# Severity Markers to Risk-Stratify Fever Syndromes

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**BLUF (Bottom Line Up Front):**
**1. Rapid triage tests for fever could improve survival and prevent brain injury by allowing early detection of severe infections**
**3. This would save lives and money by preventing referral, admission and treatment of self-limited infections and decreasing AMR**

# Problem

- *Everyone gets fevers (>1B/yr) but few become critically ill (~1% to 0.01%)*
- *→ we lack tools to recognize and triage severe infections for urgent care*
- *Once a severe infection occurs, there are high fatality rates despite ICU and antimicrobials. Survivors have neurocognitive deficits/brain injury.*
- *→ we have no treatments to improve outcome*

# Barriers: LMIC

- **>50% of children die without engaging the formal health care sector → IMPACT requires a community-based solution (i.e. no MDs/RNs)**
- **We need an integrated approach to the febrile child NOT a pathogen based one → etiology-based Dx alone (e.g. Pf RDT; 90% neg → now what?)**

# Severe Malaria: Triage

- **WHO criteria for the diagnosis and management of severe malaria (SM)**

- **Surveyed 105 health centers in Uganda for treatment of SM**

- **Referral practices for SM were appropriate in less than 10% of cases**

- **Prompt care for SM → 29%**

- **SM diagnosed correctly → 27%**

→ *"...patient triage and evaluation were extremely inadequate"*

# Barriers: West

- *Despite "resources" we are not good at triage of life-threatening infections (we miss early sepsis)*
- *Conversely we over admit self limited infections with resultant misallocation of health resources and cause harm*
- *We need risk-stratification tools for ICU admisison, prognosis and use of new high value therapeutics*

# Sepsis 2018

*Fernando S et al. Critical Care 2018;22:172*

- *Early recognition and treatment of sepsis saves lives → no tools exist for early Dx*
- N=657 febrile pts to ED
- **Mortality: 2x higher in those sent home (62%) or to the ward (43%) vs ICU (29%) P<0.001**
- **Cost per survivor: ~5x higher in those sent home (186K) or ward (187K) vs ICU (38K) P<0.001**
- *Significantly worse outcomes at higher cost!*

# "Prediction is difficult, especially about the future"

- *"..only ½ of patients requiring ICU were recognized during their initial ED visit"*

- *"..evidence suggests that ED physicians significantly under recognize sepsis…"*

- *..highlights the need for risk-stratification tools… "*

# Patient outcomes Matter

- **Patients 1<sup>st</sup>: Patients versus pathogens?**
- **Early recognition and triage of severe infections saves lives, pathogen Dx do NOT address this**
- **Risk that additional investigations may slow patient care and add to overburdened health care systems → may paradoxically increase mortality due to delays in recognition and treatment of those with critical illness**
- **Enhanced triage and early treatment of severe infections → can accelerate patient flow and saves lives in both HIC and LMIC settings**

