SAGE/MPAC recommendation for Pilot Implementations with RTS,S/AS01

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Summary of Safety for RTS,S/AS01

The European Medicines Agency (EMA) gave a **positive** opinion, indicating that in their assessment the quality of the vaccine and the risk/benefit are favourable from a regulatory perspective.

There is one identified adverse event causality related to the vaccine: **febrile convulsions** within 7 days of vaccination. In the age group 5-17 months, these occurred at a rate of 0.5/1000 doses in the control arm and 1.0/1000 doses in the RTS,S vaccinated group. All resolved without sequelae, and are a known adverse event of some other vaccines.

Two other numerical excesses in vaccinated children – **cerebral malaria, and meningitis**. Not clear whether causally related to vaccination. May be chance findings. To be addressed in Phase IV study as part of the Risk Management Plan in the submission to EMA.

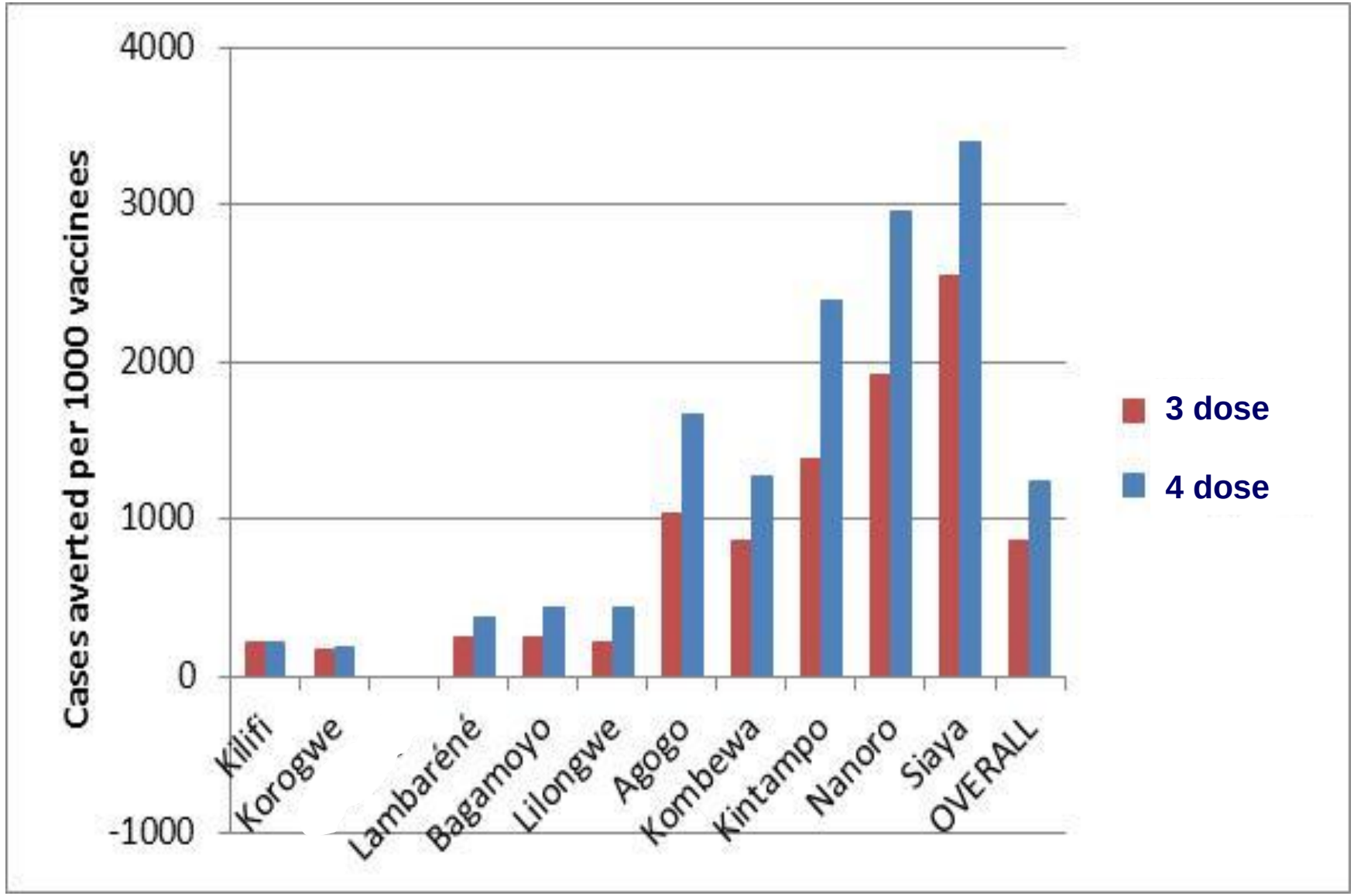
Vaccine efficacy to study end (~4 years follow-up)
Children vaccinated at ages 5-17 months

Study group	Vaccine Efficacy (Confidence Intervals)	
	Clinical malaria	Severe malaria
3 doses	**26.2%** (20.8, 31.2)	-2.2% (-31.3, 20.4)
4 doses	**39.0%** (34.3, 43.3)	**31.5%** (9.3, 48.3)

Vaccine efficacy against other outcomes

Outcome	3 doses	4 doses
Malaria hospitalization	12.1 (-5.0-26.4)	**37.2** (23.6-48.5)
Incident severe anaemia	20.6 (-32.7-52.9)	**61.2** (26.5-80.6)
All-cause hospitalization	8.8 (-2.9-19.3)	**14.9** (3.6-24.8)
All-cause mortality	-1.3 (-79.5-42.8)	-17.8 (-105-31.9)

