MSF'S FEBRILE ILLNESS DIAGNOSTIC PROGRAM

A MULTIPLEX, MULTI- ANALYTE TOOL TO IMPROVE DIAGNOSIS OF SEVERE FEBRILE ILLNESS

IN PARTNERSHIP WITH FIND

22 January 2019

Etiology of Severe Non-malaria Febrile Illness in Northern Tanzania: A Prospective Cohort Study

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*"Malaria was the **clinical diagnosis for 528 (60.7%),** but was the actual cause of **fever in only 14 (1.6%)**…….**Acute bacterial zoonoses** were identified among 118 **(26.2%) of febrile admissions**; 16 (13.6%) had brucellosis, 40 (33.9%) leptospirosis, 24 (20.3%) had Q fever, 36 (30.5%) had spotted fever group rickettsioses, and 2 (1.8%) had typhus group rickettsioses. In addition, 55 (7.9%) participants had a confirmed acute arbovirus infection, all due to chikungunya. No patient had a bacterial zoonosis or an arbovirus infection included in the admission differential diagnosis"*

northern Tanzania over the period of one year using conventional standard diagnostic tests to establish fever etiology. Malaria was the clinical diagnosis for 528 (60.7%), but was the actual cause of fever in only 14 (1.6%). By contrast, bacterial, mycobacterial, and fungal bloodstream infections accounted for 85 (9.8%), 14 (1.6%), and 25 (2.9%) febrile admissions, respectively. Acute bacterial zoonoses were identified among 118 (26.2%) of febrile admissions; 16 (13.6%) had brucellosis, 40 (33.9%) leptospirosis, 24 (20.3%) had Q fever, 36 (30.5%) had spotted fever group rickettsioses, and 2 (1.8%) had typhus group rickettsioses. In addition, 55 (7.9%) participants had a confirmed acute arbovirus infection, all due to chikungunya. No patient had a bacterial zoonosis or an arbovirus infection included in the admission differential diagnosis.

Conclusions: Malaria was uncommon and over-diagnosed, whereas invasive infections were underappreciated. Bacterial zoonoses and arbovirus infections were highly prevalent yet overlooked. An integrated approach to the syndrome of fever in resource-limited areas is needed to improve patient outcomes and to rationally tar…

PLOS Neglected Tropical Diseases, 2013

Severe febrile illness hospital management

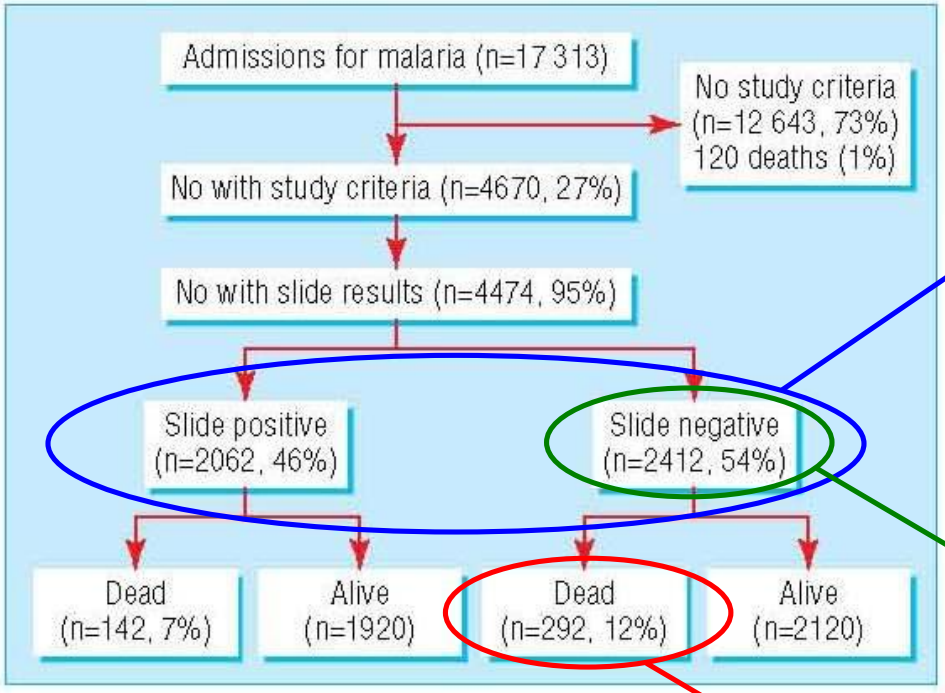


Fig 1 Patients admitted to 10 hospitals with diagnosis of malaria over one year by outcome, presence of any *P falciparum* asexual parasites on the research blood slide, and case fatality

