Possible Effect of a Malaria Vaccine on the Preventable Burden

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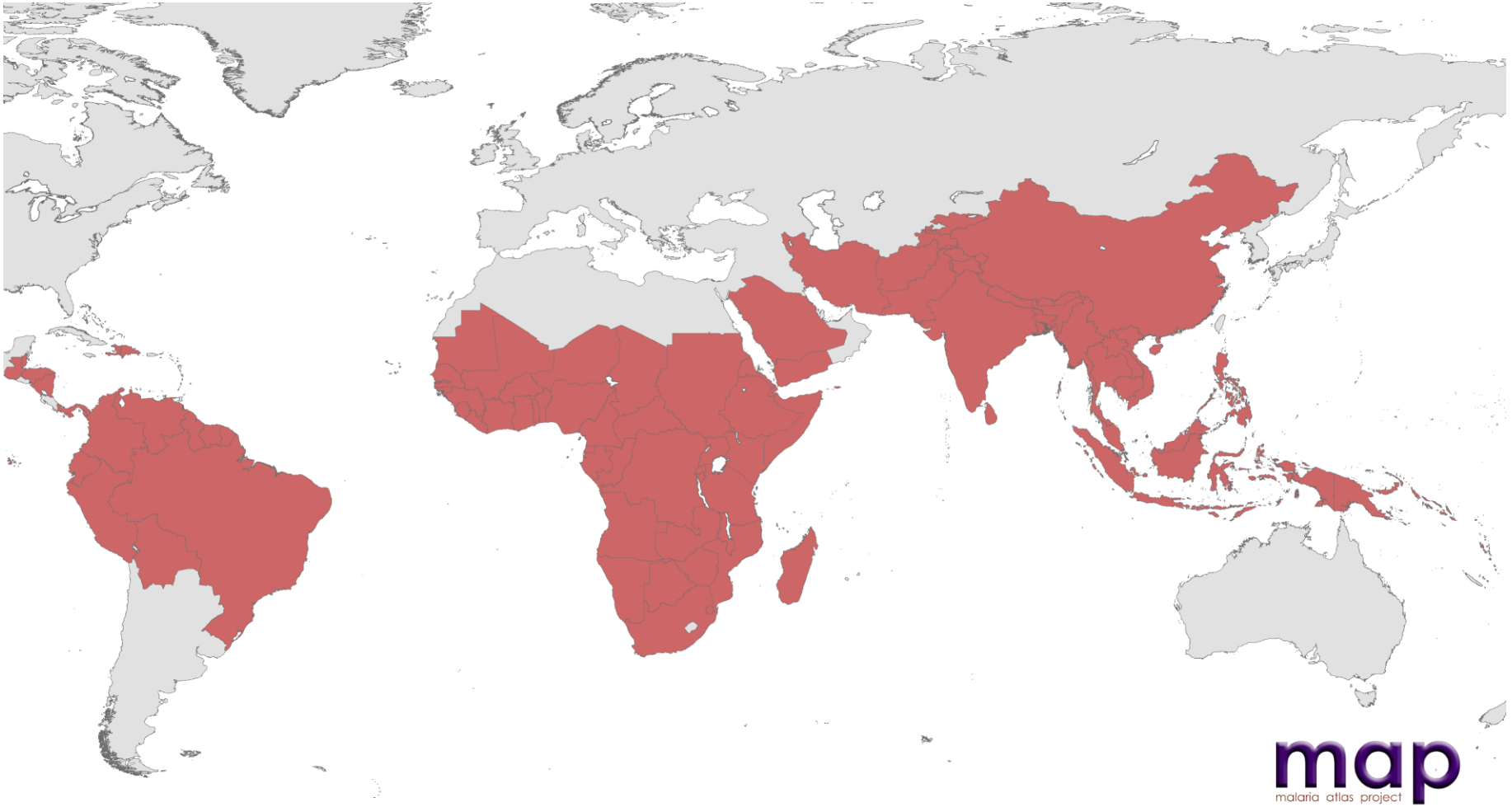
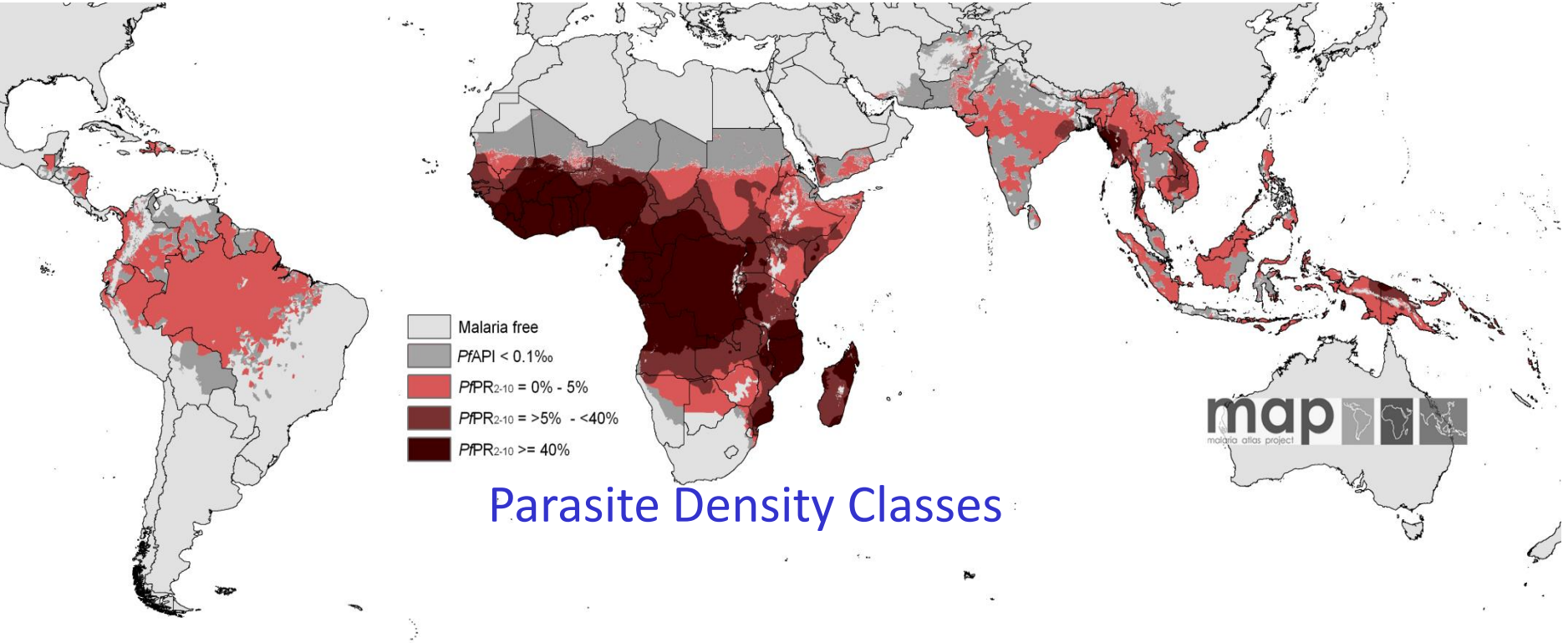
Malaria is a global problem



