Existing tools and emerging data

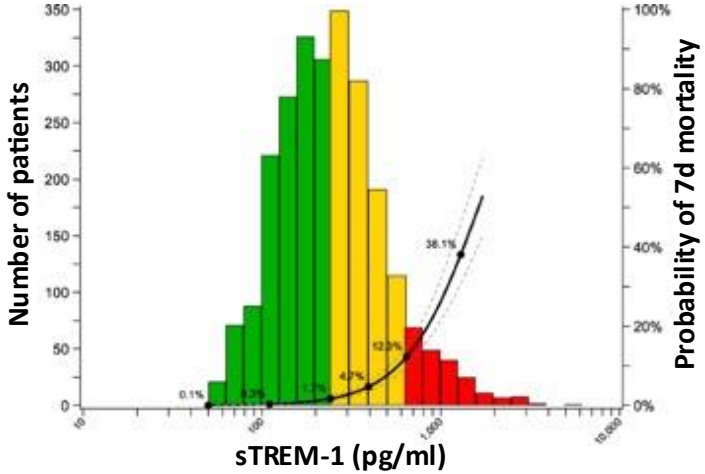
WHO Danger Signs

Seizures
Intractable vomiting
Lethargy
Prostration

Gaps

Suboptimal sensitivity and specificity

Considerable inter-observer variability



Gaps

Hospitalised children

Malaria endemic settings

Focus on predicting mortality

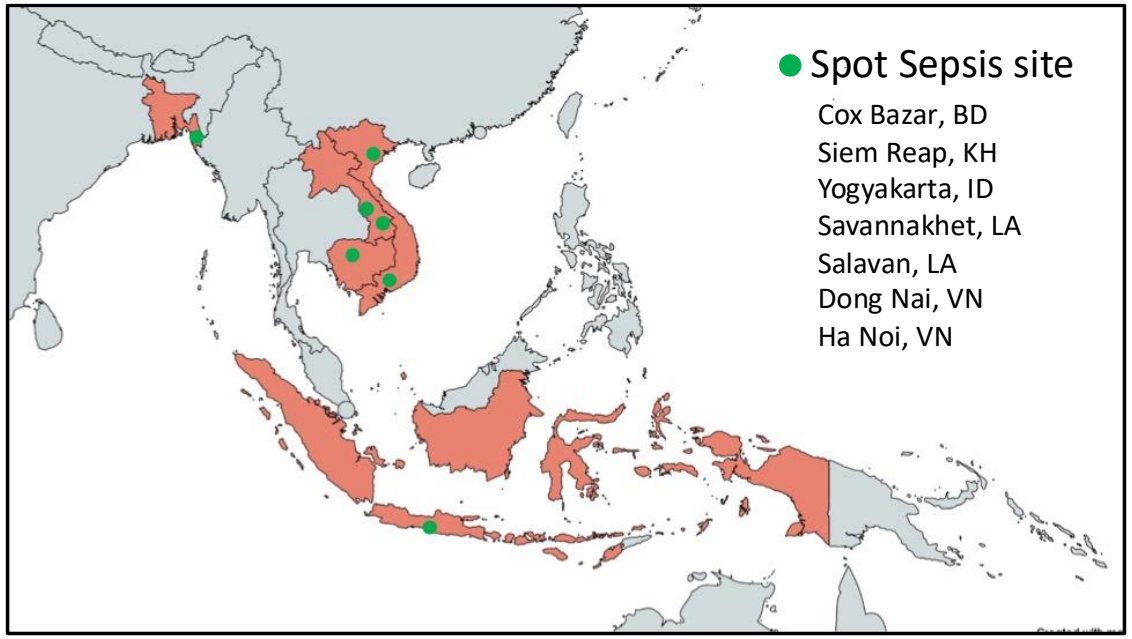
Biomarkers evaluated in isolation

Hansoti et al., BMC Ped, 2017; Keitel et al., BMC Infect Dis, 2019; Leligdowicz et al., Nat Comms, 2021