95% treated with quinine

66% received antibacterial

Higher death rate

Reyburn H, et al. Brit Med J 2004; 329: 1212

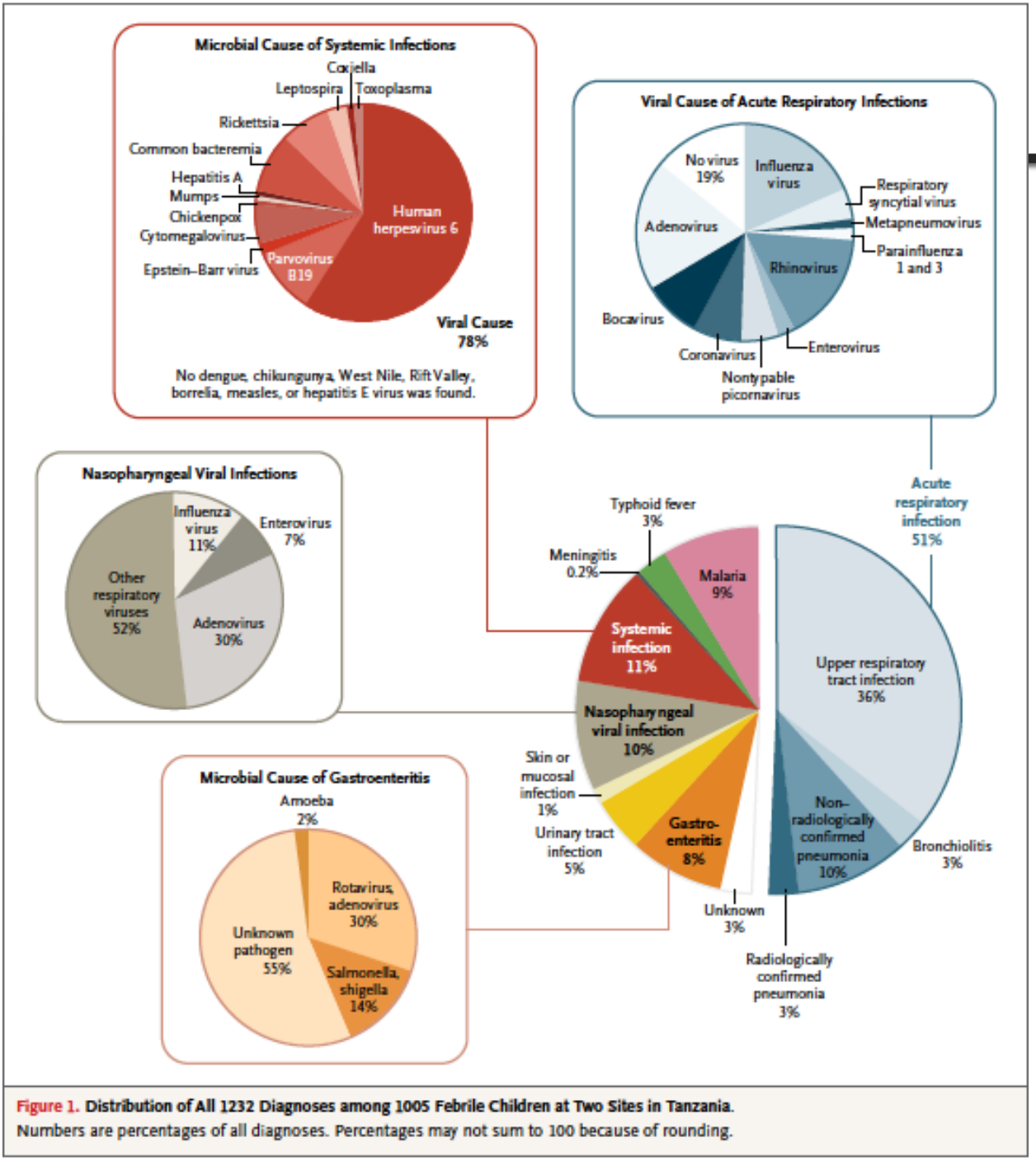


Figure 1. Distribution of All 1232 Diagnoses among 1005 Febrile Children at Two Sites in Tanzania.
Numbers are percentages of all diagnoses. Percentages may not sum to 100 because of rounding.

