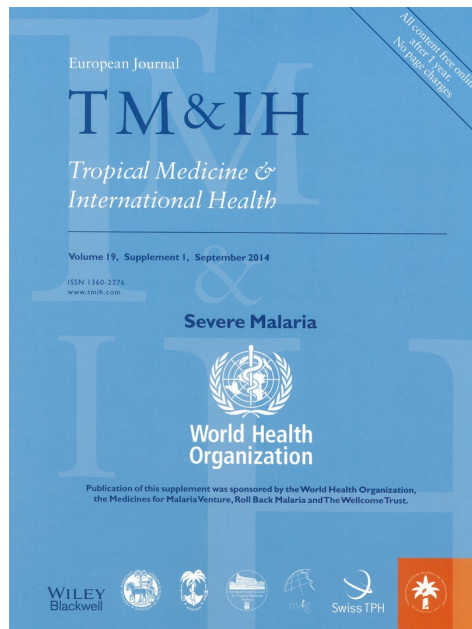


What causes severe febrile illness in the tropics?

Infection

Viral
Bacterial
Protozoal



Malaria parasitaemia + Severe febrile illness = Severe malaria?

Severe malaria is **overdiagnosed**

Bacterial septicaemia is **underdiagnosed**

Improving statistical power in severe malaria genetic association studies by augmenting phenotypic precision

James A Watson^{1,2†*}, Carolyne M Ndila^{1,2†}, Sophie Uyoga³, Alexander W Macharia³, Gideon Nyutu³, Mohammed Shebe³, Caroline Ngetsu³, Neema Mturi³, Norbert Peshu³, Benjamin Tsofa³, Kirk Rockett^{4,5}, Stije Leopold^{1,2}, Hugh Kingston^{1,2}, Elizabeth C George⁶, Kathryn Maitland^{3,7}, Nicholas PJ Day^{1,2}, Arjen Dondorp^{1,2}, Philip Bejon^{2,3}, Thomas N Williams^{3,7†}, Chris C Holmes^{8,9†}, Nicholas J White^{1,2†}

