GLOBAL VACCINE AND IMMUNIZATION RESEARCH FORUM
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Progress towards the development of a malaria vaccine

Discussion

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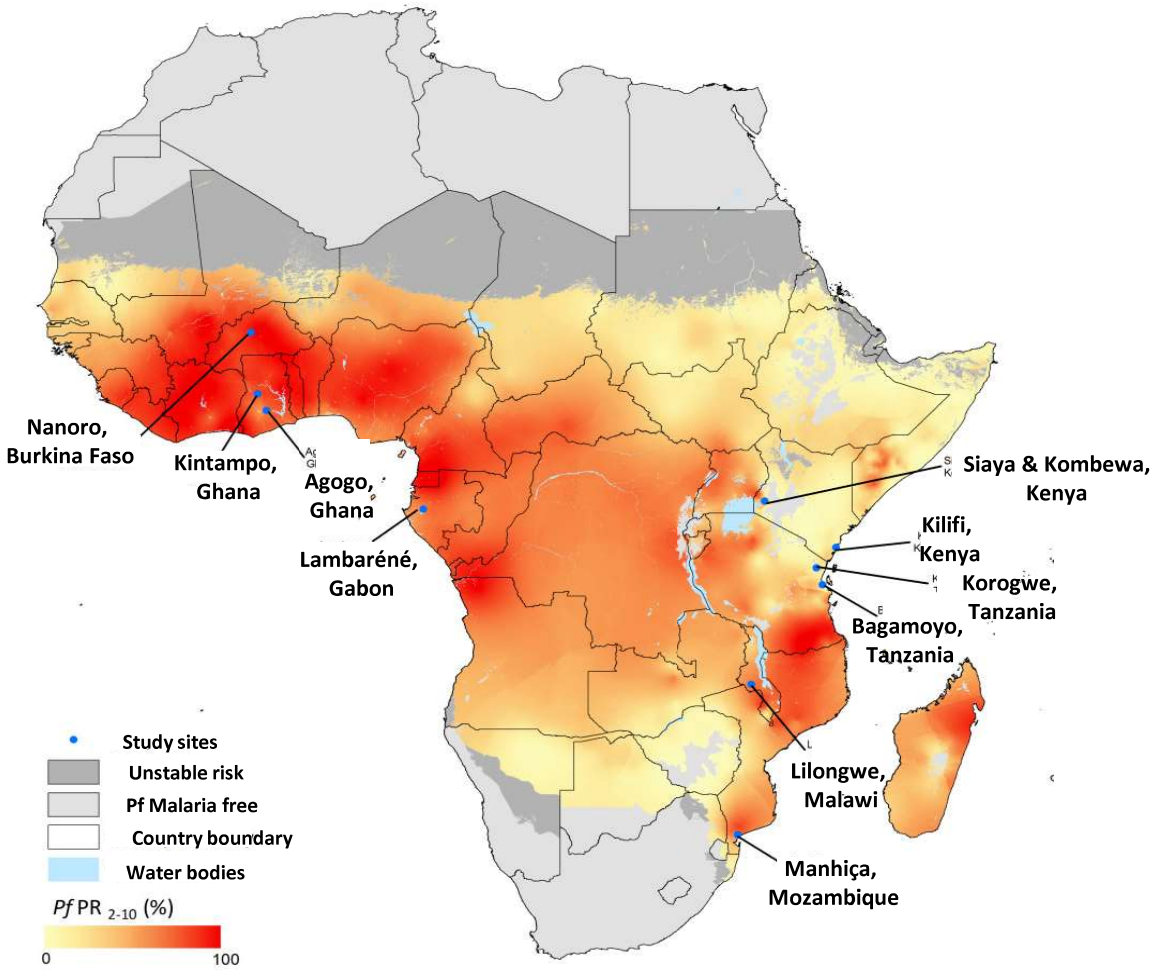
Vaccine efficacy and safety over 18 months

	VE* in children [95%CI]	VE* in infants [95%CI]
Clinical malaria	**46%** [42 to 50]	**27%** [20 to 32]
Severe malaria	**36%** [15 to 51]	**15%** [-20 to 39]
Malaria hospitalization	**42%** [29 to 52]	**17%** [-7 to 36]
All-cause hospitalization	**19%** [9 to 28]	**6%** [-7 to 17]