map
malaria atlas project

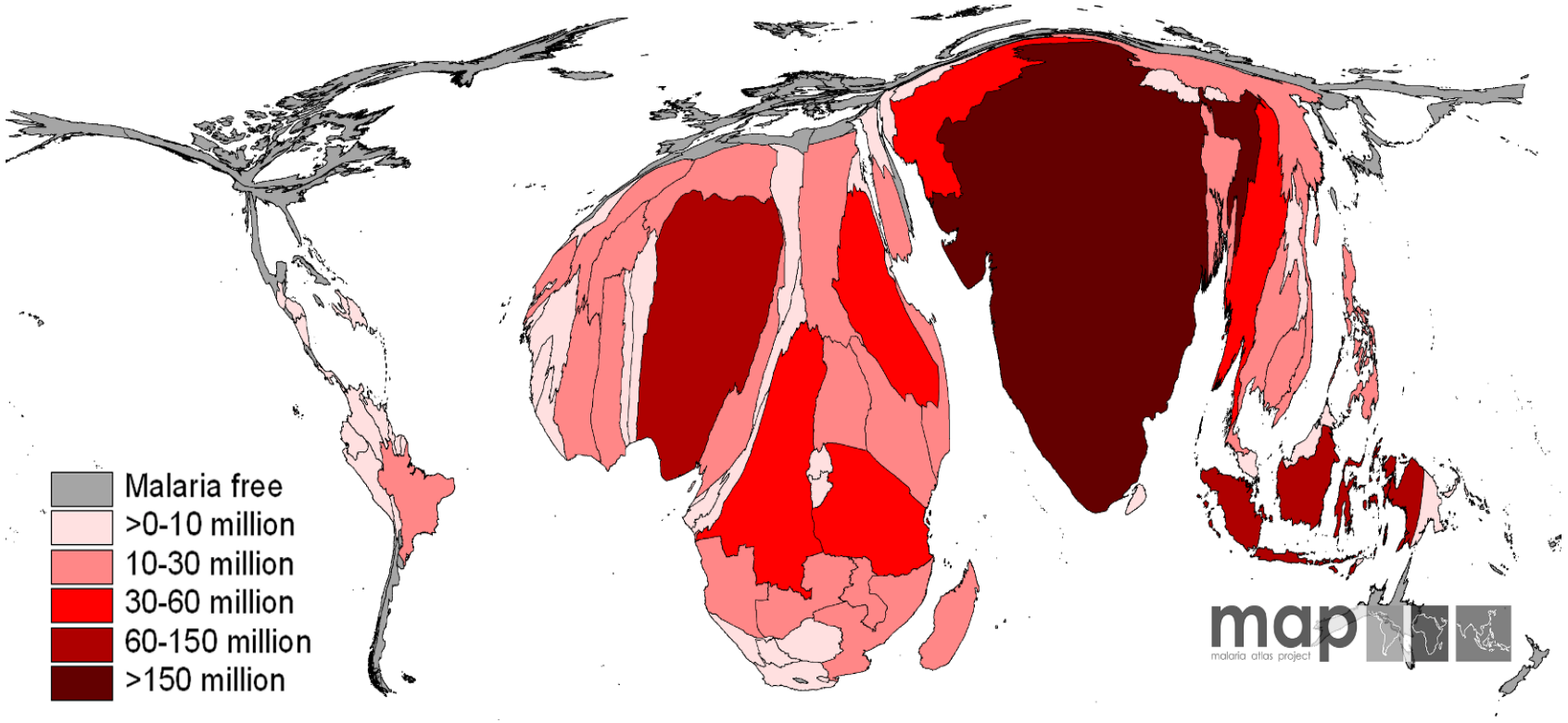
But transmission much heavier in Africa



Parasite Density Classes

Hay *et al.* (2008) *PLoS Medicine*,

Most of the people with malaria are in Africa and Asia



But around 90% of mortality still in Africa

What is the Burden?