Substantial misdiagnosis of severe malaria in African children

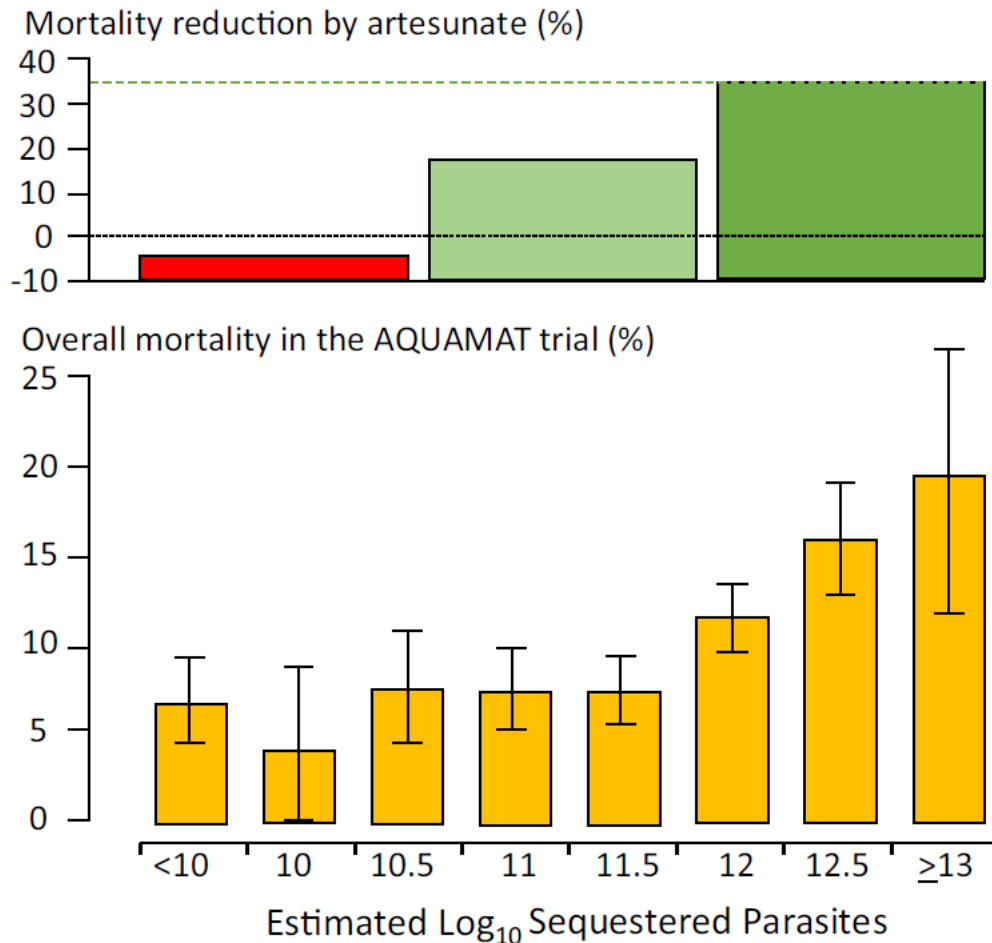
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