# **Etiology is not enough**
## *Critical Knowledge Gaps*

- *Who will get critically ill?*
- *Who needs referral? Admission?*
- *Who will benefit from ICU & high value therapeutics (HVTs)?*
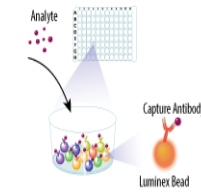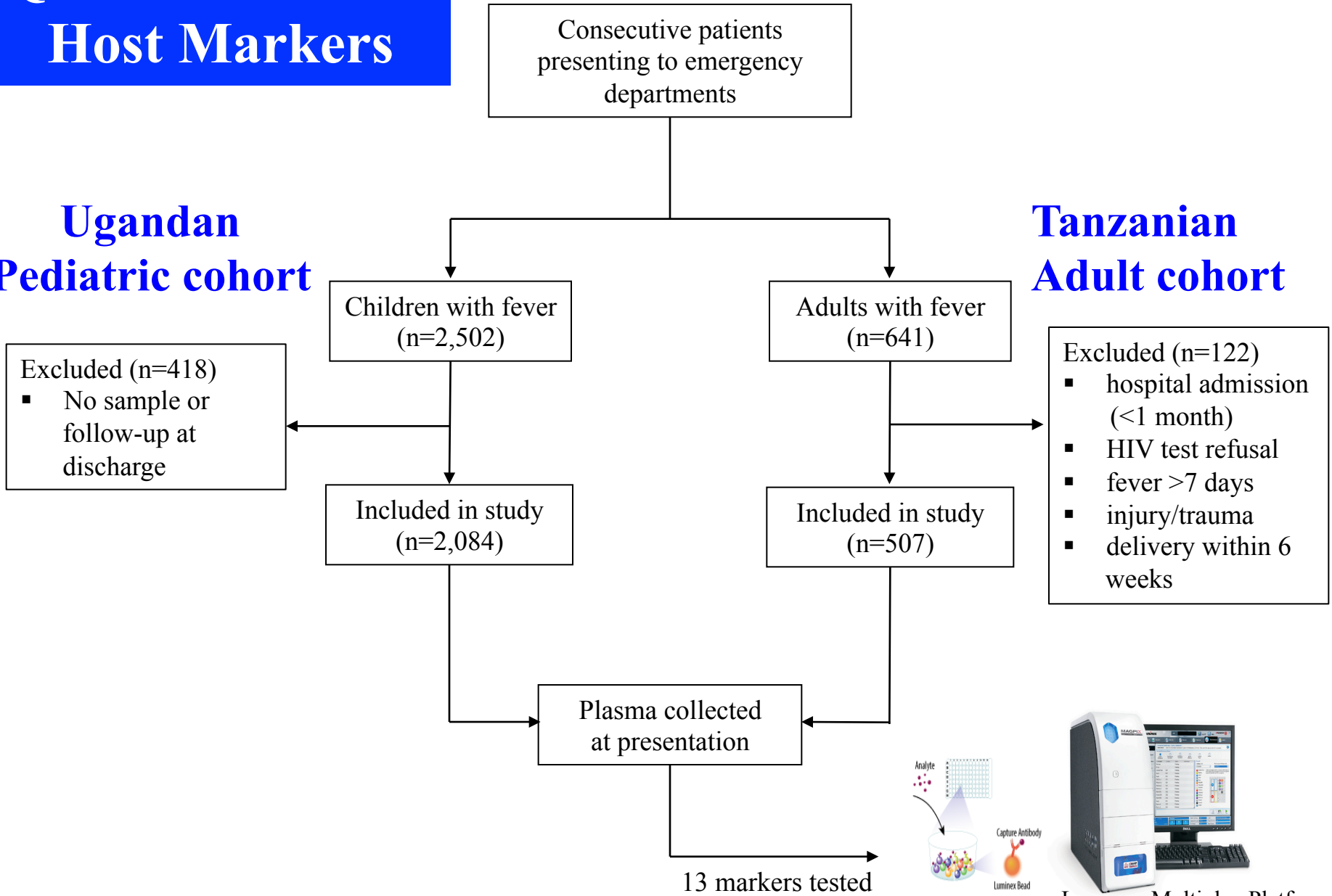- *How do we effectively allocate scarce resources to maximize impact?*

# Research Question 1

- *Can markers of immune and endothelial activation → triage, risk-stratify and prognosticate who will die without immediate treatment? (independent of etiology)*

- *YES → endothelial/inflamm markers (e.g. Ang2, sTREM-1) predict outcome with high accuracy (versus CRP, PCT, pulse ox, or lactate)*

**Quantification of Host Markers**

Consecutive patients presenting to emergency departments

**Ugandan Pediatric cohort**

**Tanzanian Adult cohort**

Children with fever (n=2,502)

Adults with fever (n=641)

Excluded (n=418)
- No sample or follow-up at discharge

Excluded (n=122)
- hospital admission (<1 month)
- HIV test refusal
- fever >7 days
- injury/trauma
- delivery within 6 weeks

Included in study (n=2,084)

Included in study (n=507)

Plasma collected at presentation

13 markers tested

Analyte

Capture Antibody

Luminex Bead

Luminex Multiplex Platform

# Research Question 2

## *Endothelial and Ig activation markers*

- *Community –based (no MDs/RNs): Can markers at presentation risk stratify "all cause fever syndromes" as well as a validated MD-administered clinical scoring system (LODS)? (i.e. could they be added them to a malaria RDT and used by CHWs?)*
- *YES → EC/inflamm markers predict outcome as well as LODS*