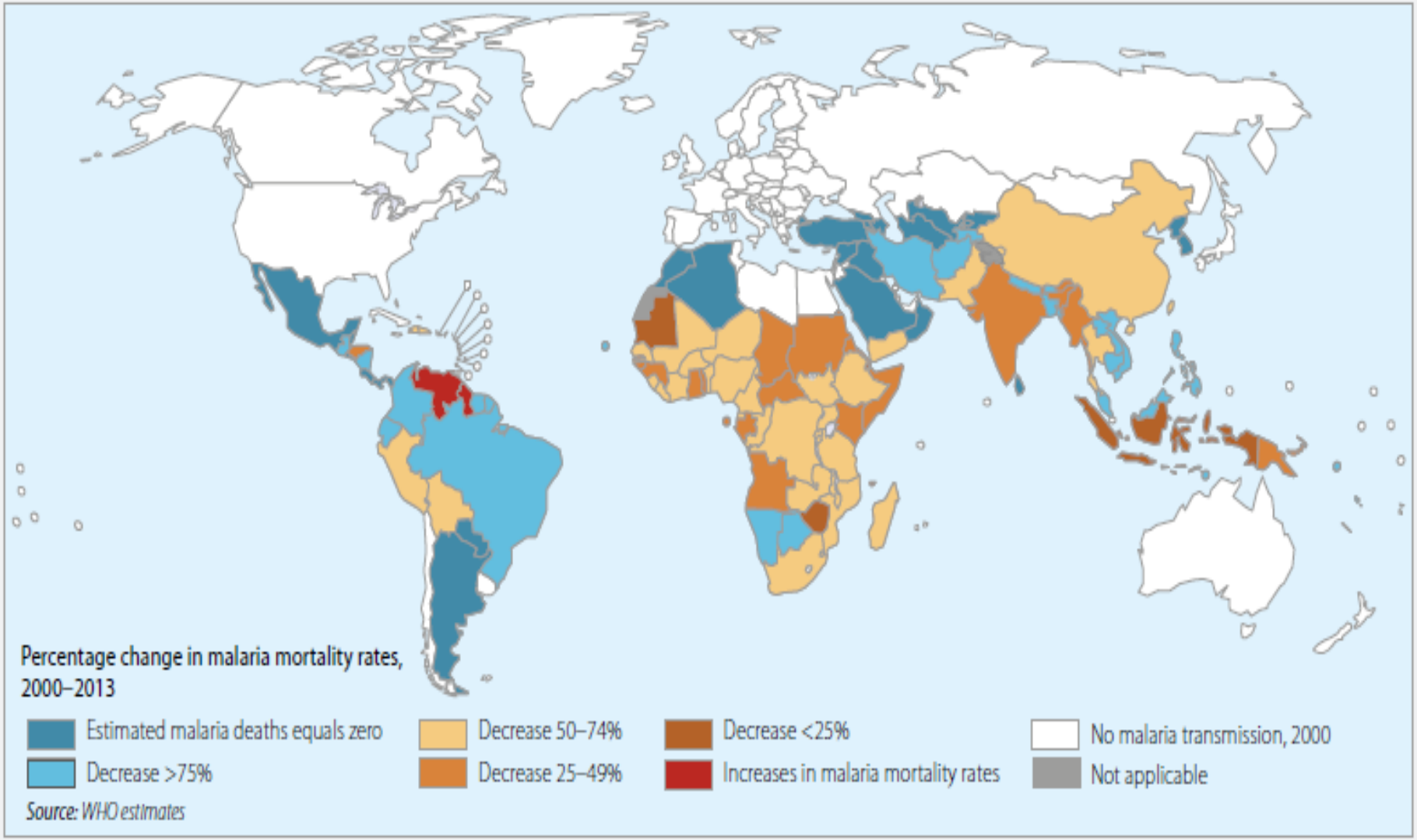
3.3 Billion at risk

198 million cases (124–283 million)

584, 000 deaths (367,000–755,000).

WHO World Malaria Report 2014

Figure 8.9 Percentage change in malaria mortality rates, 2000–2013



Malaria mortality down 47% globally and 54% in Africa

From The World Malaria Report 2014

Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial

*RTS,S Clinical Trials Partnership**

Summary

Background The efficacy and safety of the RTS,S/AS01 candidate malaria vaccine during 18 months of follow-up have been published previously. Herein, we report the final results from the same trial, including the efficacy of a booster dose.

Methods From March 27, 2009, until Jan 31, 2011, children (age 5–17 months) and young infants (age 6–12 weeks) were enrolled at 11 centres in seven countries in sub-Saharan Africa. Participants were randomly assigned (1:1:1) at first vaccination by block randomisation with minimisation by centre to receive three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20 (R3R group); three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group); or a comparator vaccine at months 0, 1, 2, and 20 (C3C [control group]). Participants were followed up until Jan 31, 2014. Cases of clinical and severe malaria were captured through passive case detection. Serious adverse events (SAEs) were recorded. Analyses were by modified intention to treat and per protocol. The coprimary endpoints were the occurrence of malaria over 12 months after dose 3 in each age category. In this final analysis, we present data for the efficacy of the booster on the occurrence of malaria. Vaccine efficacy (VE) against clinical malaria was analysed by negative binomial regression and against severe malaria by relative risk reduction. This trial is registered with ClinicalTrials.gov, number NCT00866619.

