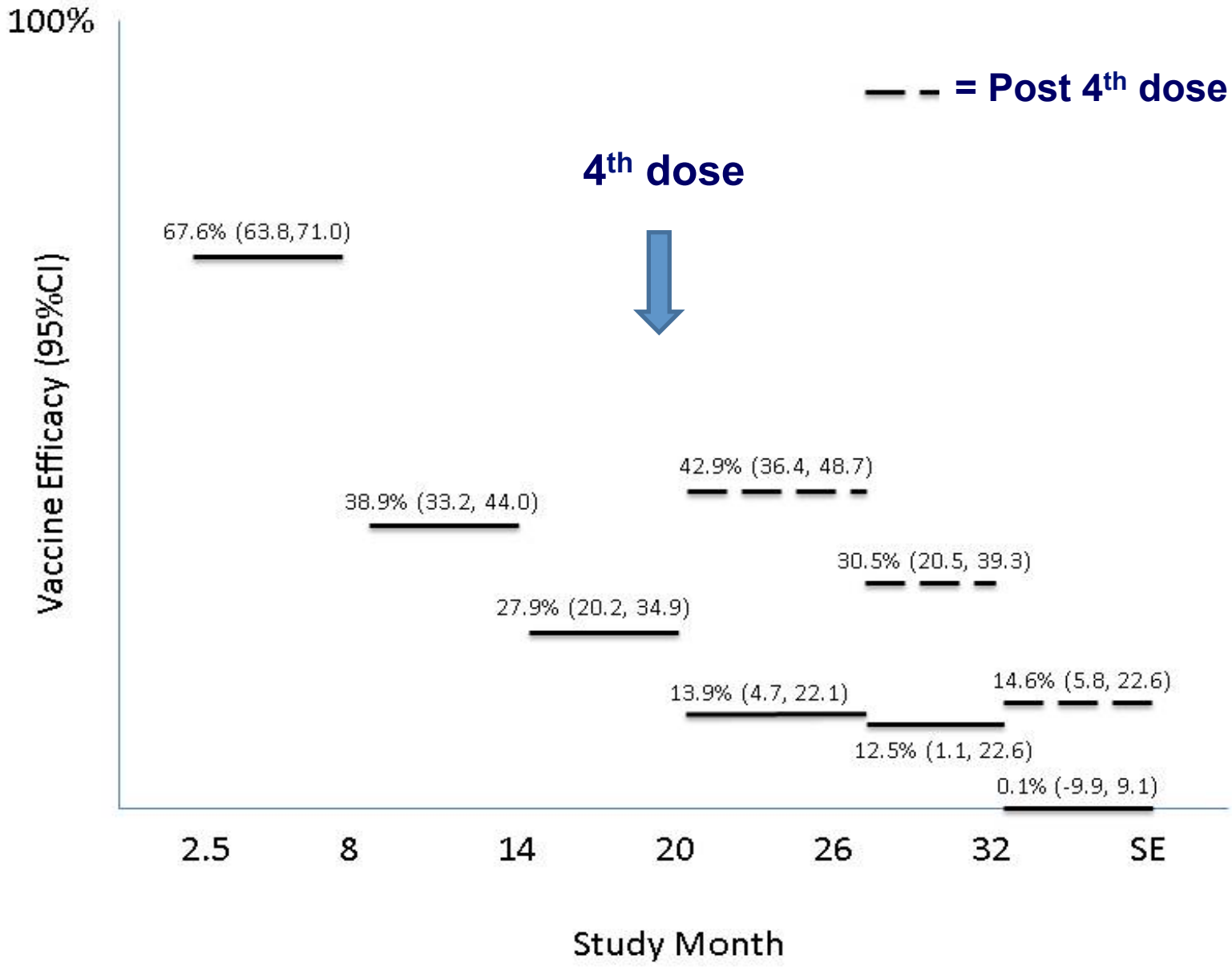
VACCINE EFFICACY

Vaccine efficacy (95%CI) against all episodes of clinical malaria and severe malaria

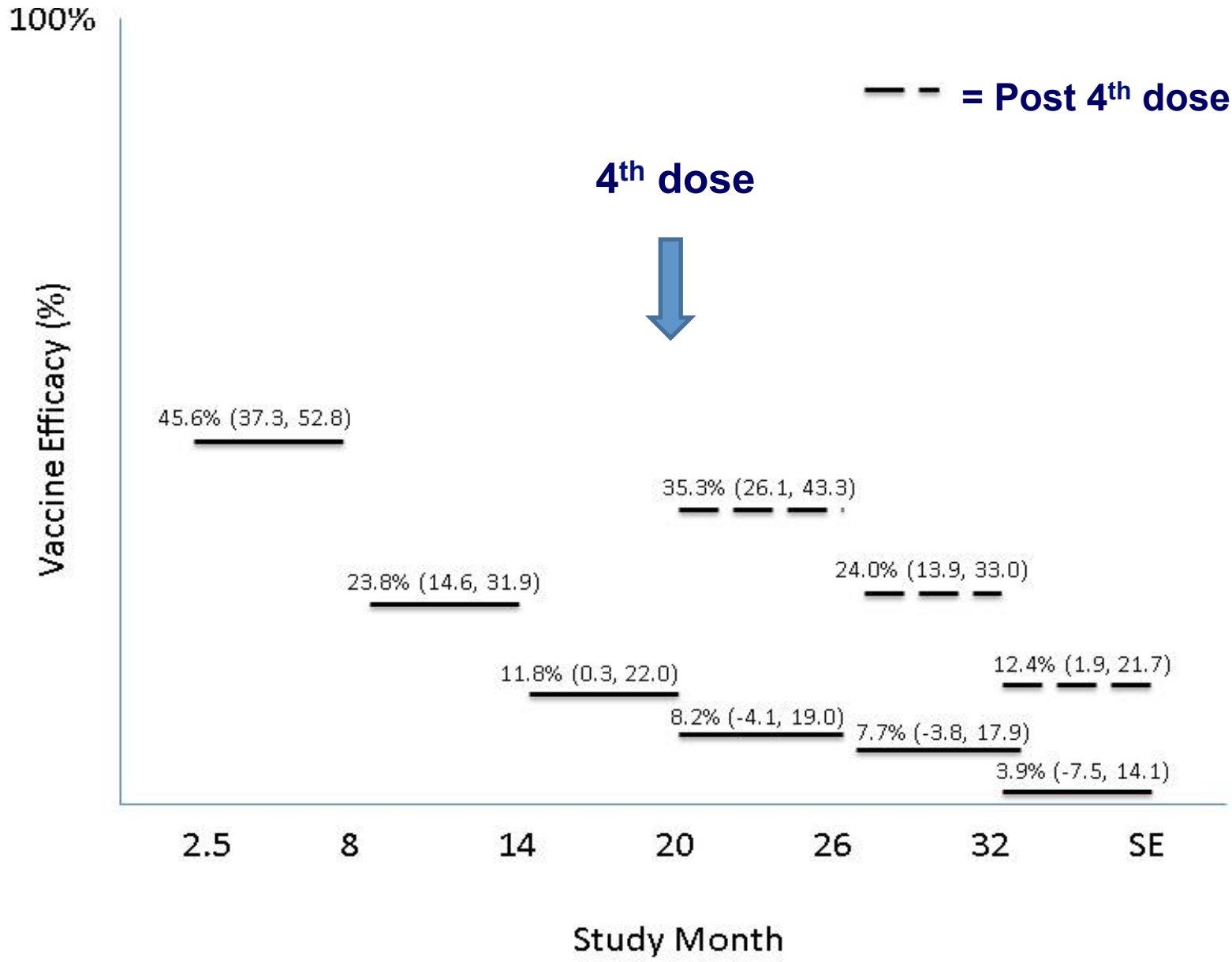
Study period	6-12 weeks		5-17 months	
	VE against clinical malaria	VE against severe malaria	VE against clinical malaria	VE against severe malaria
2.5M-14M	**32.9%** (26.3, 38.9)	**38.5%** (7.8, 59.0)	**51.3%** (47.5, 54.9)	**44.5%** (23.8, 59.6)
2.5M-20M	**26.6%** (20.3, 32.4)	17.4% (-16.2, 41.3)	**45.7%** (41.7, 49.5)	**37.7%** (18.0, 52.6)
2.5M-SE* (3 doses)	**18.2%** (11.4, 24.5)	16.0% (-14.5, 38.4)	**26.2%** (20.8, 31.2)	-2.2% (-31.3, 20.4)
2.5M-SE* (4 doses)	**26.7%** (20.5, 32.4)	20.5% (-9.8, 42.5)	**39.0%** (34.3, 43.3)	**31.5%** (9.3, 48.3)

*median 38 months for 6-12 weeks; 48 months for 5-17 months

Vaccine efficacy against clinical malaria stratified by time since entry in the 5-17 month group