# Research Question 3
## *Endothelial and Ig activation markers*

- *Formal Health Care Settings: Can severity markers measured at clinical presentation significantly improve predictive accuracy of an excellent clinical score (LODS or qSOFA) for fever triage?*
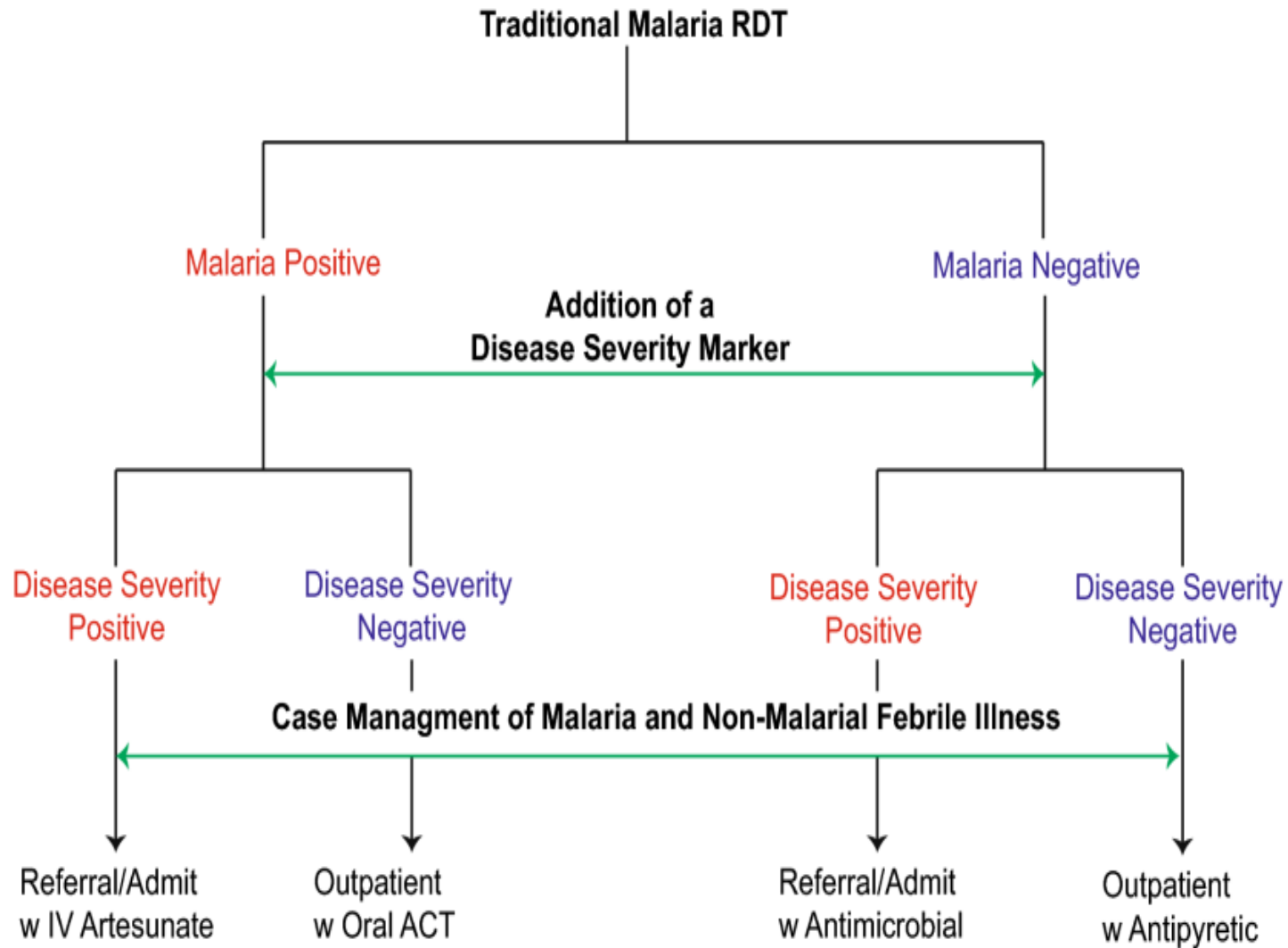
*Mervyn Singer, MD*
University College London
London, United Kingdom

*Manu Shankar-Hari, MD*
Guy's and St. Thomas' NHS Foundation Trust and
   King's College London
London, United Kingdom

*"The Holy Grail is to have early warning systems in place that accurately flag all patients who are at risk for deterioration ….. Such patients should be prioritized for care…"*