Findings 8922 children and 6537 young infants were included in the modified intention-to-treat analyses. Children were followed up for a median of 48 months (IQR 39–50) and young infants for 38 months (34–41) after dose 1. From month 0 until study end, compared with 9585 episodes of clinical malaria that met the primary case definition in

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See Editorial *Lancet* 2015; 385: 1581

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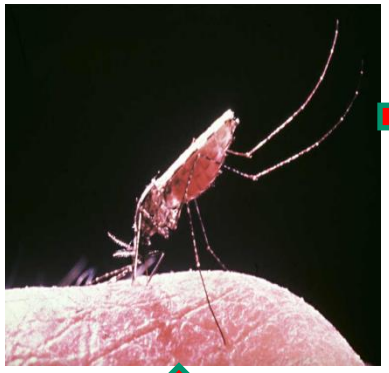
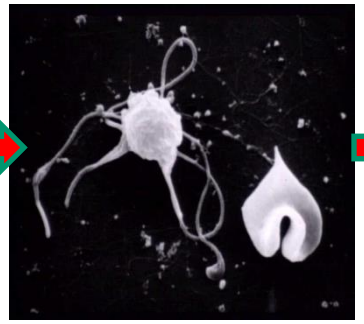
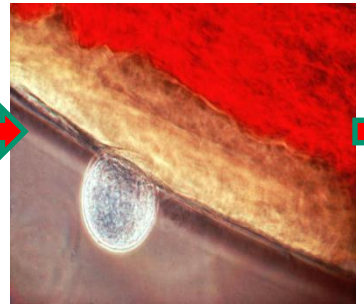
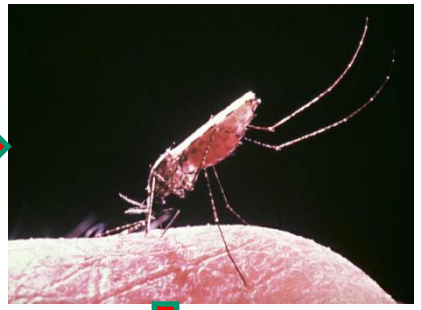
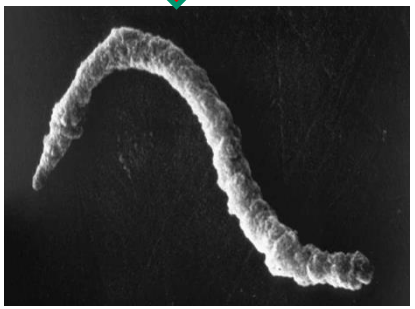
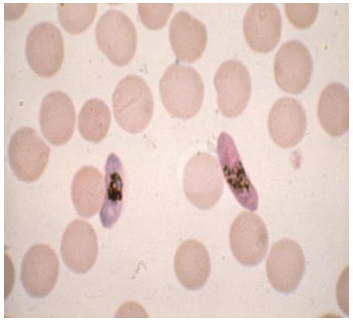
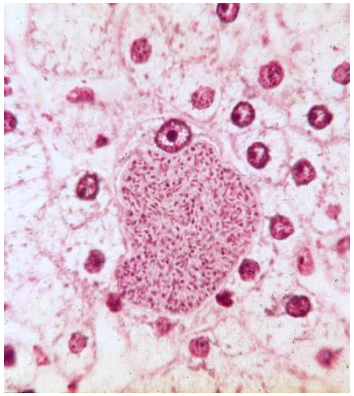
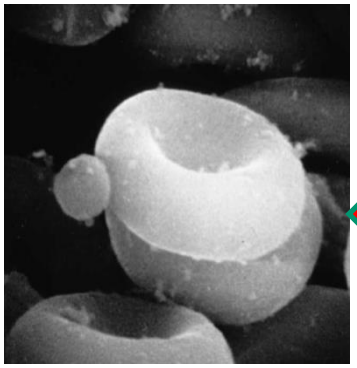
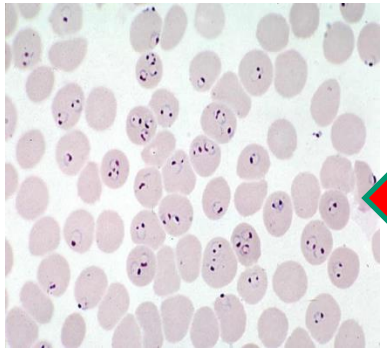






RTS,S




RTS,S Phase 3 Key Results

11 sites in 7 countries

8,922 5-17 months 6,537 6-12 weeks

PE (with booster): Children **36.3%** (31.8-40.5) Infants **25.9%** (19.9-37.5)