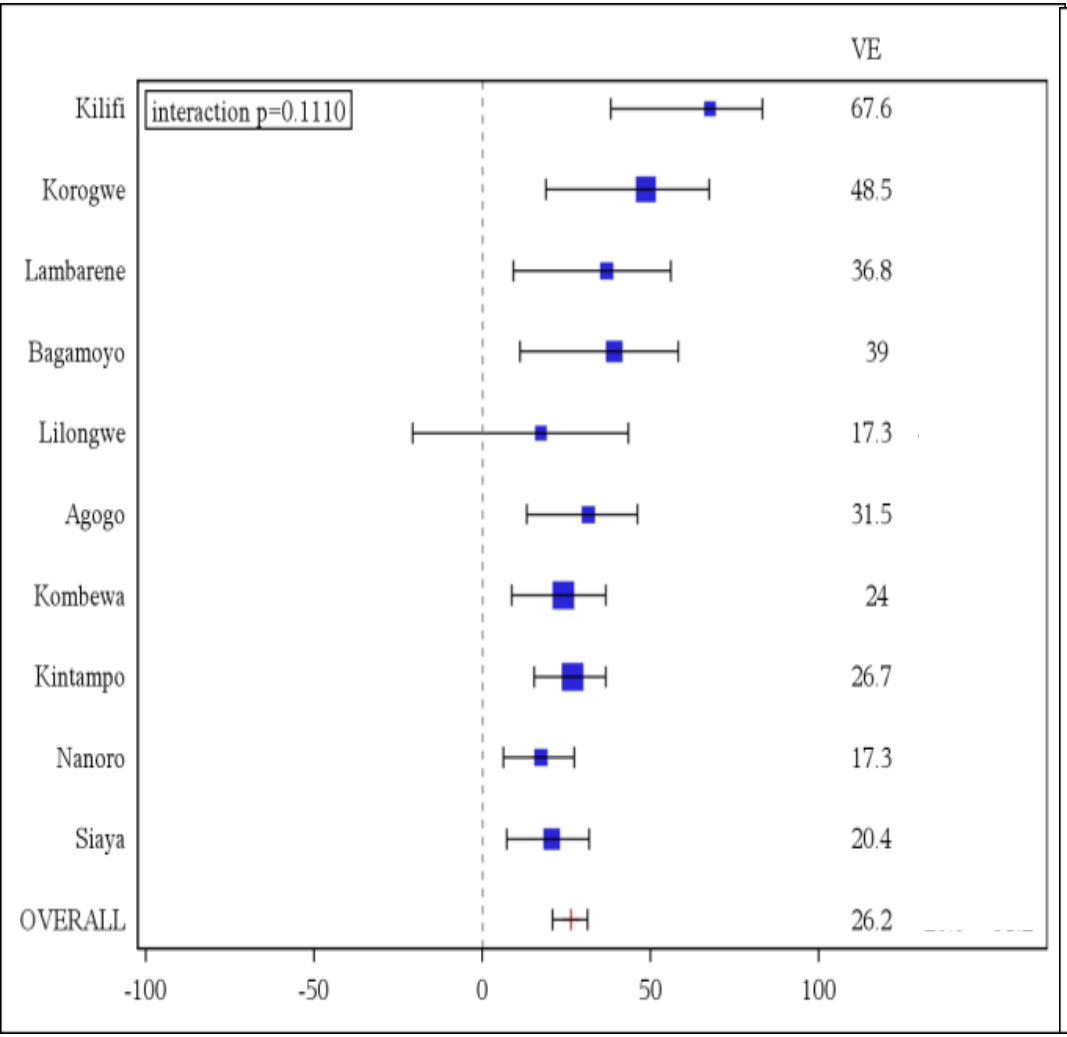


Vaccine efficacy against clinical malaria stratified by time since entry in the 6-12 week group