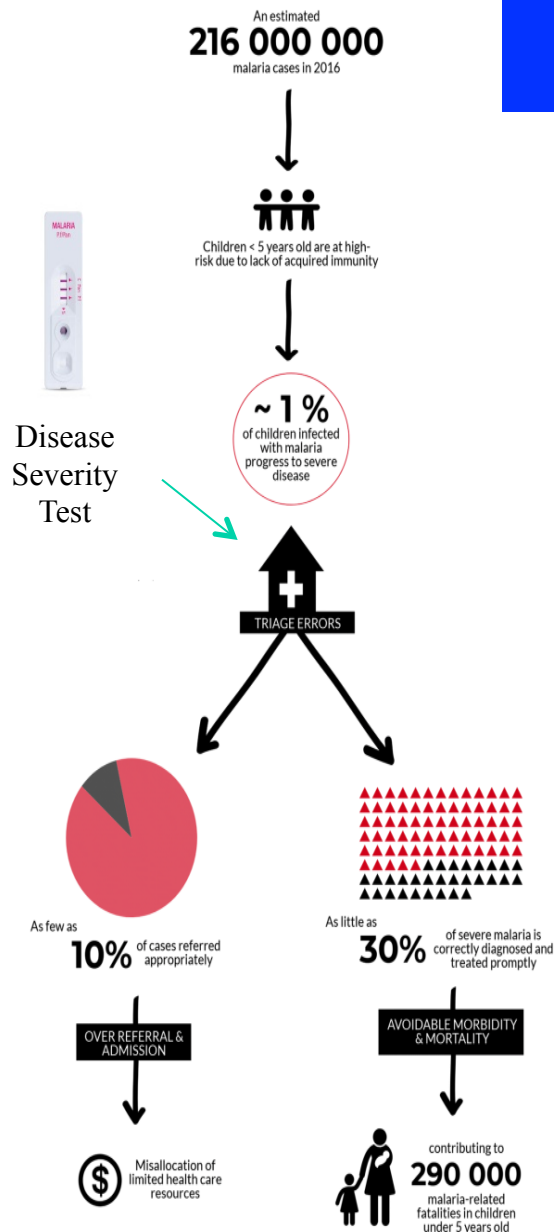# Implementation of a Triage Test into the Management of Febrile Illness



McDonald et al. Malar J (2018) 17:353.

# Triaging Febrile Illness in All Health Settings

An estimated
**216 000 000**
malaria cases in 2016

Children < 5 years old are at high-risk due to lack of acquired immunity

**~ 1 %**
of children infected with malaria progress to severe disease

Disease Severity Test

**TRIAGE ERRORS**

As few as
**10%** of cases referred appropriately

As little as
**30%** of severe malaria is correctly diagnosed and treated promptly

**OVER REFERRAL & ADMISSION**

**AVOIDABLE MORBIDITY & MORTALITY**

Misallocation of limited health care resources

contributing to
**290 000**
malaria-related fatalities in children under 5 years old

## Outcomes:

- **Early recognition of severe infection**

    →**Reduce death and disability**

- **Reduce unnecessary treatment and hospital referral**

    → **Decrease costs/misallocation of health resources**

    → **Decrease antimicrobial resistance**

    → **Decrease risk of iatrogenic harm**

McDonald *et al*. Malar J (2018) 17:353

# Acknowledgments

**Kain Lab:**

Sarah Higgins

Stephen Rogerson, University of Melbourne

Chandy John, Univ.
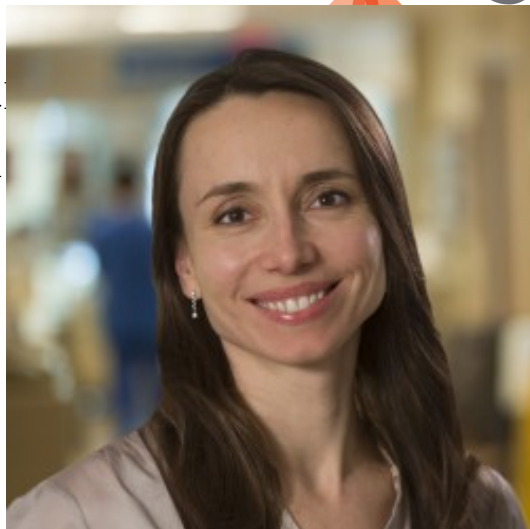
Bob Opoka, Makerere University, Uganda