



# Severe Malaria

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## Definition of Severe Malaria

- ❖ **World Health Organisation (WHO)**
- ❖ **Severe Malaria in African Children (SMAC)**

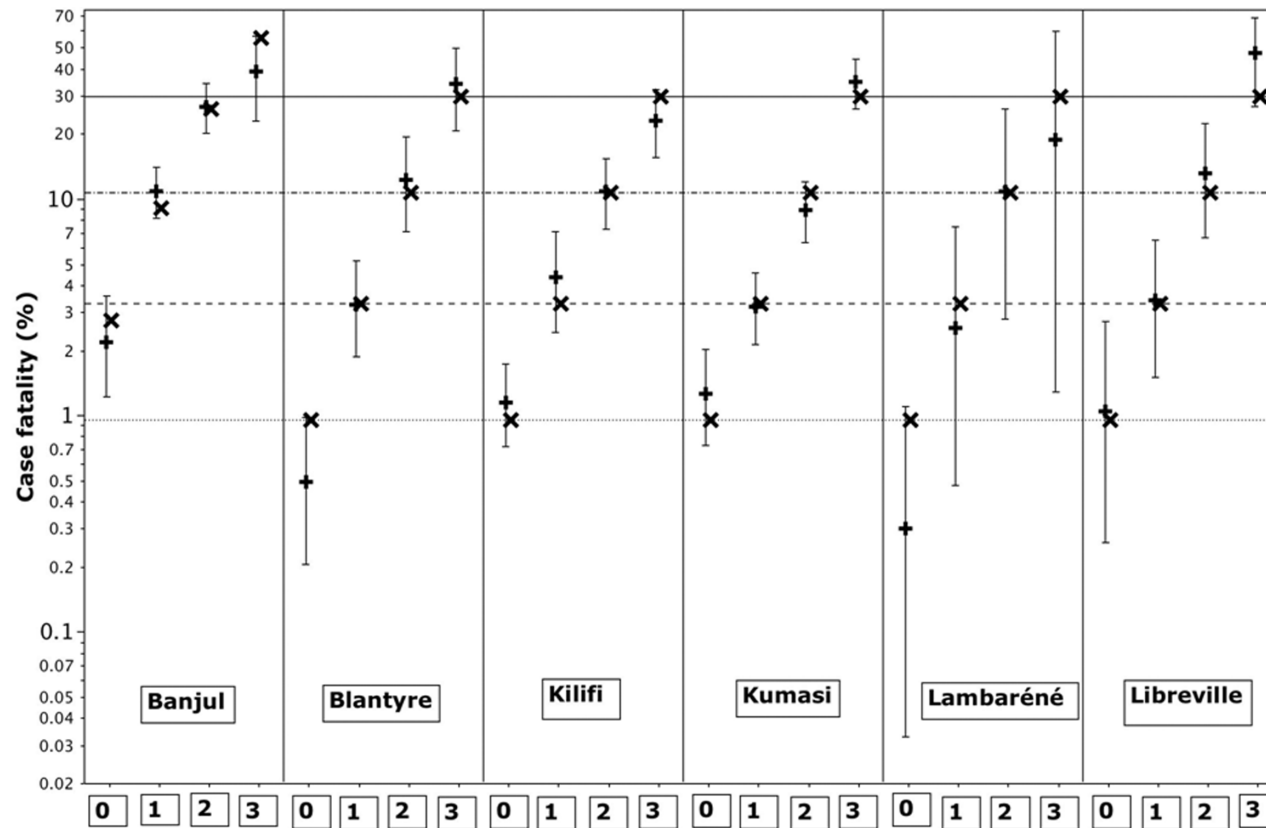


## SMAC Studies

- ❖ **Prospective studies of more than 26,000 children with severe malaria**
- ❖ **LODS**
- ❖ **Site heterogeneity in disease manifestation**
- ❖ **Mortality 4%**