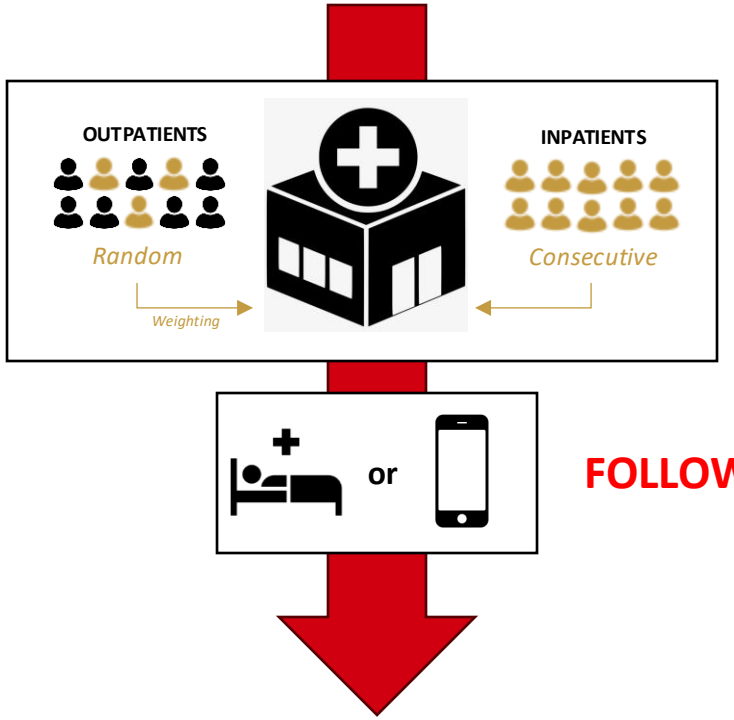
Spot Sepsis

Multi-country prospective cohort study

Children < 5y presenting with acute febrile illness



PRESENTATION TO CARE



ENROLMENT = D0

FOLLOW-UP = D1 + 2 + 28

Death or Vital Organ Support within 2 days of presentation

Objectives

Confirm predictive performance of biomarkers (in children presenting from the community in Asia)

Develop referral tool (combining simple clinical parameters and biomarkers)

Ethical approval from MSF ERB, University of Oxford, and relevant institutions in all participating countries

Results: referral tool – development

3,423 participants recruited with 0.5% (18/3,423) loss to follow-up

133 met the primary outcome (weighted prevalence = 0.4%)

Cohort split into **derivation** (n = 2,581; events = 94) and **external geographic validation** (n = 824; events = 39)

Clinical parameters alone vs. tools containing pulse oximetry and/or biomarkers

Referral tool (clinical prediction model)	**Heart rate**	**Respiratory rate**	**Temperature**	**Mental state**	**Capillary refill time**	**Prostration**	**Seizures**	**Intractable vomiting**
Clinical	✓	✓		✓	✓	✓		✓
Clinical + SpO_2	✓	✓				✓	✓	✓
Clinical + sTREM-1	✓	✓		✓		✓		✓
Clinical + CRP	✓	✓	✓	✓	✓	✓		✓
Clinical + CRP + sTREM-1	✓	✓	✓	✓		✓		✓

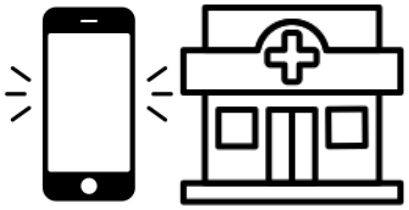
Tools developed using weighted logistic regression with backward stepwise selection

Results: referral tool – clinical utility

Remote and rural community setting

DISCHARGE

MONITOR



REFER

Photo credit: Malaria Elimination Task Force, Médecins Sans Frontières, Medical Action Myanmar

Results: referral tool – clinical utility

Referral tool	Disposition			Accuracy		NNT	Referrals/1000
	Discharge (%)	Monitor (%)	Refer (%)	Sensitivity (95% CI)	Specificity (95% CI)		
Clinical	90.6	8.4	1.0	**0.75** (0.62-0.87)	**0.99** (0.98-1.00)	-	10
Clinical + SpO_2	94.6	5.1	0.3	**0.89** (0.80-0.97)	**1.00** (1.00-1.00)	2,300	3
Clinical + sTREM-1	90.4	7.4	2.2	**0.89** (0.80-0.97)	**0.98** (0.96-0.99)	2,300	22
Clinical + CRP	89.3	9.0	1.7	**0.86** (0.76-0.96)	**0.98** (0.97-0.99)	3,000	17
Clinical + CRP + sTREM-1	89.8	8.4	1.8	**0.92** (0.84-1.00)	**0.98** (0.97-0.99)	2,000	18

NNT = number needed to test

Compared to WHO Danger Signs:

Sensitivity 0.56 and Specificity 0.57

NNT between 1,000 (pulse oximetry or biomarker tools) and 2,000 (clinical tool)

Referrals reduced from between 440/1,000 to between 3-22/1,000

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SCIENTIFIC DAYS

Results: referral tool – cost-effectiveness

Compared to WHO Danger Signs:

All tools dominate (cost-saving and more effective)

Compared to clinical tool:

Tool containing pulse oximetry dominates (cost-saving and more effective)

Tools containing biomarkers cost-effective: incremental cost-effectiveness ratios ~300 USD/DALY averted

As referral costs increase:

Tool containing pulse oximetry become more advantageous due to higher specificity

Tools containing biomarkers remain cost-effective up to a referral cost of ~600 USD

Results consistent across cost-effectiveness thresholds (459-2551 USD/DALY averted)

Conclusions

Possible to improve on existing standard of care using simple clinical parameters

Further important gains possible with pulse oximetry and biomarker testing

Limitations

Differences between study population and intended target population (hospital vs. community)

Majority of children met the endpoint quickly*

Next steps

Development of quantitative point-of-care tests for biomarkers (meeting RE-ASSURED criteria)

Definitive randomised controlled and implementation trials needed

London Calling: Recognise research as fundamental to MSF's social mission

Land et al., Nat Microbiol, 2019

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SCIENTIFIC DAYS

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...and many many more!

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