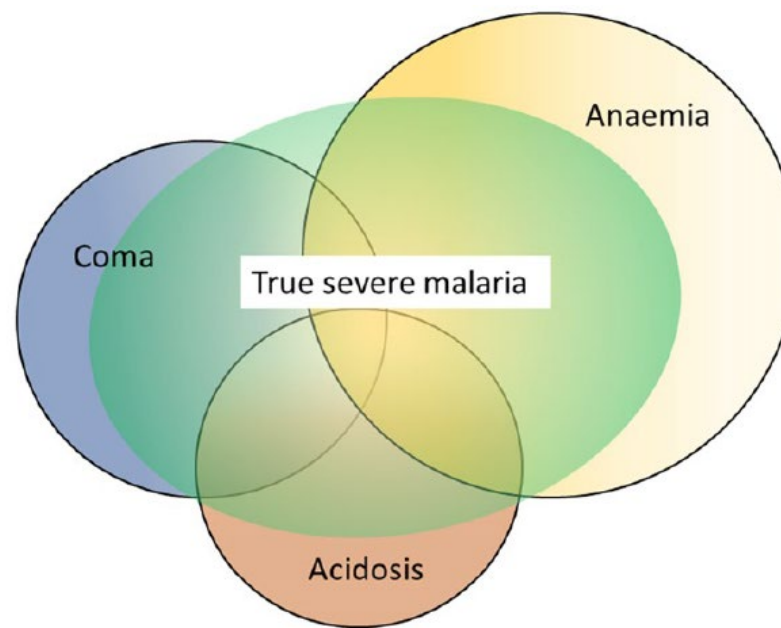
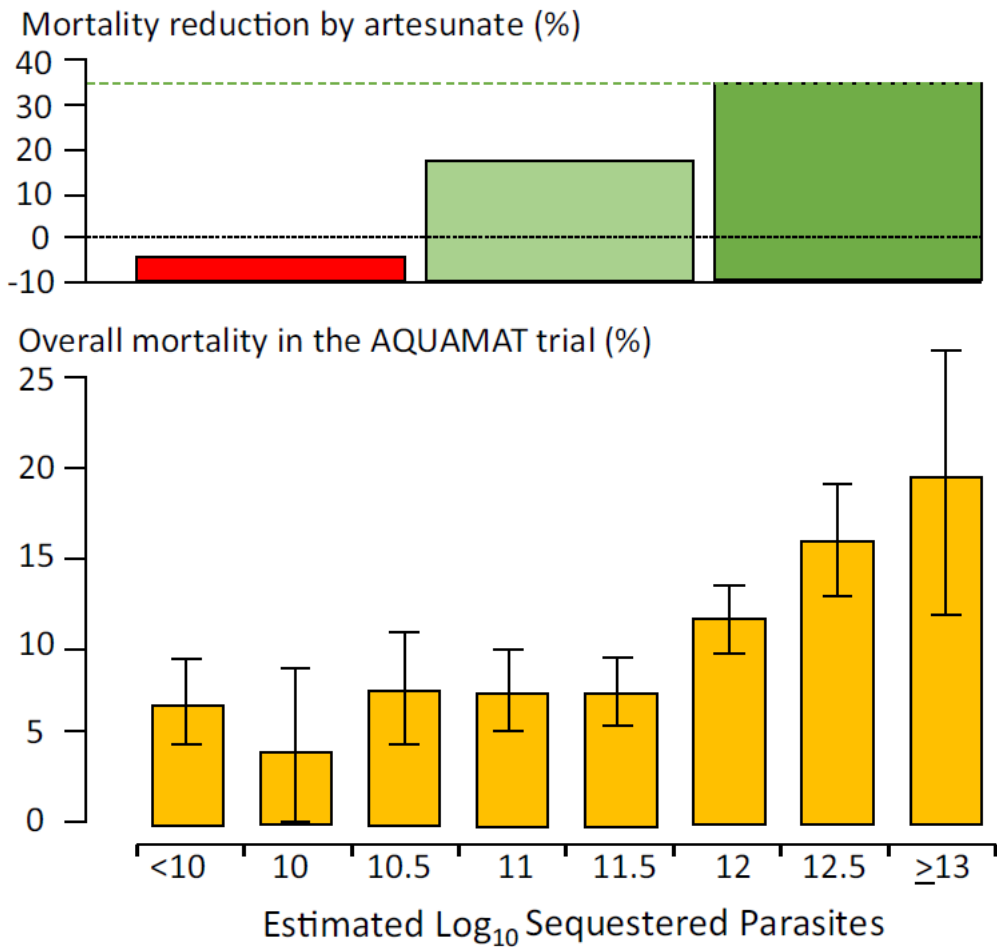
Sci Transl Med. 2022 July 20; 14(654): eabn5040. doi:10.1126/scitranslmed.abn5040.