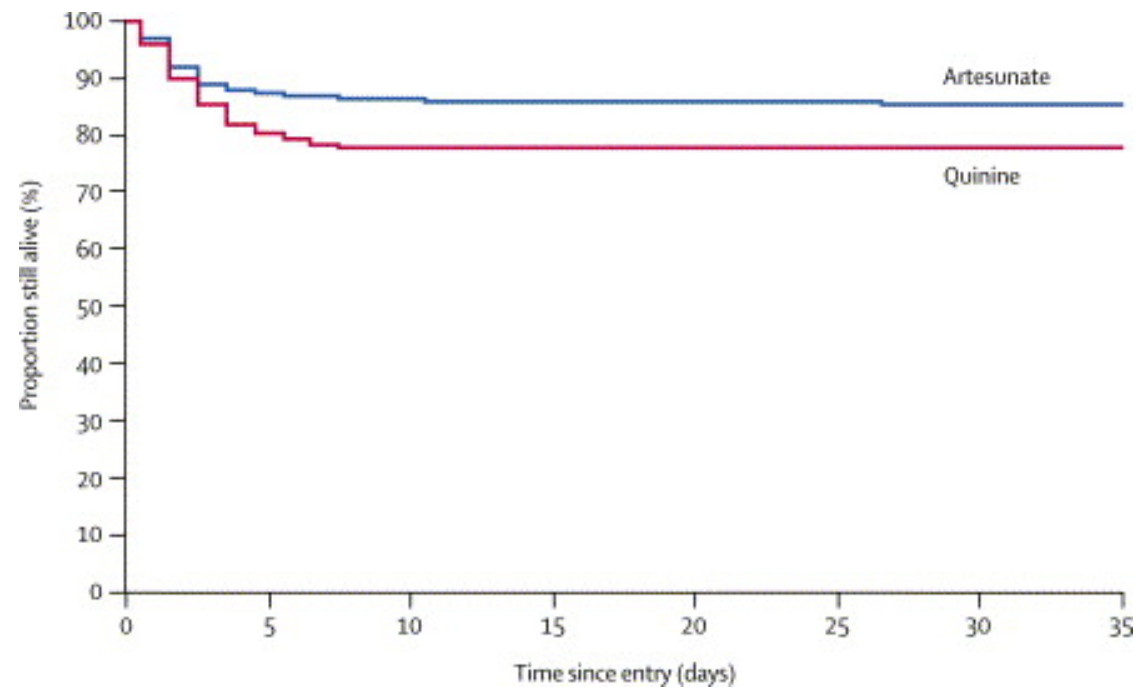


## SMAC LODS Studies (JID 2009)



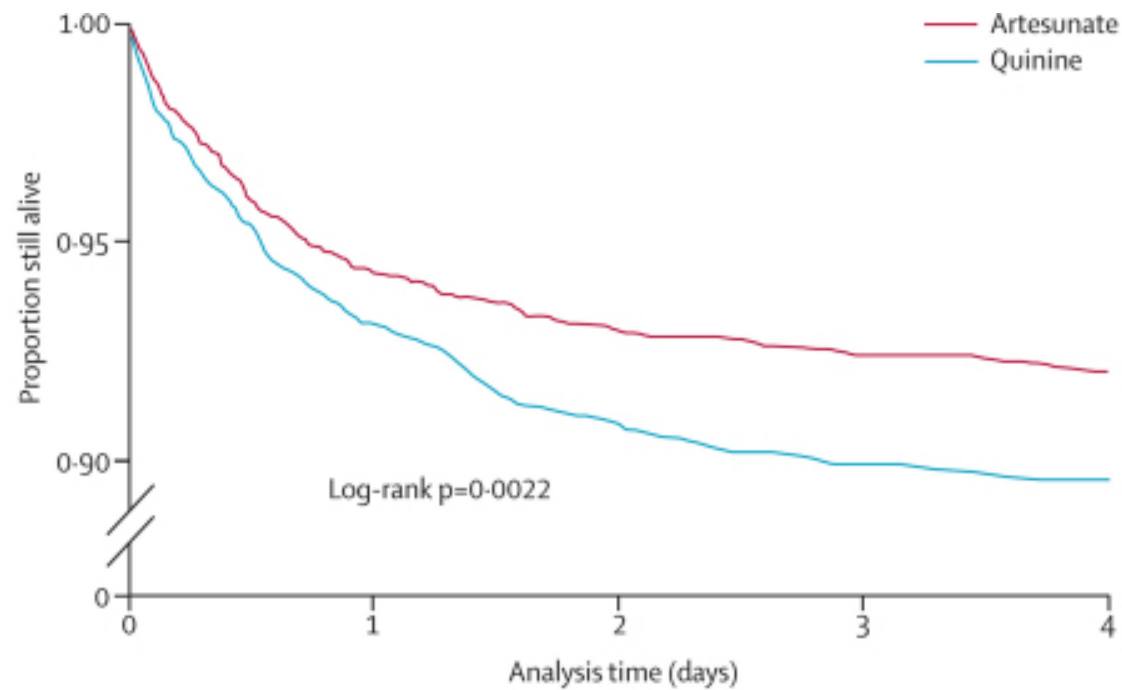


## SEAQUAMAT Study (Lancet 2005)





## AQUAMAT Study (Lancet 2010)



**Number at risk**

Artesunate	2712	(158)	2554	(32)	2522	(16)	2506	(13)	2493	(11)
Quinine	2713	(186)	2527	(63)	2464	(26)	2438	(10)	2428	(12)



## **Simplified Artesunate (JID 2012)**

- ❖ **2 study arms (5 doses vs. 3 doses of iv Artesunate)**
- ❖ **197 patients at 3 African study sites**



## Simplified Artesunate (JID 2012)

**Table 2. Secondary Efficacy Analyses: Time in Hours to Parasite Clearance**

Degree of Clearance	Time to Clearance, Median (IQR), h	
	5-Dose Group	3-Dose Group
PCT100	36 (30–48)	36 (30–48)
PC99	24 (18–24)	18 (18–30)
PCT90	18 (12–18)	12 (12–18)
PCT50	12 (6–12)	12 (6–12)

Abbreviations: IQR, interquartile range, PCT100, 100% parasite clearance; PC99, 99% parasite clearance; PCT90, 90% parasite clearance; PCT50, 50% parasite clearance.





## Artesunate Dose Optimization Study

- ❖ **3 study arms (3 doses iv vs. 3 doses im vs. 5 doses im of Artesunate)**
- ❖ **1054 patients at 7 African study sites**



## Artesunate Dose Optimization Study

*Analysis of preliminary data shows comparable safety and efficacy profiles in all 3 cohorts.*

*Study results, e.g. regarding clearance rates can be revealed upon database lock and completion of data analysis in early 2014.*



# Co-Infections: Background

- ❖ **Disease manifestation**
- ❖ **Therapeutic relevance**



## Co-Infections: Future Studies

- ❖ **Use of antibiotics in combination with antimalarial treatment**