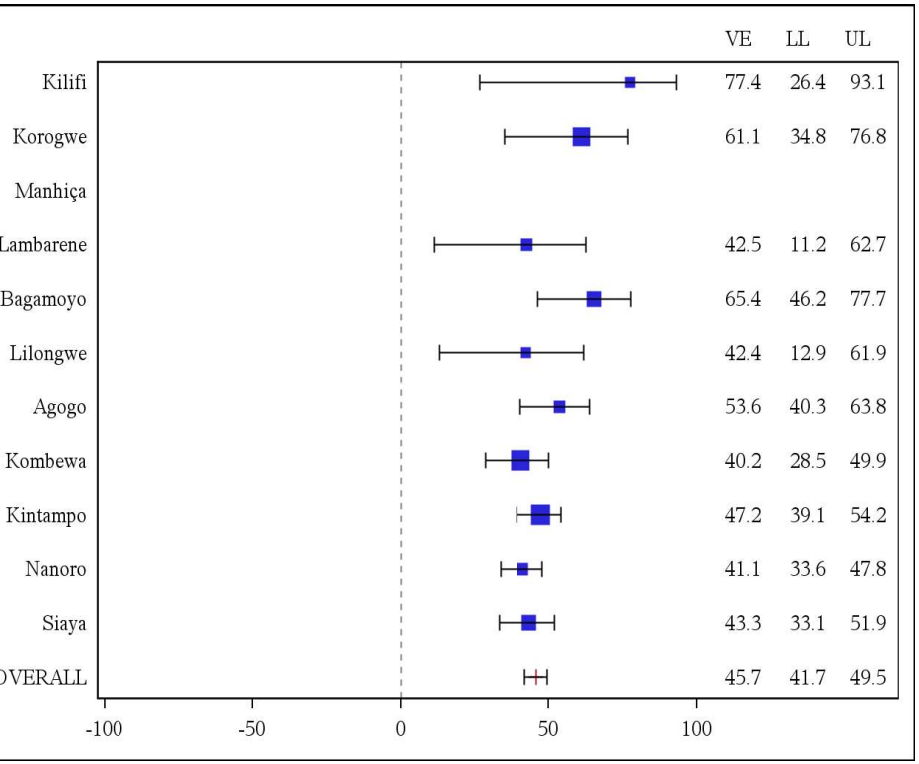
Pivotal Phase III RTS,S malaria vaccine efficacy trial

- Phase 3, randomized, controlled, double-blind trial conducted in
  11 centers in 7 African countries
- 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: 86% ITN coverage in 6-12 weeks and 75% in 5-17 months