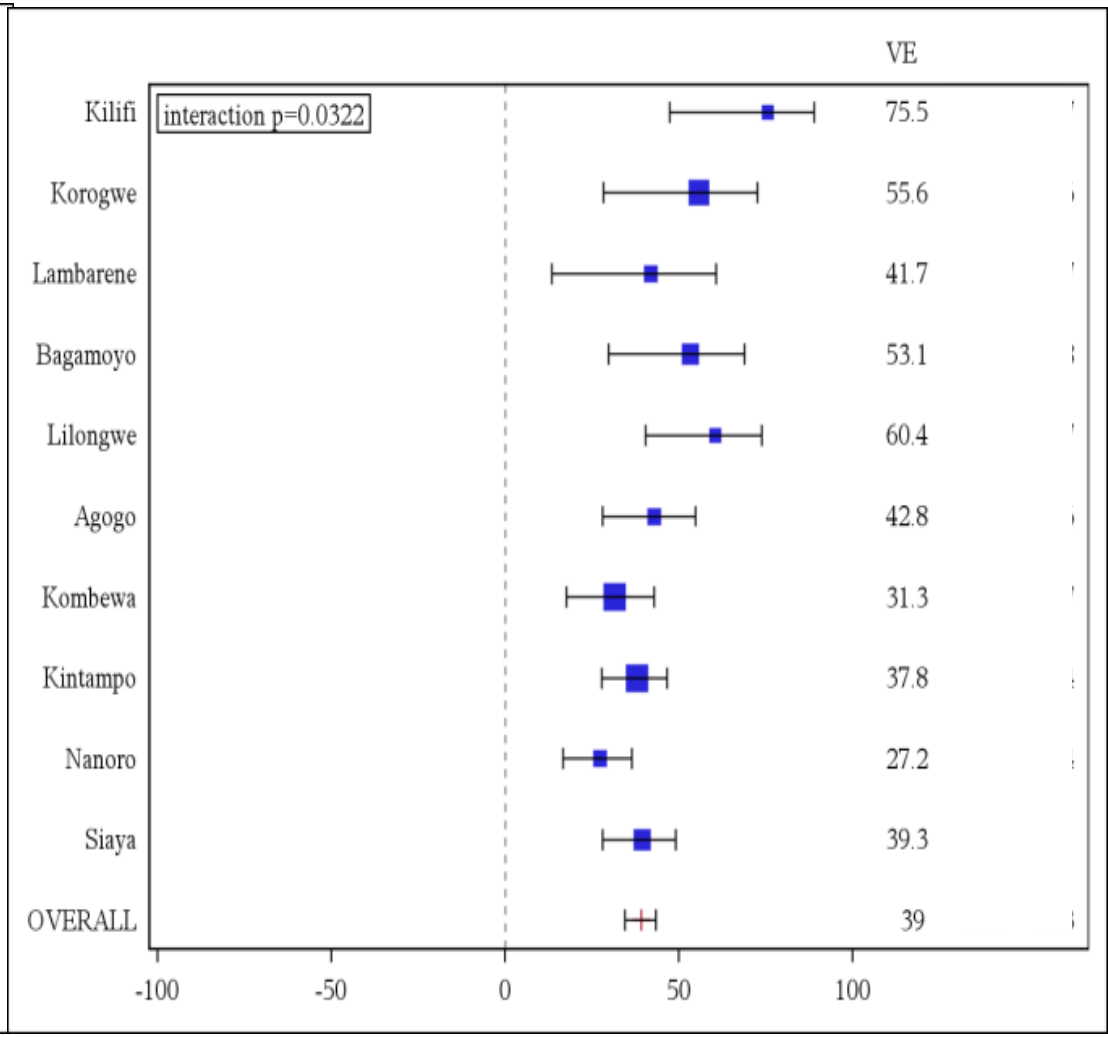


VE against clinical malaria 5-17 months group, by site

M2.5-SE 3-dose schedule

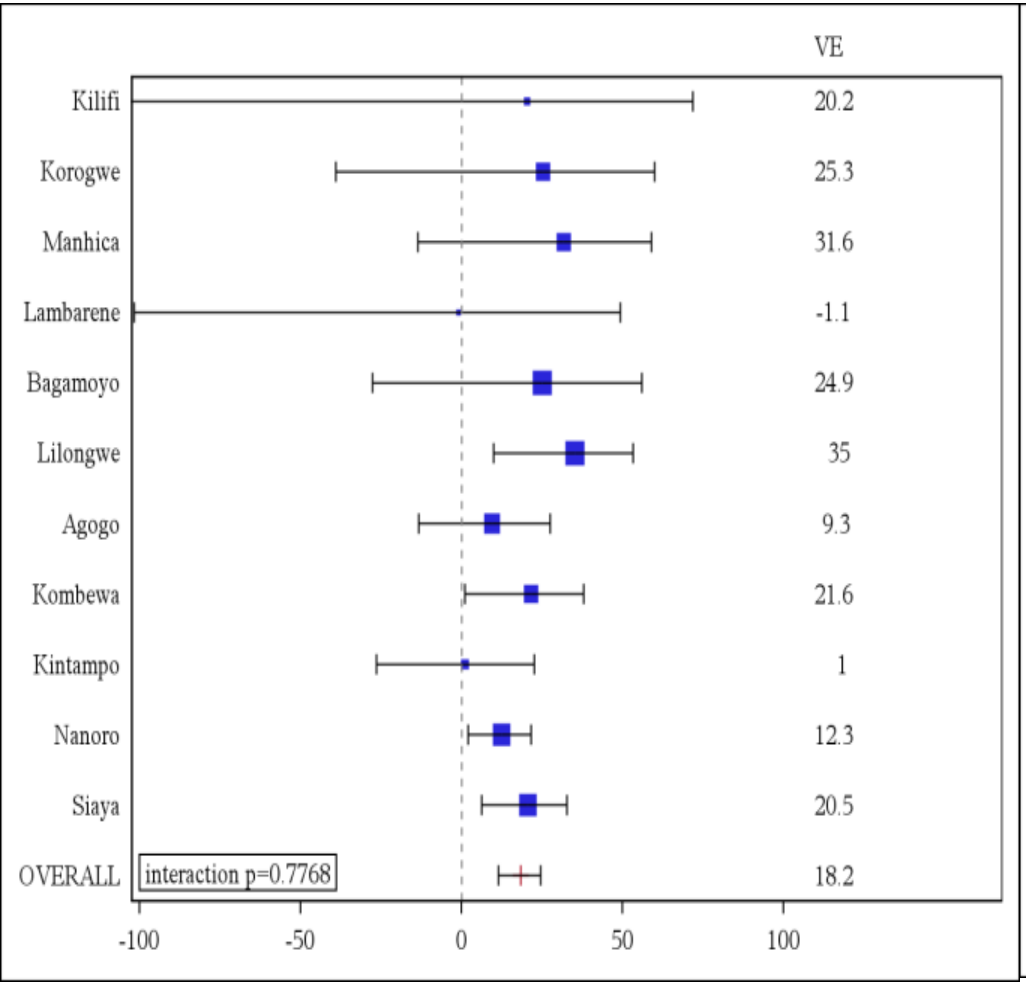


M2.5-SE 4-dose schedule

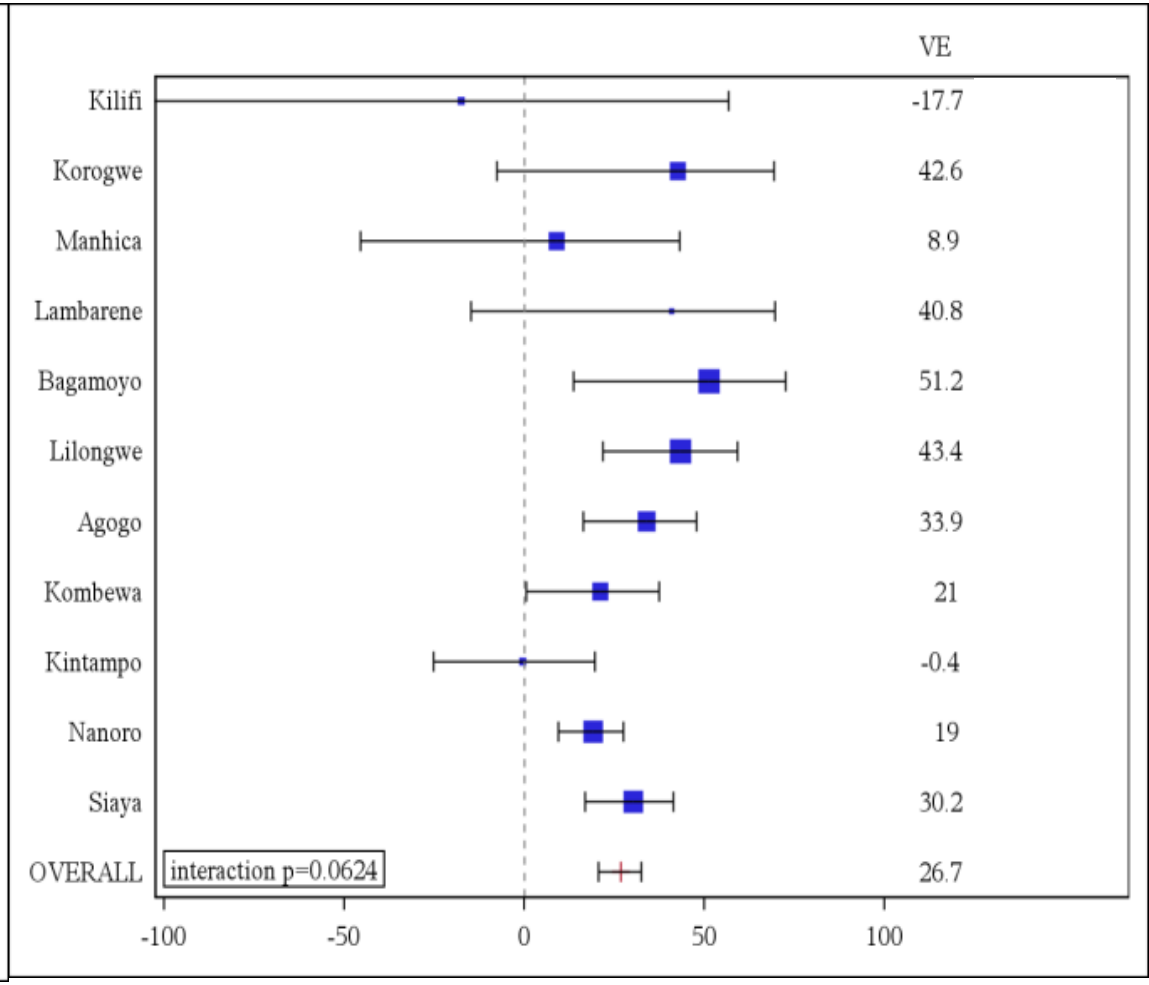


VE against clinical malaria 6-12 weeks group, by site

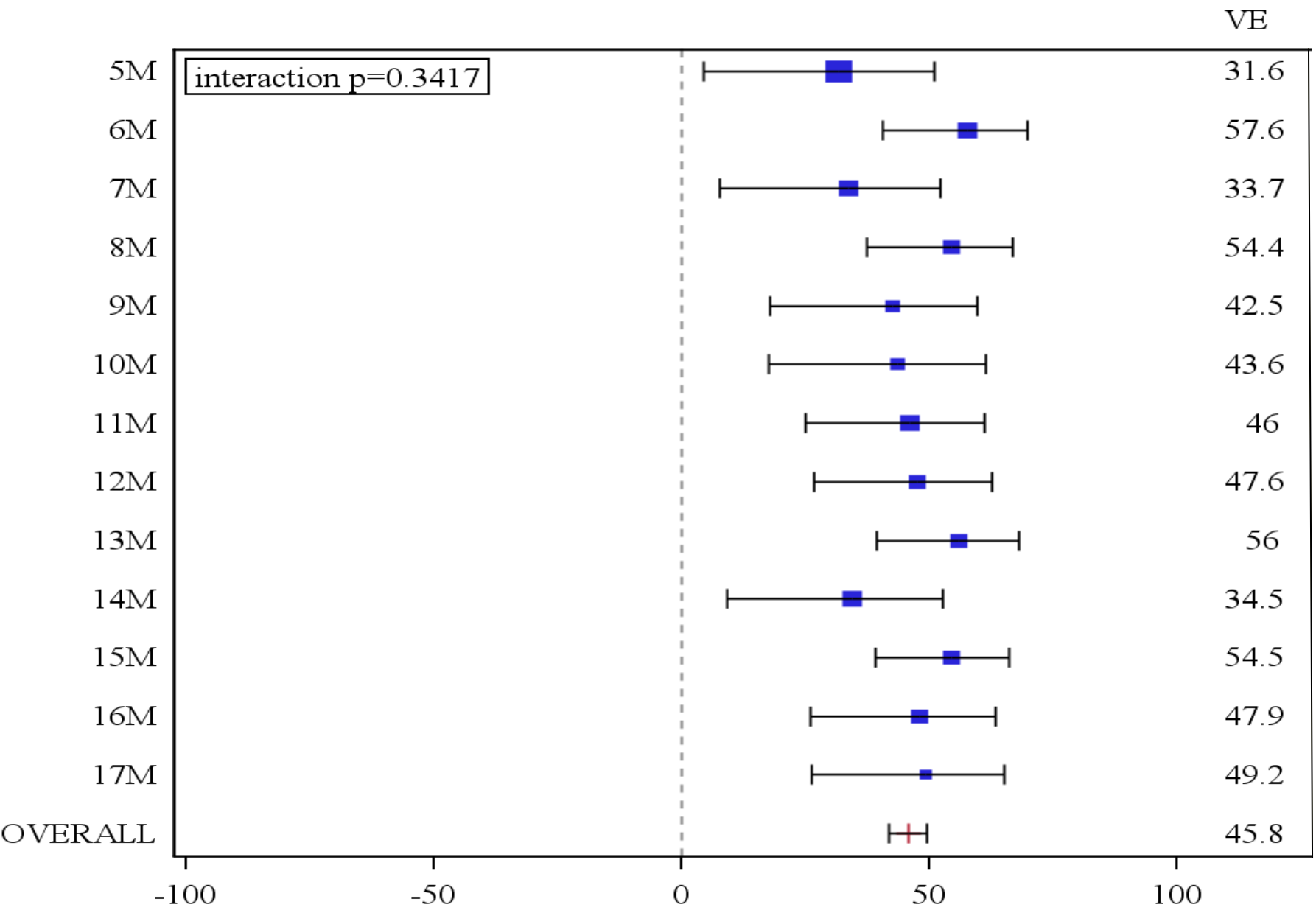
M2.5-SE 3-dose schedule



M2.5-SE 4-dose schedule



VE against clinical malaria , 5-17 month group, by MONTH of 1st dose

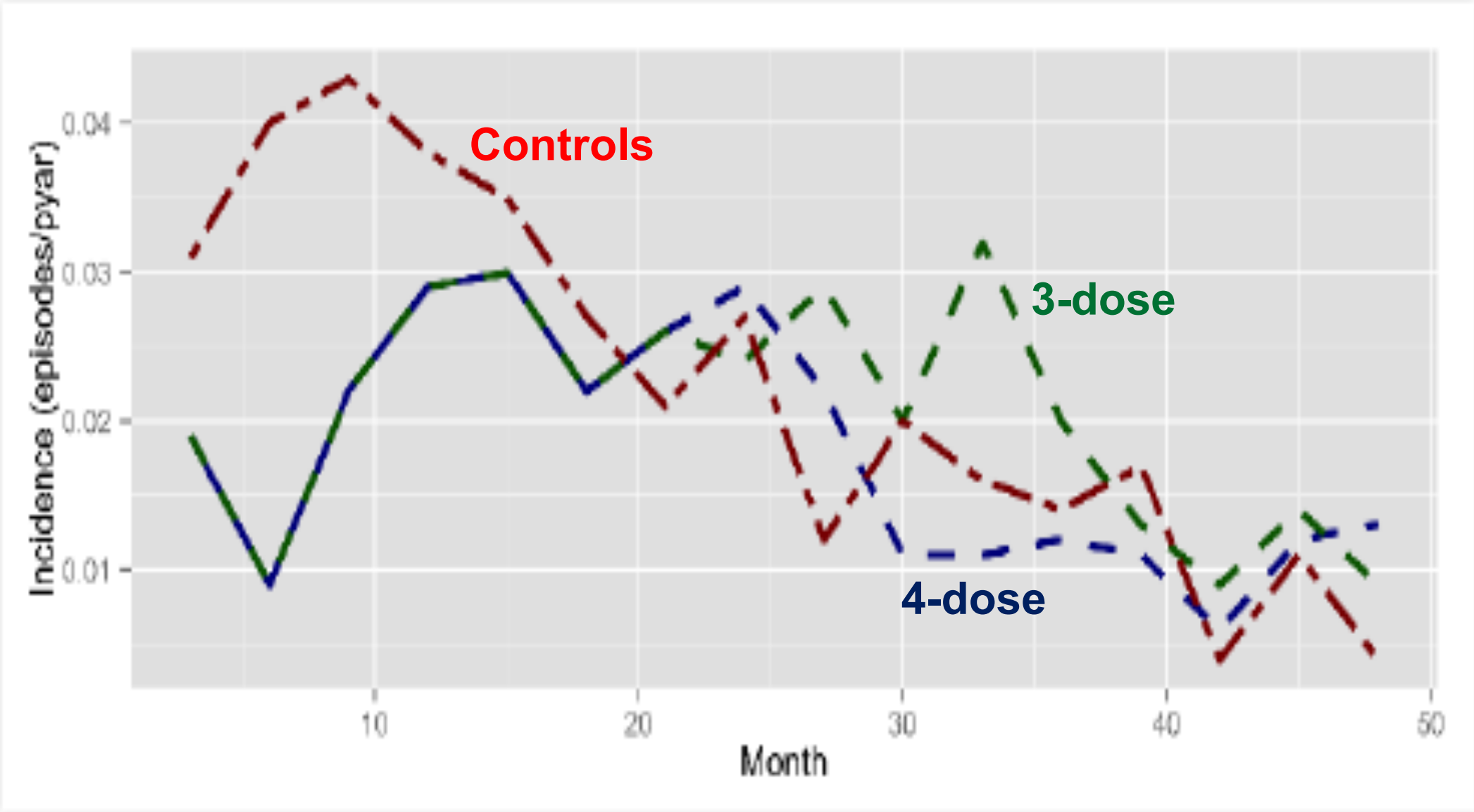


Vaccine efficacy against severe malaria by time interval

5-17 months	3-dose schedule	4-dose schedule
M2.5-M8	**70.1** (49.0, 82.5)	
M9-M14	**20.5** (-17.8, 46.4)	
M15-20	**14.6** (-41.0, 48.2)	
M21-32	**-47.9** (-134.6, 6.8)	**-6.0** (-75.2, 35.9)
M33-SE	**-74.2** (-220.0, 5.2)	**-22.7** (-137.9, 36.8)
M2.5-SE	**-2.2** (-31.3, 20.4)	**31.5** (9.3, 48.3)

6-12 weeks	3-dose schedule	4-dose schedule