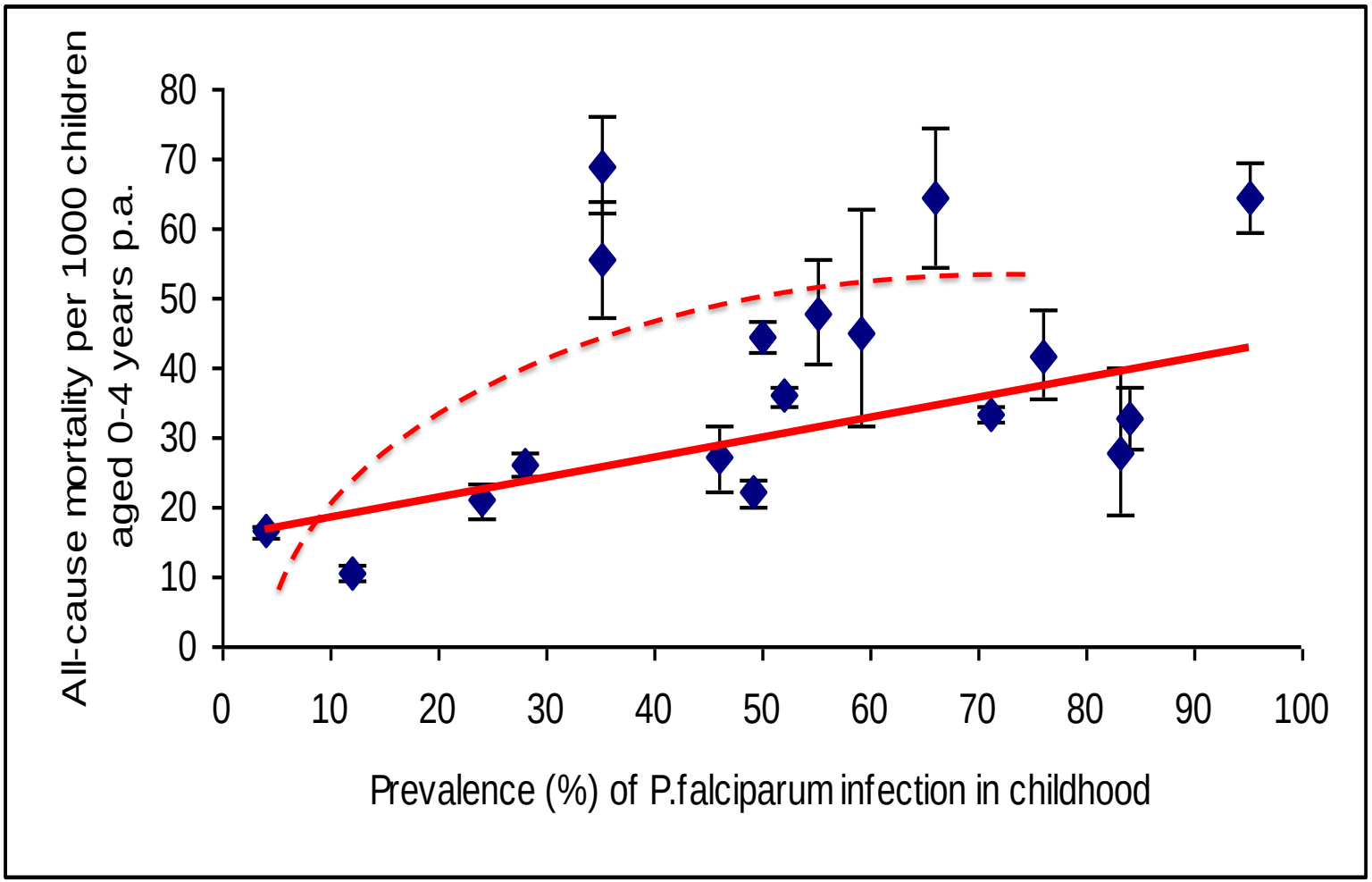
PE severe malaria: Children **32.2%** (13.7-46.9) Infants **17.3** (-9.4-37.5)

Cases Averted: Children **1774/1000** Infants **983/1000**

Other potential effects (?direct ? indirect)

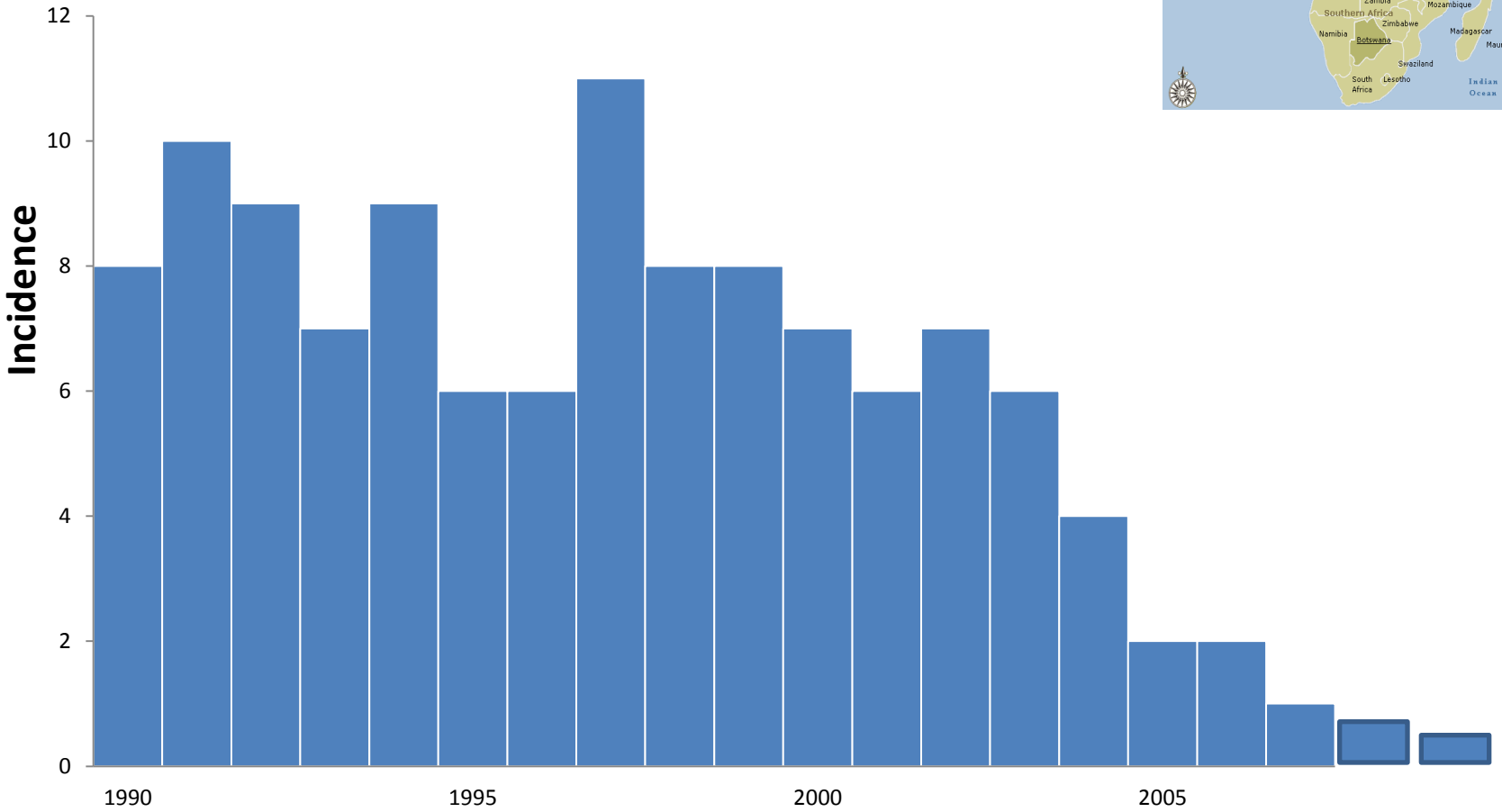
- Herd effect of reducing transmission
- Reduced neurological sequelae of cerebral malaria
- Reduction in febrile seizures (70-80%) and in epilepsy
- Reduced cognitive/educational impairment
- Reduced all cause mortality