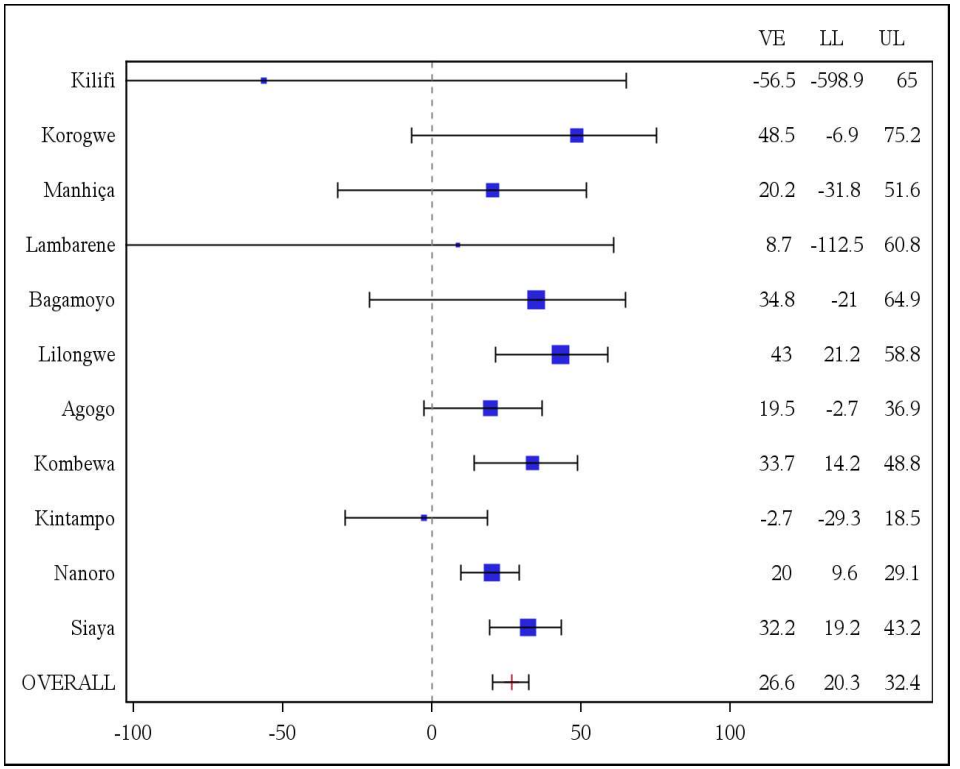


Vaccine efficacy over 18 mo by site – all episodes of clinical malaria

Children 5-17 months



Infants 6-12 weeks



- No clear variation in efficacy according to transmission level.
- Benefit of the vaccine (episodes prevented) likely to be greatest in high transmission settings.
- 3-fold higher immunogenicity for anti-CS IgG in older age group.
  - Immunological immaturity?
  - Interference from maternal antibodies?
  - Interference from co-administration with other vaccines?

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- For every 1,000 children/infants, vaccination averted:
  - In children (ITT)**: 37 to 2365** [average: 829] **cases** of **clinical malaria; -1 to 49** [average:18] **cases of severe malaria**
  - In infants (ITT): **-10 to 1402** [average: 449] **cases** of **clinical malaria; -13 to 37** [average: 6] **cases of severe malaria**

Vaccine efficacy against clinical malaria over 18 months

Time since vaccination	VE* in children [95%CI]	VE* in infants [95%CI]
0-6 months	**68%** [64 to 72]	**47%** [39 to 54]
6-12 months	**41%** [36 to 46]	**23%** [15 to 31]
12-18 months	**26%** [19 to 33]	**12%** [1 to 21]

- Results for 1 year follow-up after booster dose at 18 mo. will be available later in 2014
- Will booster dose restore efficacy to level seen after primary course?
- Will decline in efficacy after booster dose mirror that seen after primary course?
- Will booster dose to those with primary course in infancy bring efficacy up to level of that seen in those who received primary course as child?

Licensure and use of RTS,S

- Efficacy is superior in the 5-17 month age group compared to the 6-12 week age group. (No data on vaccination beyond age 17 months)
- Efficacy is waning substantially by 18 months post vaccination, and hence the booster dose data will be important
- While original target group was infants aged 6,10,14 weeks (EPI), the published results raise the question of implementation in children aged 5-17 months
- WHO is commissioning work to model the proportion of malaria hospitalizations “missed” by different possible schedules
- It is likely that if use is recommended (by SAGE/MPAC - late 2015 or early 2016) this will be in relation to some minimal level of transmission
- In the event of licensure, district-scale studies appear desirable to better characterise risk/benefit and to measure impact on mortality

Challenges for trials of 2nd generation malaria vaccines

Field efficacy trial options	2nd generation vs placebo	2nd generation vs 1st generation	2nd + 1st generation vs 1st generation	2nd generation vs 1st generation vs placebo
Estimate of efficacy	Absolute efficacy estimated.	Relative efficacy estimated.	Relative efficacy estimated.	Absolute and relative efficacy estimated.
Type of assessment	Superiority to no treatment.	Non-inferiority to 1st generation or superiority to 1st generation.	Superiority to 1st generation.	Superiority to 1st generation and to no treatment.
Limitations and Considerations	Unethical if 1st generation vaccine is available and recommended in country?	Large sample sizes may be needed. Non-inferiority design would not clearly show progress towards the 75% efficacy goal, but could make alternative vaccines available.	Large sample sizes may be needed. 1st and 2nd generation vaccines could be given together or as prime-boost strategy.	Large sample sizes may be needed. Unethical if 1st generation vaccine is available and recommended in country?
	Efficacy relative to 1st generation vaccine would not be estimated with confidence	Efficacy relative to no treatment would not be estimated with confidence.	Would not demonstrate efficacy of the 2nd generation vaccine independent of the 1st generation vaccine. Efficacy relative to nothing would not be estimated with confidence.	

WHO Consultation on Ethics of Use of Placebos in Vaccine Trials
http://apps.who.int/iris/bitstream/10665/94056/1/9789241506250_eng.pdf