M2.5-M8	**53.7** (18.7, 73.6)	
M9-M14	**18.2** (-43.8, 53.5)	
M15-20	**-38.9** (-143.2, 20.6)	
M21-32	**4.7** (-52.8, 40.6)	**37.7** (-4.8, 63.0)
M33-SE	**7.3** (-113.0, 59.9)	**13.8** (-91.6, 61.2)
M2.5-SE	**16.0** (-14.5, 38.4)	**20.5** (-9.8, 42.5)

Incidence of severe malaria in 3-month periods since initial vaccination in children 5-17 months.

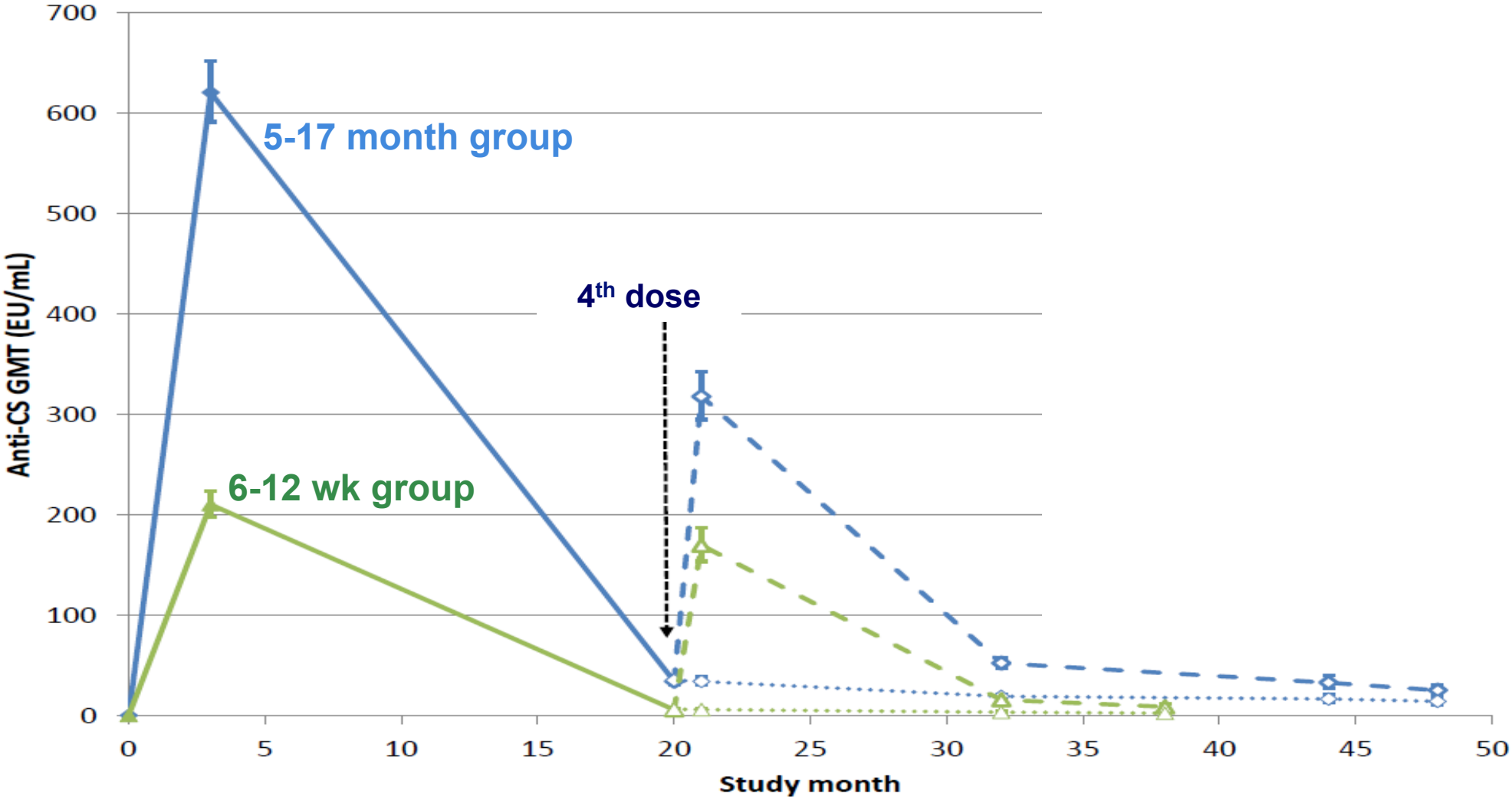


Vaccine efficacy against other outcomes (M2.5-SE)

Outcome	5-17 months		6-12 weeks	
	3-dose	4-dose	3-dose	4-dose
Malaria hospitalization	12.1 (-5.0-26.4)	**37.2** (23.6-48.5)	13.2 (-9.2-31.1)	**27.1** (7.1-42.9)
Incident Severe anaemia	20.6 (-32.7-52.9)	**61.2** (26.5-80.6)	12.8 (-50.9-49.9)	31.5 (-23.1-62.6)
All-cause hospitalization	8.8 (-2.9-19.3)	**14.9** (3.6-24.8)	4.8 (-8.3-16.4)	7.0 (-6.0-18.4)
All-cause mortality	-1.3 (-79.5-42.8)	-17.8 (-105-31.9)	-21.5 (-108-28.5)	-15.6 (-99.2-32.6)