Could Malaria Cause More Deaths?



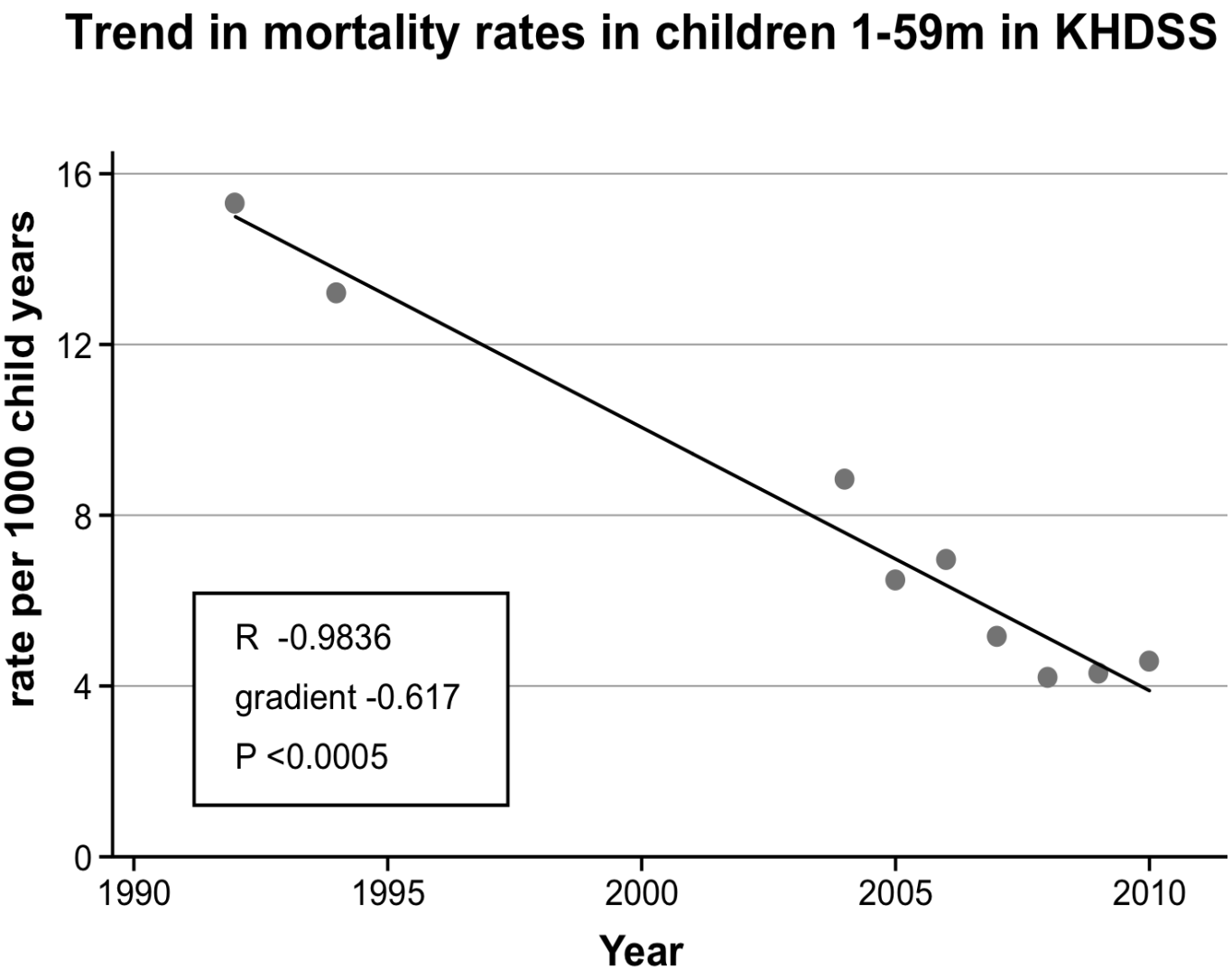
Snow and MarshTrends Parasitology. **2001**