# Malaria Diagnosis: Background

- ❖ **Thick blood smear**
- ❖ **Rapid tests**



## Malaria Diagnosis: Future Studies

- ❖ **Rapid tests for detecting parasites and their antimalarial resistance patterns plus other microbes**



# Malaria Prevention: Background

- ❖ Malaria control measures
- ❖ Malaria vaccine



## Malaria Prevention: Future studies

- ❖ **Investigation of severe malaria in interventional preventive trials (e.g. vaccine studies)**





## **Malaria Adjunct Therapy: Background**

- ❖ **Multifactorial cause of complications**
- ❖ **Many published studies with many different interventions over the last 30 years – no success**
- ❖ **Mortality:**

<b>AQUAMAT:</b>	<b>10%</b>
<b>SMAC1:</b>	<b>4%</b>
<b>SMAC2:</b>	<b>2%</b>
<b>RTSS:</b>	<b>0%</b>



# Malaria Adjunct Therapy: Future studies

- ❖ Investigation of pathophysiology of severe malaria



## **Malaria Chemotherapy: Background**

- ❖ **AQUAMAT: Artesunate reduced mortality from 11% to 9% compared to quinine**
- ❖ **SMAC studies: Artesunate three dose regimen vs. five dose regimen**
- ❖ **SMAC studies: Artesunate intramuscular vs. intravenous**



## **Malaria Chemotherapy: Background**

- ❖ **Resistance: first reports from South East Asia**
- ❖ **Haemolytic anaemia: first described in travellers; in SMAC studies 9%**



## **Malaria Chemotherapy: Future Studies**

- ❖ **Immediate studies: haemolytic anaemia**
- ❖ **Long-term studies: development of artemisinin alternatives (e.g. artemisone, OZ439, spiroindolones)**