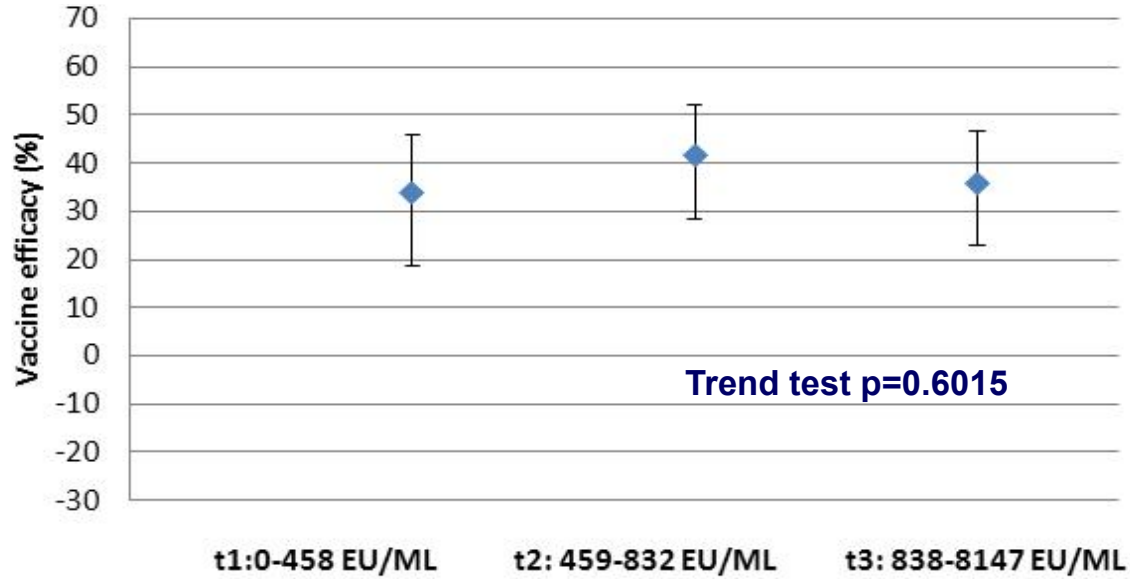
IMMUNOGENICITY

Immune response following initial series and 4th dose

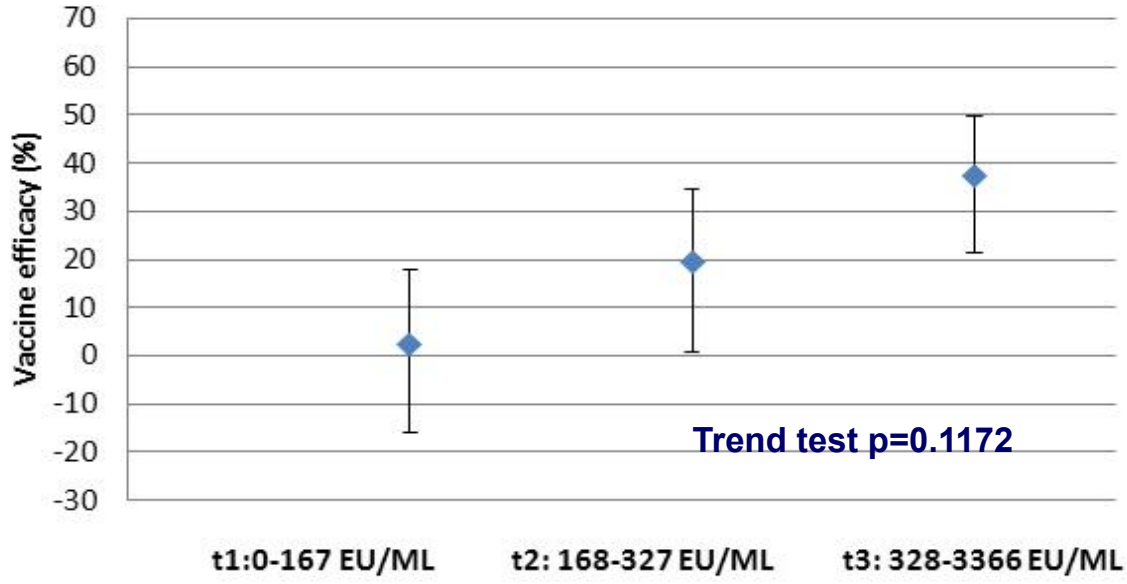


Relationship between immune response and VE to M32 (Tertiles of anti-CS antibody titre 1 month post dose 3)

5-17 months group



6-12 weeks group



SAFETY

Summary of Safety in EMA positive opinion

The safety profile of this vaccine is acceptable and quite similar to others apart from a higher risk for febrile convulsions in the older age group within 7 days after a dose (mostly the third dose) of Mosquirix. There also is no safety signal from the supportive studies that might indicate a general problem with the antigens. All identified potential safety issues are addressed in the Risk Management Plan. Ongoing and planned studies will also provide new data for safety and especially following a possible rebound.

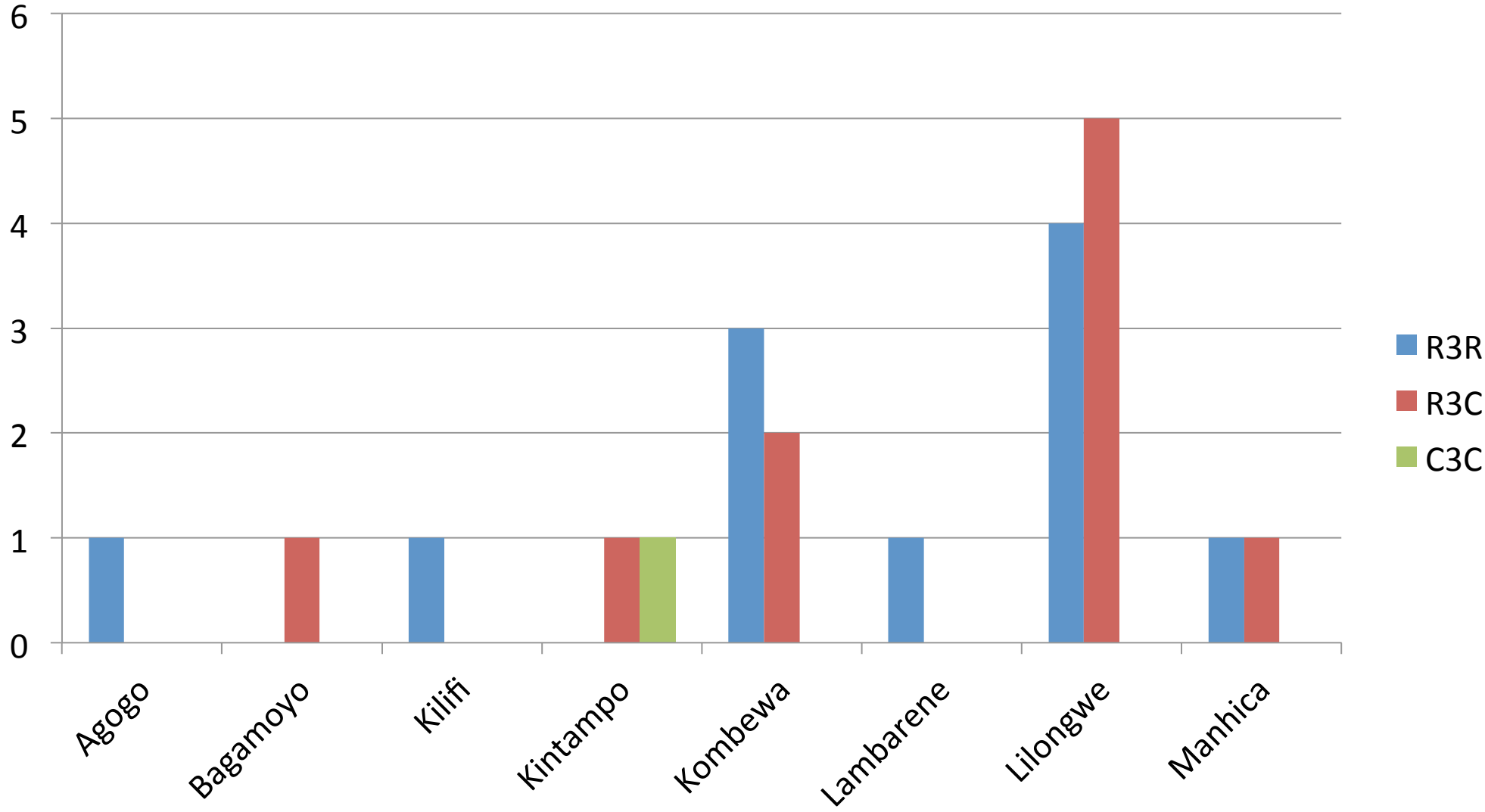
Serious Adverse Events: 5-17 months group

5-17 Month Age Group	4-dose schedule N=2976		3-dose schedule N=2972		Controls N=2974	
	n	%	n	%	n	%
At least one SAE	720	24.2	752	25.3	846	28.4
At least one SAE excluding malaria	673	22.6	704	23.7	784	26.4
Fatal SAE	61	2.0	51	1.7	46	1.5
At least one related SAE	8	0.3	4	0.1	1	0.0
Meningitis (any pathogen)	11	0.4	10	0.3	1	0.0

Serious Adverse Events: 6-12 weeks group

6-12 Week Age Group	4-dose schedule N=2976		3-dose schedule N=2178		Controls N=2179	
	n	%	n	%	n	%
At least one SAE	580	26.6	602	27.6	619	28.4
At least one SAE excluding malaria	562	25.8	582	26.7	591	27.1
Fatal SAE	51	2.3	55	2.5	42	1.9
At least one related SAE	6	0.3	1	0.0	3	0.1
Meningitis (any pathogen)	5	0.2	7	0.3	6	0.3