Malaria Admissions in Kilifi

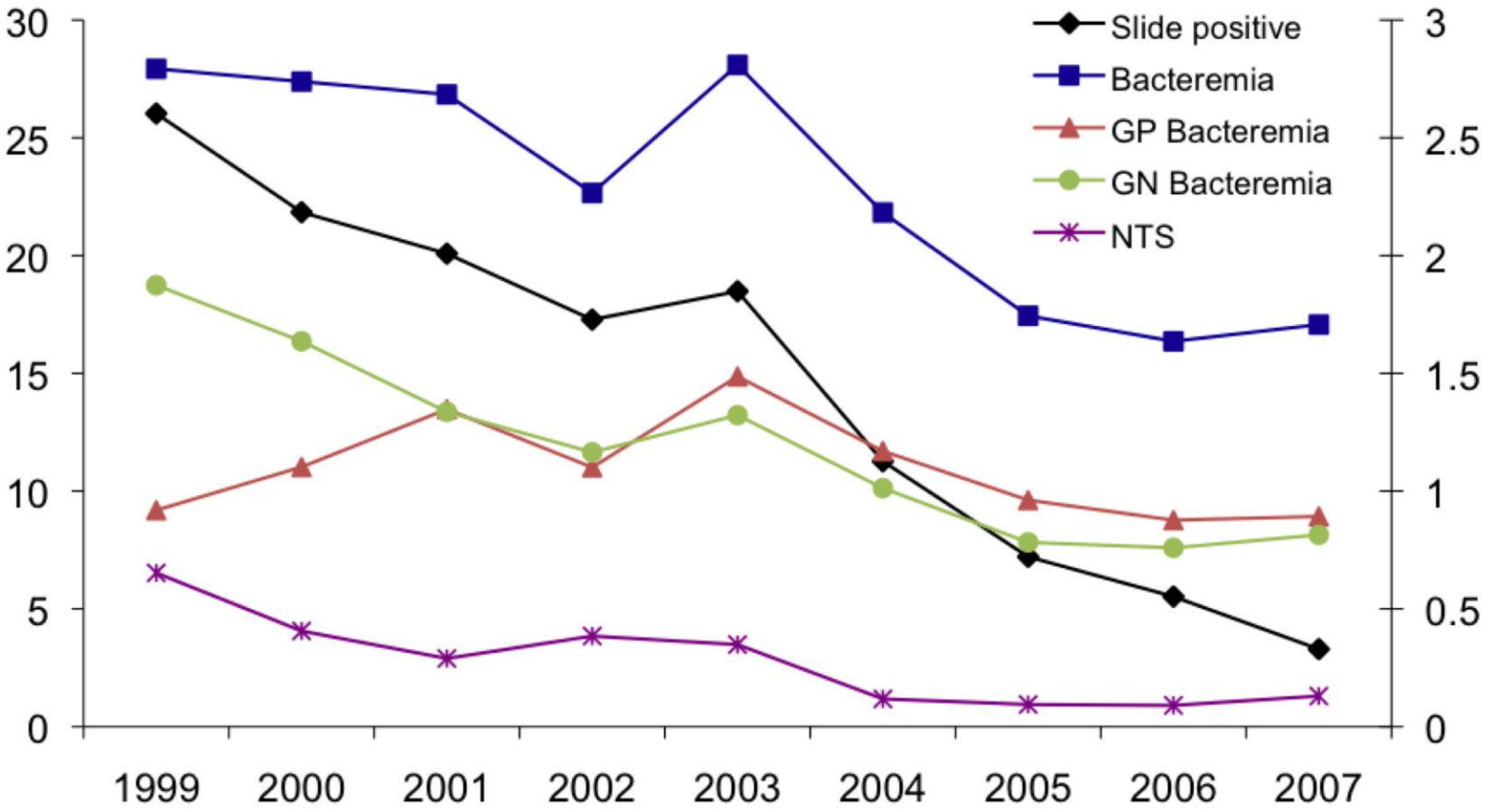


O'Meara *et al*., Lancet; 372 (2008)