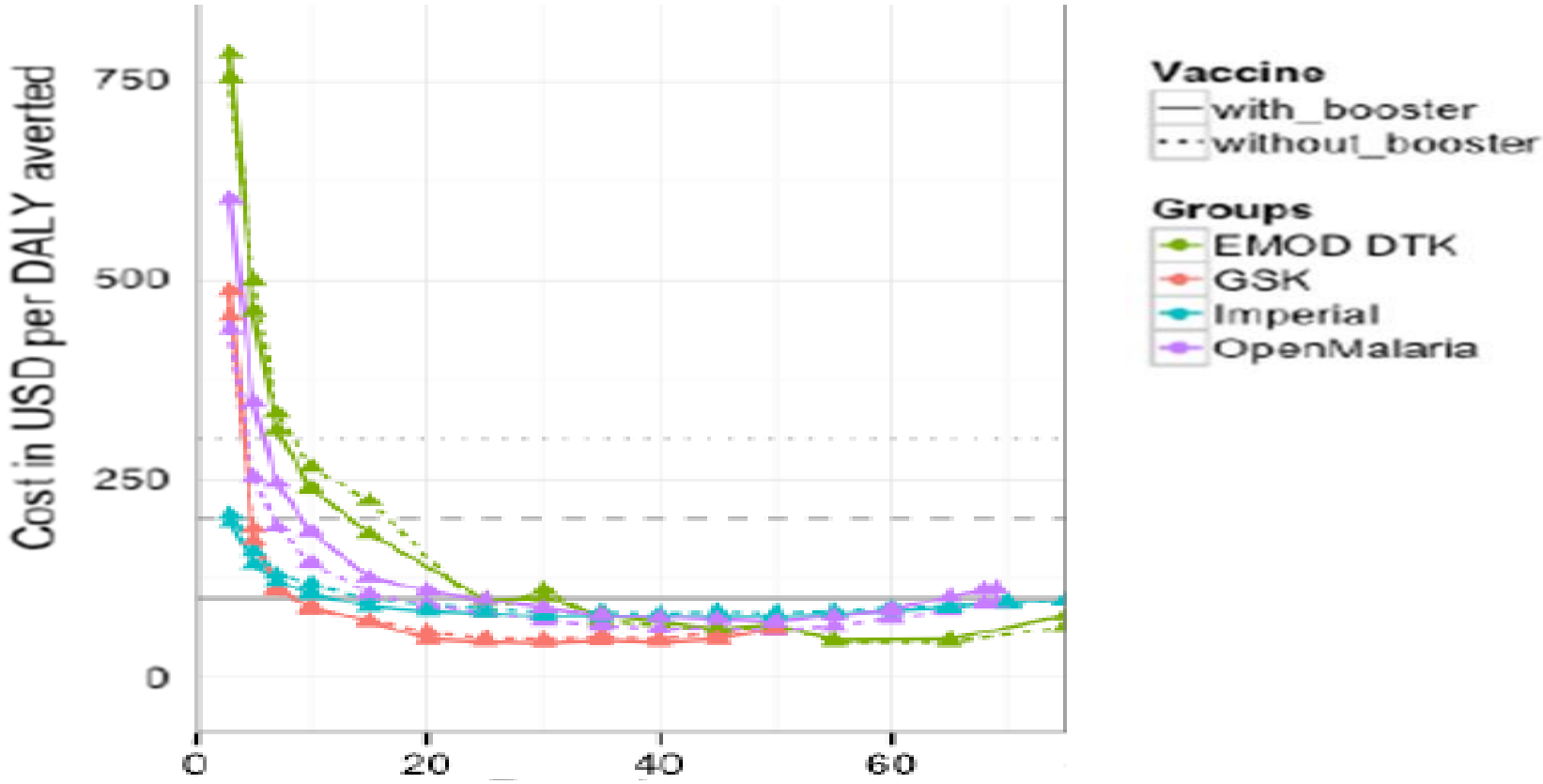
Cases of clinical malaria averted per 1000 vaccinees at each site



Conclusions of model comparisons

- All models predict an overall beneficial impact of the vaccine on mortality
- Consensus range is 10% to 28% reduction for under 5 malaria-related deaths among fully vaccinated children (with a 3 or 4 dose schedule)
- 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

WHO Advisory Committees for RTS,S/AS01

Joint Technical Expert Group (JTEG)	Malaria Policy Advisory Committee (MPAC)	Strategic Advisory Group of Experts (SAGE)
Peter Smith	*Kevin Marsh*	Jon Abramson
Fred Binka (MPAC)	*Salim Abdulla*	Yagob Yousef Al-Mazrou
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Frederick Were (SAGE)	*Marcel Tanner*	Piyanit Tharmaphornpilas
	Neena Valecha	Nicola Turner
	Nick White	Frederick Were
		Charles Wiysonge

SAGE/MPAC Policy Recommendations

SAGE/MPAC recommends the initial introduction of 4 doses of the malaria vaccine in 3-5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, as pilot implementation projects.

The main purposes of these would be to assess:

- The feasibility of administering 4 doses of RTS,S in routine vaccination programmes
- The impact of the vaccine on child mortality

Further information will also be provided on the safety of the vaccine to complement the Phase IV study

These could generate data to support widespread introductions in 3-5 years time.