Meningitis cases in 5-17 month group by study site

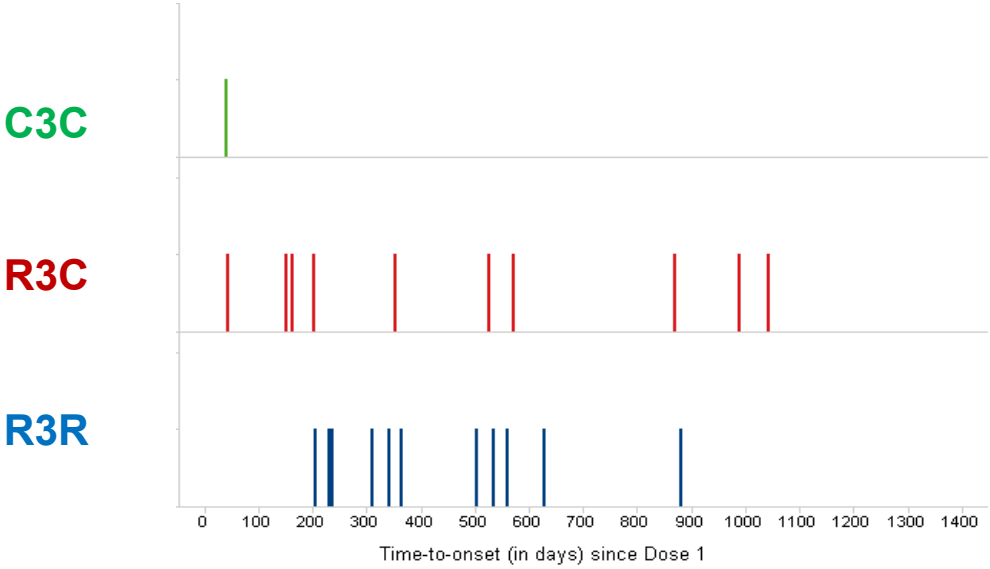


Meningitis cases in 5-17 month age group

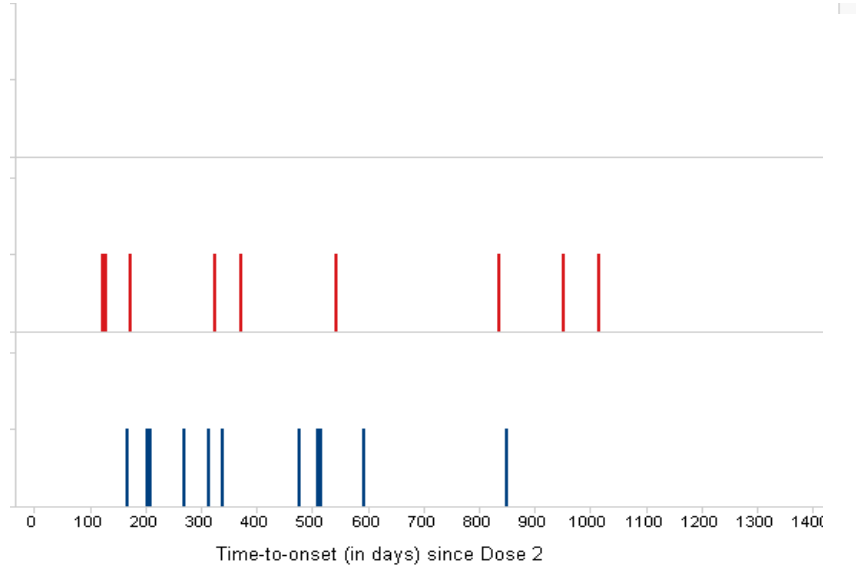
Months 0-20	4-dose schedule N=2976	3-dose schedule N=2972	Controls N=2974
Meningitis	4	5	1
Meningitis haemophilus	1	0	0
Meningitis meningococcal	3	1	0
Meningitis pneumococcal	0	1	0
Meningitis viral	1	0	0
Meningitis total	**9**	**7**	**1**
Months 21- SE	**4-dose schedule N=2681**	**3-dose schedule N=2719**	**Controls N=2702**
Meningitis	1	0	0
Meningitis haemophilus	0	2	0
Meningitis meningococcal	0	1	0
Meningitis tuberculous	1	0	0
Meningitis total	**2**	**3**	**0**

Meningitis case in 5-17 months group – by time since doses

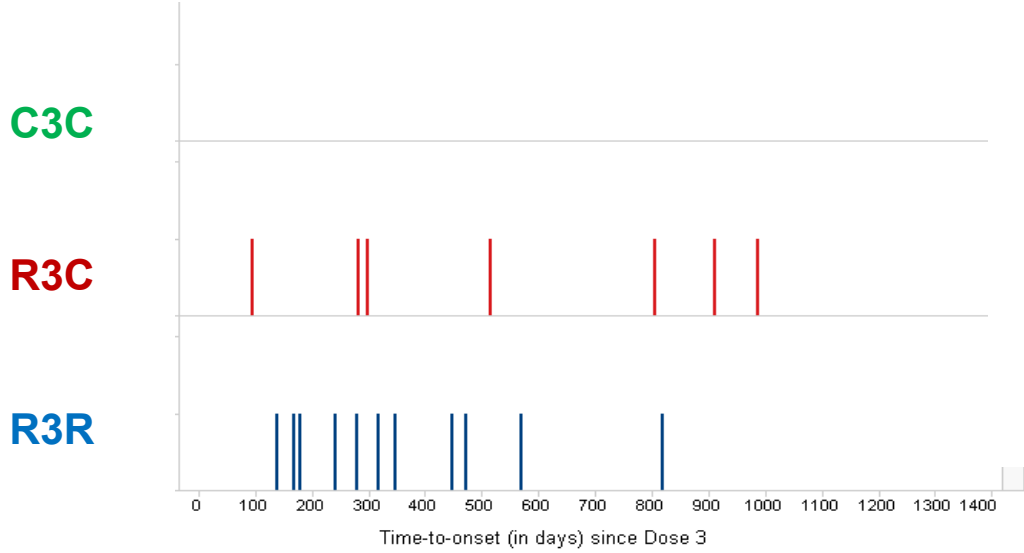
Post dose 1



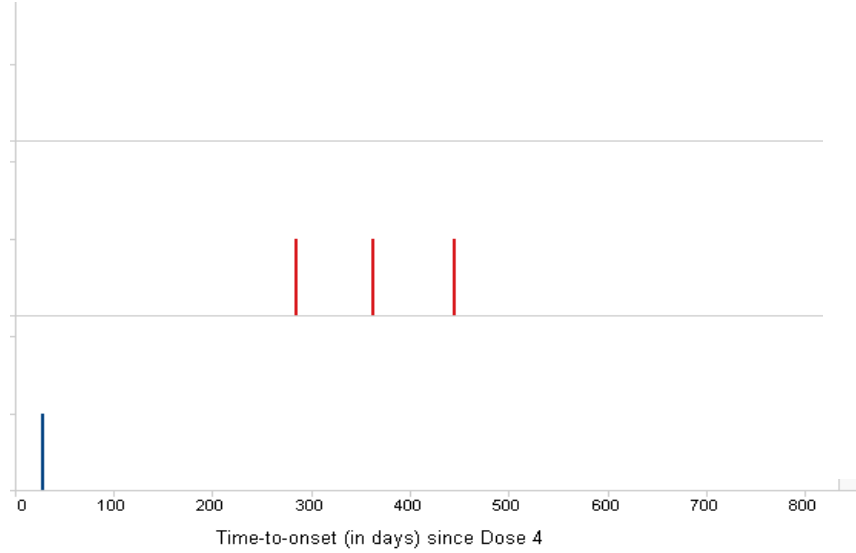
Post dose 2



Post dose 3



Post time of dose 4



Review of CNS infection/inflammation cases classified by experts' assessment (both age categories)

- Experts review 55 cases : 41 cases of meningitis as reported by the investigators and 14 cases of other CNS infection and inflammation

5-17 months

After 3-doses	R3R	R3C	C3C
Confirmed meningitis	5	4	0
No meningitis	4	2	2
Undetermined	4	2	3

After 4-doses	R3R	R3C	C3C
Confirmed meningitis	1	2	0
No meningitis	1	2	0
Undetermined	1	0	0

6-12 weeks

After 3-doses	R3R	R3C	C3C
Confirmed meningitis	3	4	1
No meningitis	2	2	3
Undetermined	2	0	0

After 4-doses	R3R	R3C	C3C
Confirmed meningitis	0	1	2
No meningitis	0	0	1
Undetermined	0	1	0
Unassessed	0	0	1

Febrile seizures in 7 days following vaccination : 5-17 months group

Initial series	RTS,S N=17306 doses		Control N=8728 doses	
	n	Rate per 1000 doses (95%CI)	n	Rate per 1000 doses (95%CI)
Febrile seizures within 7 days	**18**	1.04 (0.62, 1.64)	**5**	0.57 (0.19, 1.34)

After time of 4th dose	4-dose schedule N=2447 doses		3-dose schedule N=2472 doses		Control N=2473 doses	
	n	Rate per 1000 doses (95%CI)	n	Rate per 1000 doses (95%CI)	n	Rate per 1000 doses (95%CI)
Febrile seizures within 7 days	**6**	2.5 (0.9, 5.3)	**3**	1.2 (0.3, 3.5)	**1**	0.4 (0.0, 2.3)

Febrile seizures in 7 days following vaccination : 6-12 weeks group

Initial series	RTS,S N=12739 doses		Control N=6403 doses	
	n	Rate per 1000 doses (95%CI)	n	Rate per 1000 doses (95%CI)
Febrile seizures within 7 days	**2**	0.16 (0.02, 0.57)	**3**	0.47 (0.10, 1.37)

After time of 4th dose	4-dose schedule N=1825		3-dose schedule N=1837		Control N=1827	
	n	Rate per 1000 doses (95%CI)	n	Rate per 1000 doses (95%CI)	n	Rate per 1000 doses (95%CI)
Febrile seizures within 7 days	**4**	2.2 (0.6, 5.6)	**0**	- (0, 2)	**1**	0.5 (0.0, 3.0)

Severe malaria in the 5-17 month age group

Time Period	Malaria Syndrome	Initial series N=5948		Control N=2974	
		N	Died	N	Died
M0-M20	All Cases	205	6	158	2
	Cerebral	16	3	5	1
	Cerebral + Anaemia	6	1	1	0
	Anaemia	25	0	29	1
	Other	157	2	123	0
	Missing	1	0	0	0

Time period	Malaria Syndrome	3-dose schedule N=2719		4-dose schedule N=2681		Control N=2702	
		N	Died	N	Died	N	Died
M21-SE	All Cases	103	6	76	3	76	2
	Cerebral	9	4	11	2	2	0
	Cerebral + Anaemia	0	0	1	0	2	1
	Anaemia	18	1	11	0	17	0
	Other	75	1	53	1	54	1