Improving the diagnosis of severe malaria in African children using platelet counts and plasma *PfHRP2* concentrations

Approximately **one third** of African children diagnosed with severe malaria in research centres *did not have severe malaria*



In children with the highest likelihood of having true severe malaria artesunate reduced mortality by one third-*exactly* the same amount as in SE Asia



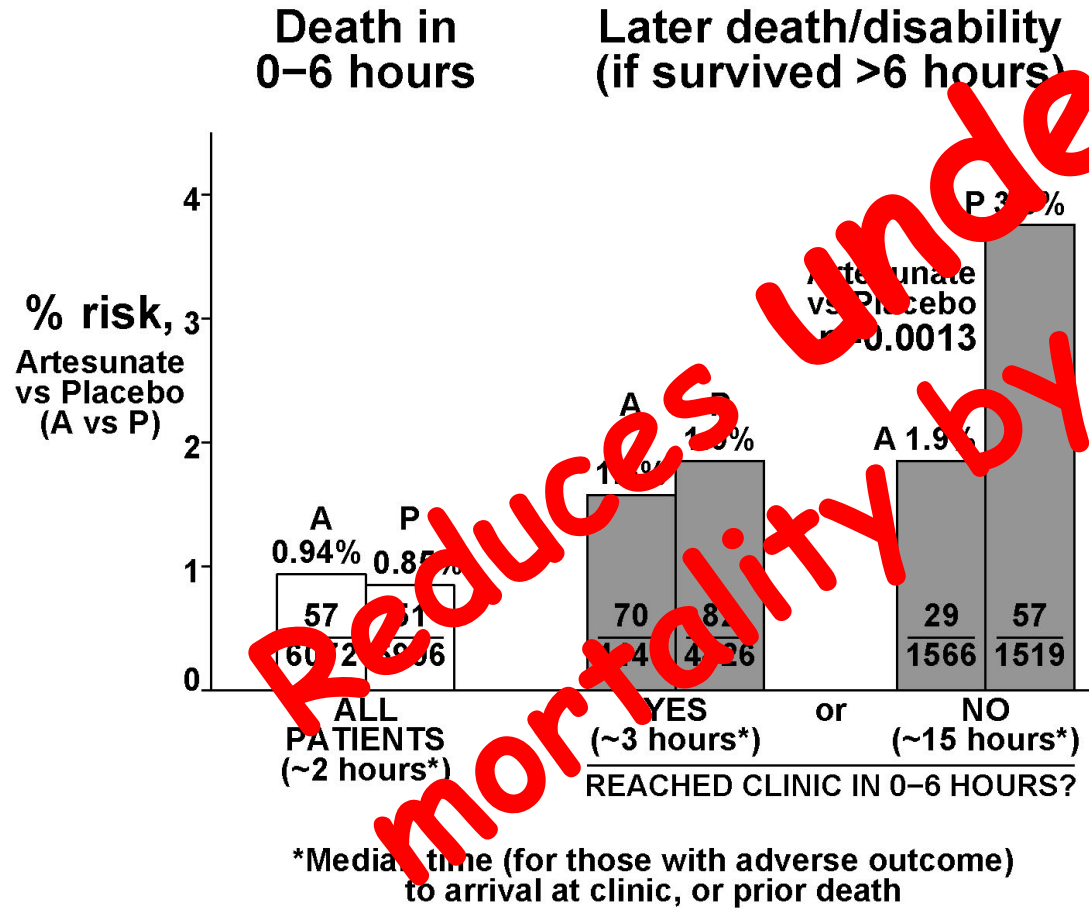
Hendriksen I et al. PLoS Med 2012
 Watson J et al. eLife 2022
 Watson J et al. Sci Trans Med 2022
 White NJ. Malaria J 2022
 White NJ et al. Lancet 2022

**Severe malaria is overdiagnosed in African children.
 Parenteral artesunate reduces mortality by one third
 in *true* severe malaria**

So what do the other children have?

Bacterial sepsis

Lethal delays in receiving antimalarial drugs



IMCI Current Management Schedule

If any danger sign,
REFER URGENTLY to health facility:

ASSIST REFERRAL to health facility:
 Explain why child needs to go to health facility. **GIVE FIRST DOSE OF TREATMENT:**

<input type="checkbox"/> If Fever, AND <input type="checkbox"/> Convulsions or <input type="checkbox"/> Unusually sleepy or unconscious or <input type="checkbox"/> Not able to drink or feed anything <input type="checkbox"/> Vomits everything	<input type="checkbox"/> Give rectal artesunate suppository (100 mg) <input type="checkbox"/> Age 6 months up to 5 years --> 1 suppository
---	---

<input type="checkbox"/> If Chest indrawing, or <input type="checkbox"/> Fast breathing	<input type="checkbox"/> If child can drink, give first dose of oral antibiotic (amoxicillin tablet—250 mg) <input type="checkbox"/> Age 2 months up to 12 months --> 1 tablet <input type="checkbox"/> Age 12 months up to 5 years --> 2 tablets
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Children who cannot take oral medications, in a malaria endemic area, get an artesunate suppository

Children with chest indrawing who cannot take oral medication are referred - because no pre-referral medication

Goal: to save lives of children who have symptoms overlapping between malaria, pneumonia, meningitis & sepsis

Lethal delays in receiving antibiotics



A Ceftriaxone Rectal Dosage Product to Prevent Neonatal Sepsis Deaths

Practical implications

1. Severe malaria : parenteral artesunate+ parenteral antibiotics
2. Pre-referral: rectal artesunate +/- oral antibiotics
3. A rectally bioavailable antibiotic formulation or coformulation would be beneficial.