Mortality Trends in Kilifi DSS

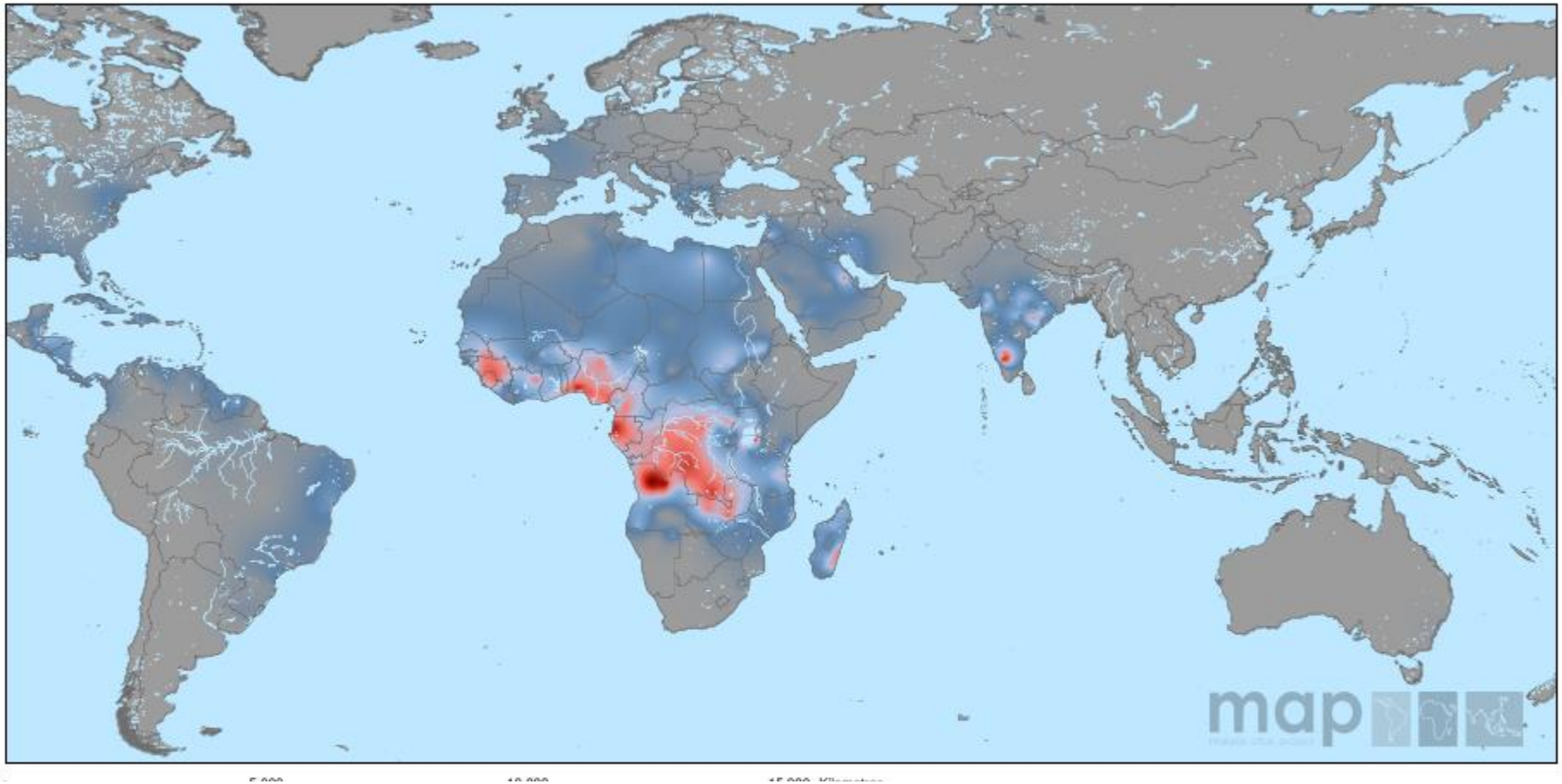


Bacteraemia declines with malaria



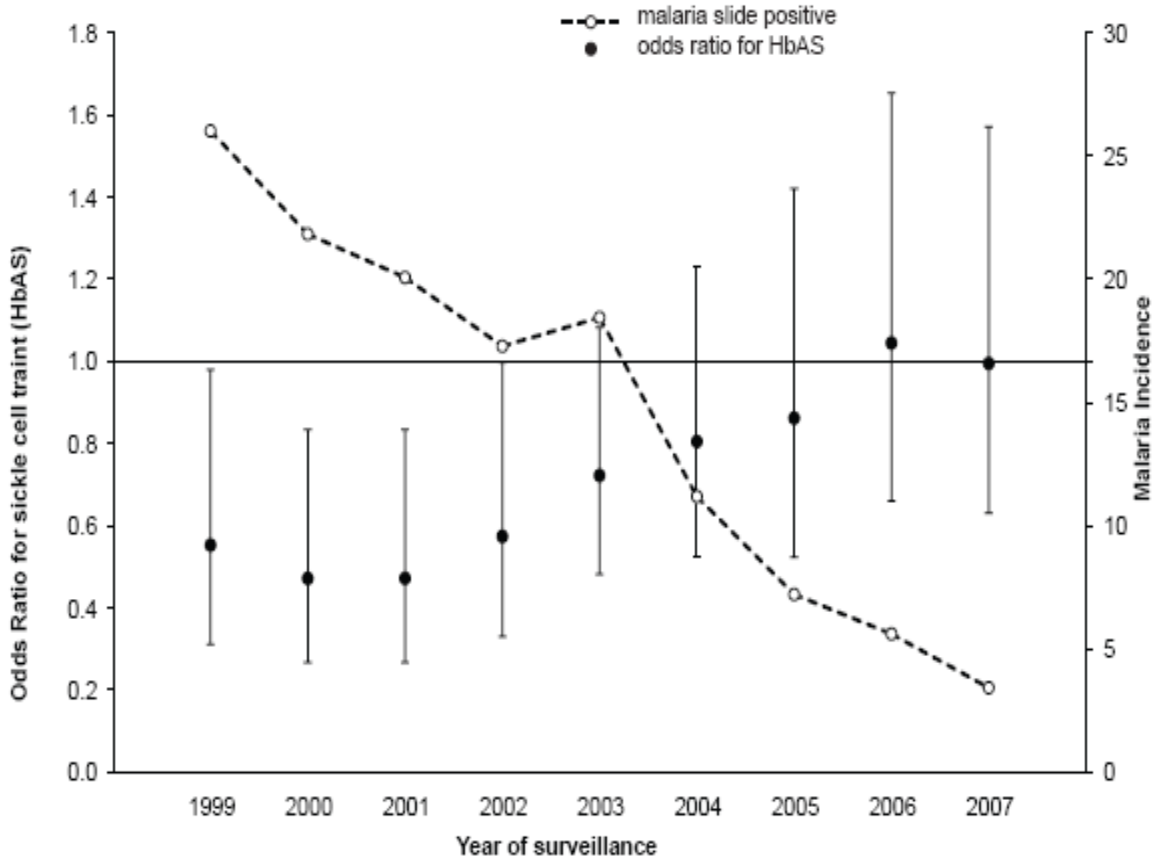
Scott et al Lancet 2011

Sickle Cell Trait and Malaria



Sickle cell trait provides strong protection against malaria but in mid 1990's we observed apparent strong protective effect against bacteraemia

Protective effect of AS against bacteraemia 1999-2007



Malaria may "cause" 50% of cases of bacteraemia

Scott et al Lancet 2011

Malaria control and Child Mortality Bioko

Year	CMR per 1000 births
2000	157
2001	189
2002	137
2003	111
2000-2003	157
2004	51
2004	72
2006	39
2007	59
2004-2008	55

51

Kleinschmidt I, et al.Am J Trop Med Hyg. 2009

But…….

RTS,S phase 3 trial showed no effect on bacteraemia, pneumonia, malaria mortality or all cause mortality

Summary

- An effective malaria vaccine could potentially prevent most cases and deaths due to malaria ***and*** as many more other deaths due to other causes

- RTSS will prevent around a third of cases over 4 years

- Reasonable to expect (but not proven) that RTSS will prevent a third of malaria deaths

- Not clear if RTSS will prevent additional deaths