Cerebral malaria cases in the 5-17 month age category by site

Site	No. of subjects	Cases of cerebral malaria
Siaya	799	9
Kintampo	1002	14
Nanoro	600	8
Agogo	600	8
Manhica	1002	3
Lambarene	704	3
Kombewa	1000	4
Lilongwe	800	2
Bagamoyo	903	2
Korogwe	912	0
Kilifi	600	0
Total	**8922**	**53**

Severe malaria in the 6-12 week age

Time Period	Syndrome	RTS,S group (R3) N=4358		Control group (C3) N=2179	
		N	Died	N	Died
M0-M20	All Cases	148	1	86	2
	Cerebral	2	0	3	0
	Cerebral + Anaemia	3	0	1	0
	Anaemia	30	0	17	0
	Other	111	1	65	2
	Missing	2	0	0	0

Time period	Syndrome	3-dose schedule (R3C) N=1996		4-dose schedule (R3R) N=1966		Control (C3C) N=1976	
		N	Died	N	Died	N	Died
M21-SE	All Cases	63	2	53	3	68	0
	Cerebral	4	1	4	2	2	0
	Cerebral + Anaemia	0	0	0	0	1	0
	Anaemia	15	0	15	0	19	0
	Other	42	0	34	1	45	0
	Missing	2	1	0	0	1	0

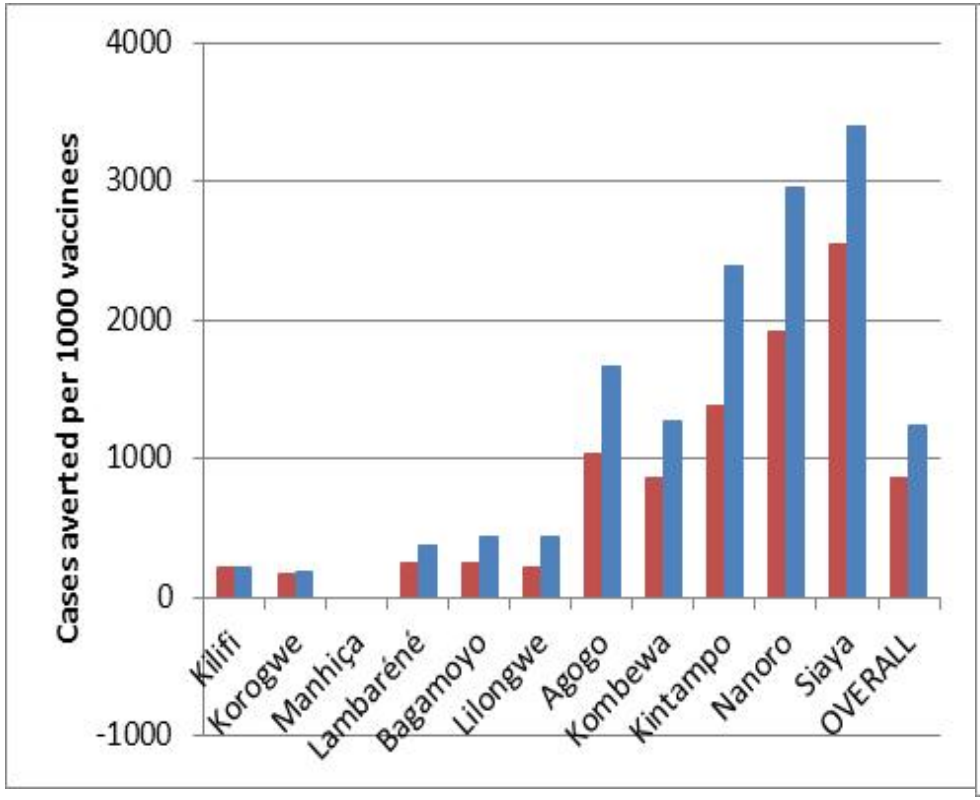
VACCINE IMPACT

Cases of clinical malaria averted per 1000 vaccinees

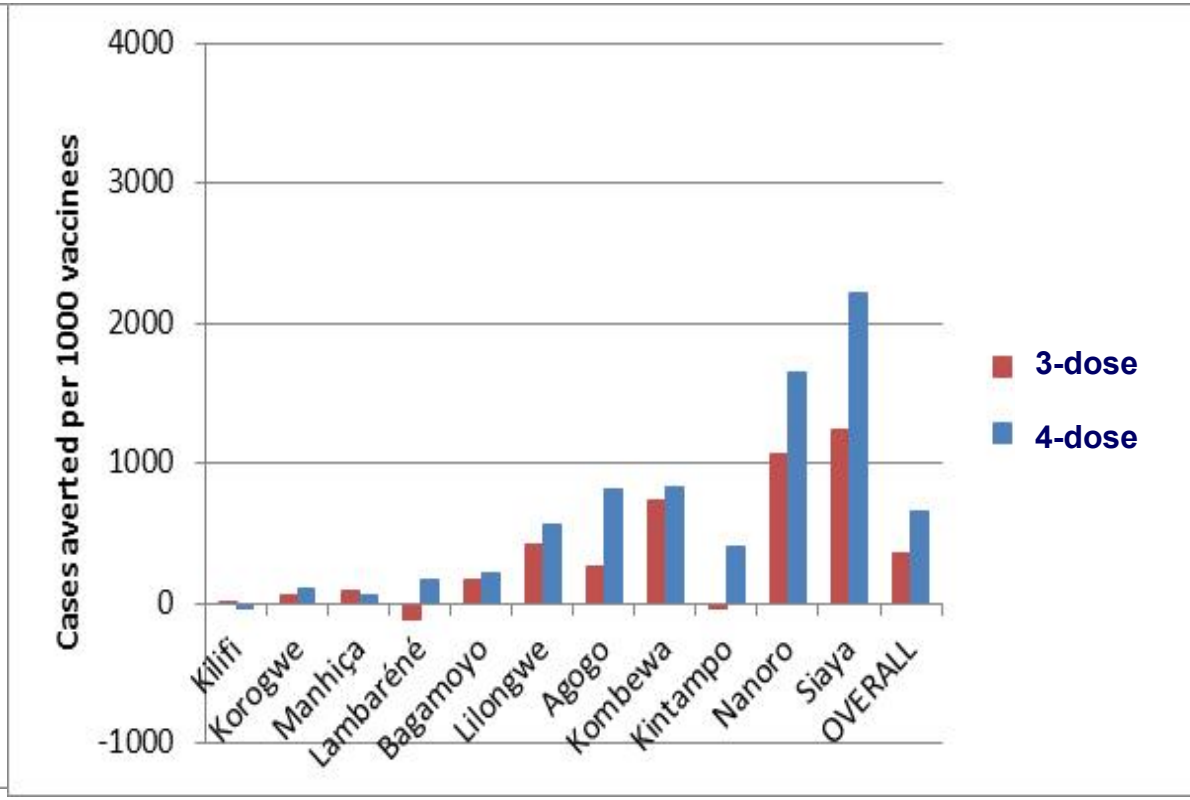
Up to Study month	5-17 months age group		6-12 weeks age group	
	3-dose schedule	4-dose schedule	3-dose schedule	4-dose schedule
21	**721** (591, 847)		**296** (179, 413)	
33	**855** (653, 1053)	**1097** (894, 1295)	**336** (103, 558)	**583** (374, 798)
SE	**860** (534, 1166)	**1239** (908, 1552)	**368** (73, 638)	**665** (407, 922)

Cases of clinical malaria averted (to SE) per 1000 vaccinees at each site

5-17 months



6-12 weeks



Summary of mathematical model comparison process

- In 2010, WHO initiated an extensive comparison exercise of four mathematical models (Imperial College, Swiss Tropical and Public Health Institute, Intellectual Ventures and GlaxoSmithKline)
- Developed to estimate the public health impact and cost-effectiveness of RTS,S/AS01 in a range of scenarios.
- Extensive comparison of intermediate outputs of epidemiological models without vaccination. This enabled better inter-group understanding of baseline models
- Efficacy against infection fitted to reproduce Phase 3 trial clinical malaria efficacy by site

Outcomes of model comparisons

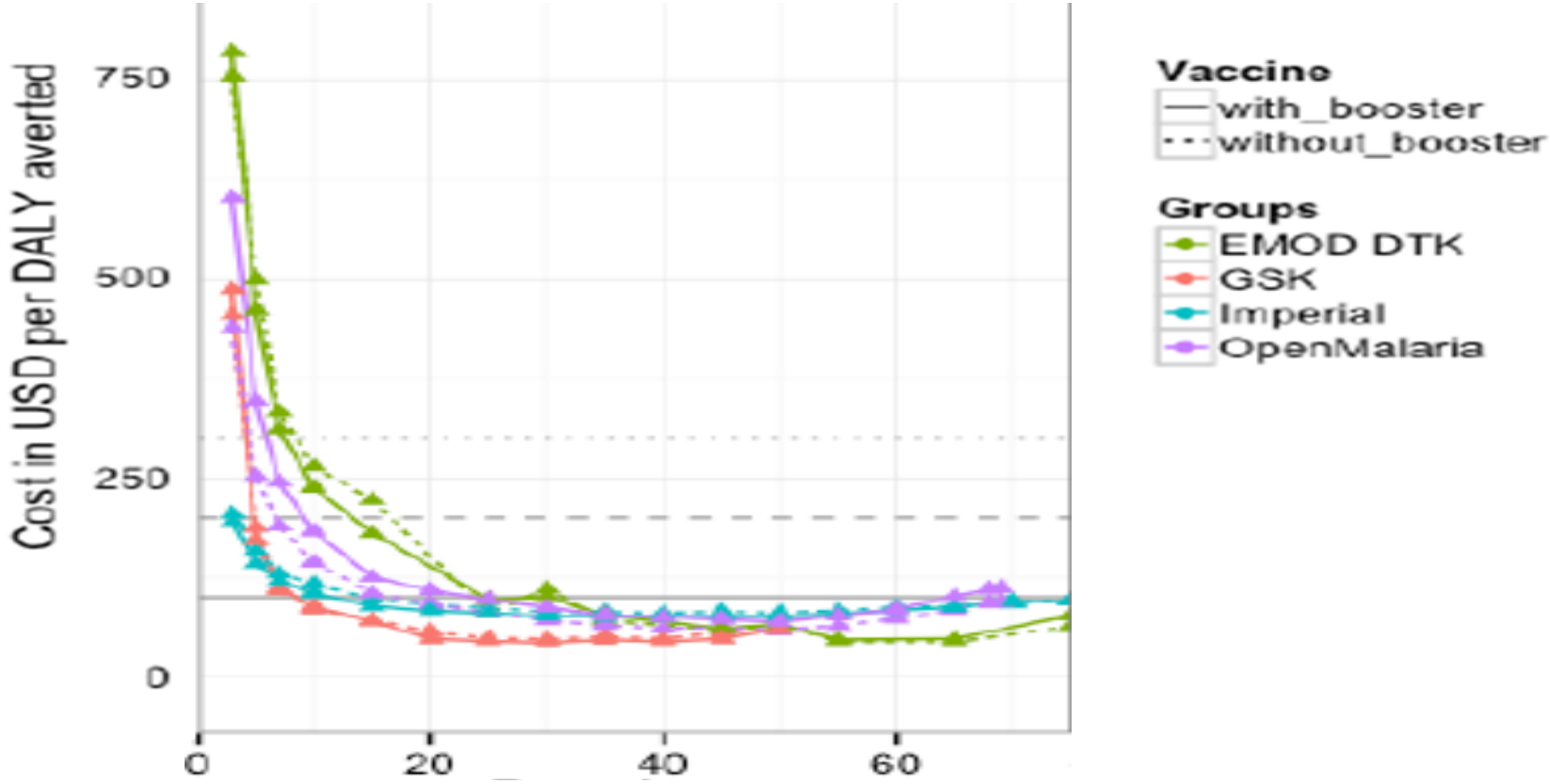
- In all models, vaccination is predicted to lead to an age shift in malaria incidence. In high prevalence settings, and for more severe disease endpoints, this age shift is predicted to occur sooner after vaccine introduction than in low prevalence settings. This predicted effect is general to any preventive malaria intervention (including bed-nets and SMC).

- The models that were designed to include indirect effects of vaccination predict little herd protection from RTS,S/AS01 vaccination when introduction is limited to this 5-9 month age group, given the role of infected individuals of all ages in contributing to transmission.

Conclusions of model comparisons

- All models predict an overall beneficial impact of the vaccine on mortality but with a small excess of deaths in older age groups (a feature of malaria preventive interventions, not the vaccine, also predicted for SMC)
- Consensus range is 10% to 28% reduction for under 5 malaria-related deaths among fully vaccinated children (with a 3 or 4 dose schedule)
- Contrary to the results seen in the trial for severe malaria, the models were consistent for predicting an overall beneficial effect on severe malaria and mortality even in the absence of a 4th dose
- Sensitivity analysis: Key drivers of cost-effectiveness are transmission intensity and vaccine price

Cost-effectiveness by prevalence level (assuming $5/dose) (Incremental cost-effectiveness ratio (ICER) in USD 2013)



- Cost per DALY averted decreases with transmission intensity, with plateau at prevalence 10%-65%, where cost per DALY averted is <$100, assuming $5/dose

Conclusions of comparative cost effectiveness work

(Imperial College model only)

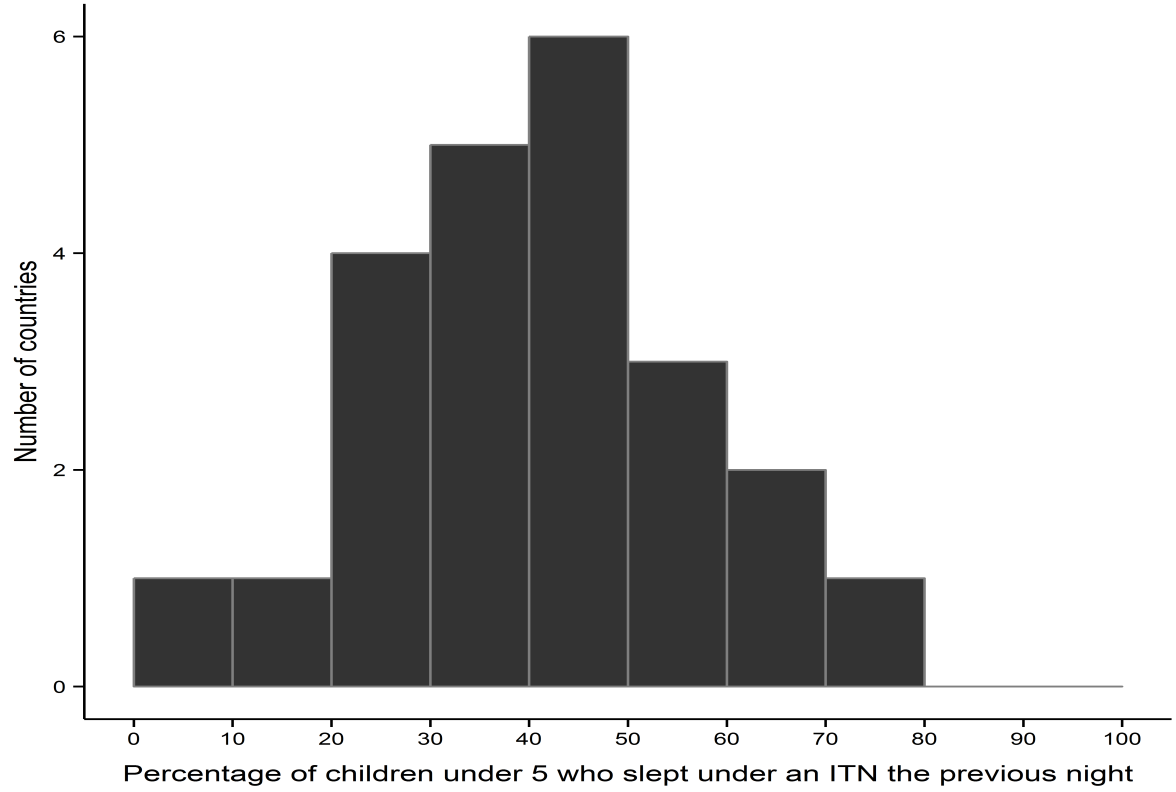
- RTS,S/AS01, under 3- and 4-dose schedule, compared to LLINs and SMC were examined across a range of transmission settings in Africa.
- In all settings LLINs are the most cost-effective initial intervention, followed by SMC in areas where recommended, and then RTS,S/AS01
- RTS,S/AS01 remains cost-effective as a second/third intervention at levels of parasite prevalence > 10% (consistent with the wider modelling exercise)

Conclusions of comparative cost effectiveness work

(Imperial College model only)

- The most cost-effective prevention package is to scale-up LLINs to between 60% and 75% usage before introducing the vaccine
- Data from 2011-2013 show rates below this in many countries (though additional progress made between 2013 and 2015)

ITN usage in children <5y, based on most recent DHS/MIS surveys (2011-2013)



Indicative estimates of cost-effectiveness of other vaccines

Vaccine	Rotavirus	PCV7	HPV	RTS,S 4-dose schedule
Price	$1.50-7.50 per dose	$5 per dose	$25 per course	$5 per dose
Cost per DALY averted	$42 ($31-$64)	$100	$400 ($200-$500)	$60-$100

Care should be taken when making inter-vaccine comparisons *as the cost-effectiveness of each vaccine is evaluated using different models and hence is based on different modelling assumptions.*

RISK-BENEFIT ASSESSMENT

Risk/benefit assessment over median 48 months follow-up in those aged 5-17 months

	BENEFITS	RISKS	UNCERTAINTIES
4-dose schedule	**VE clinical malaria**: **39.0%** (95%CI 34.3, 43.3) **VE severe malaria**: **31.5%** (95%CI 9.3, 48.3) **VE malaria hospitalization: 37.2%** (95%CI 23.6, 48.5) **VE all-cause hospitalization**: **14.9%** (95%CI 3.6, 24.8) **VE incident severe anaemia: 61.2%** (95%CI 26.5, 80.6)	<u>Identified Risk</u> Excess of **febrile convulsion** after any of the first three doses (0.5/1000 doses within 7 days of vaccination) after fourth dose (2.0/1000 doses within 7 days of vaccination) <u>Potential Risk</u> **Meningitis** (numerical excess, no clear association with time since vaccination, biological model not well established, excess predominantly in only 2 of 11 sites)	Uncertain overall protection against severe malaria **beyond trial period** Beneficial overall effect on severe malaria is **dependent on delivery of fourth dose** Relevance of **imbalance of cerebral malaria** cases, possibly due to chance

Risk/benefit assessment over median 38 months follow-up in those aged 6-12 weeks

	BENEFITS	IDENTIFIED RISKS	UNCERTAINTIES
4-dose schedule	**VE clinical malaria**: **26.7%** (95%CI 20.5, 32.4) **VE malaria hospitalization: 27.1%** (95%CI 7.1, 42.9)	Excess **of febrile convulsion** after fourth dose (1.6/1000 doses within 7 days of vaccination)	NA

End of presentation