Beyond malaria: causes of fever

- Most causes of fever in patients at a community level are viral (70.5% vs 22% bacterial and 10% parasitic) – although co-infections common
- Generally poor knowledge of local disease epidemiology and seasonality

(D'Acremont et al 2014 NEJM)

Why improve management of febrile illness?

- = 50% of consultations (WHO 2013)
- one of most common reasons for admission to hospitals in LMICs (Reddy 2010)
- → high mortality and loss of life expectancy (WHO 2013)
- In 2017, 490,000 admissions in MSF hospitals in pediatric IPDs in Africa
  - 10% SFWS = 49,000 per year

SFWS definition

Severe Febrile Illness without a Known Source is defined as

A febrile illness independent of duration, without evidence of localised infection by history, physical examination, and diagnostic tests according to MSF's laboratory working group standards, and severity identified by danger signs. The danger signs include hypotension, tachycardia, tachypnoea, cyanosis, severe pallor or altered level of consciousness.

Work Streams Devised to Respond to Addressing the Problem

Work Streams
WS1: Target product profile development: consensus TPP for hypothetical improved diagnostic incl instrument (MAPDx) – WHO endorsed* - & 1st SFWS test, & PPL
WS2: Fever realities in the field: Literature review, clinician survey on management of fever, & retrospective chart review on SFWS in 2 MSF hospitals to better understand the scope of the medical need inside and outside MSF contexts.
WS3: Algorithm development: Clinical algorithm development to measure impact of a diagnostic for the PPL.
WS4: Prevalence study: Studies on pediatrics in Uganda and Mali to better understand prevalence of pathogens of interest in MSF contexts.
WS5: Business case and IP strategy development: Business for investment into MAPDx.
WS6: Landscapes: Expanded landscape review of existing and pipeline diagnostic technologies relevant to SFWS to describe the gaps.

*https://www.who.int/medical_devices/TPP_20180327_final.pdf

MAPDx – Select TPP Characteristics

	Characteristic	Minimum Requirement	Optimal Requirement
	Scope of the Platform		
1	**Intended Use**	In the context of infectious diseases, intended for individual patient management for patients presenting with symptoms consistent with severe febrile illness without a known source	Same, plus offering an expanded test menu to increase market size for product sustainability
2	**Description of System**	The system will consist of an instrument designed for use in combination with a self-contained, disposable assay cartridge(s) containing all required reagents to execute a test from sample to result	
3	**Target Use Setting**	Level 2 Healthcare Facility (District Hospital or above) defined as having a functioning laboratory with trained personnel, water, electricity with intermittent surges and/or outages, limited climate control, dust, and medical staff onsite. The target use setting does not include mobile testing facilities	Level 1 Healthcare Facility with rudimentary staffed/equipped laboratory, inconsistent electricity, including frequent surges and/or outages, no climate control, dust, but trained medical staff on-site for result interpretation and patient management
20	**List Price of Instrument**	≤$15,000 (USD)	≤$5,000 (USD)

MAPDx – Select TPP Characteristics

	Characteristic	Minimum Requirement	Optimal Requirement
	Assay Cartridge		
21	**Description of Assay Cartridge**	Self-contained, disposable cartridge(s) compatible with the universal cartridge port(s) of the instrument, containing all required reagents to execute a test from sample input to result. The assay cartridge will meet universal, 'semi-open' design specifications made available by the manufacturer of the multiplex diagnostic platform to selected assay developers worldwide for use on such platform.	
22	**Analytes**	Ability to simultaneously detect multiple analyte types (e.g. nucleic acids and serologic markers [antibodies, antigens and host biomarkers]) to achieve the intended use at the same time, from a single specimen, in one or more assay cartridges	Ability to simultaneously detect multiple analyte types (e.g. nucleic acids and serologic markers [antibodies, antigens and host biomarkers]) to achieve the intended use at the same time, from a single specimen, in a single assay cartridge; additional analyte detection capabilities preferred (e.g. clinical chemistries, cell counts)
23	**Multiplexing Capabilities**	Ability to detect a minimum of 6 pathogens at the same time, from the same sample, in one or more assay cartridges	Ability to detect a minimum of 15 pathogens at the same time, from the same sample, in the same assay cartridges
41	**List Price of Assay Cartridge**	≤$15 (USD) at volume production	≤$5 (USD) at volume production

PPL: Analytical Hierarchy Process

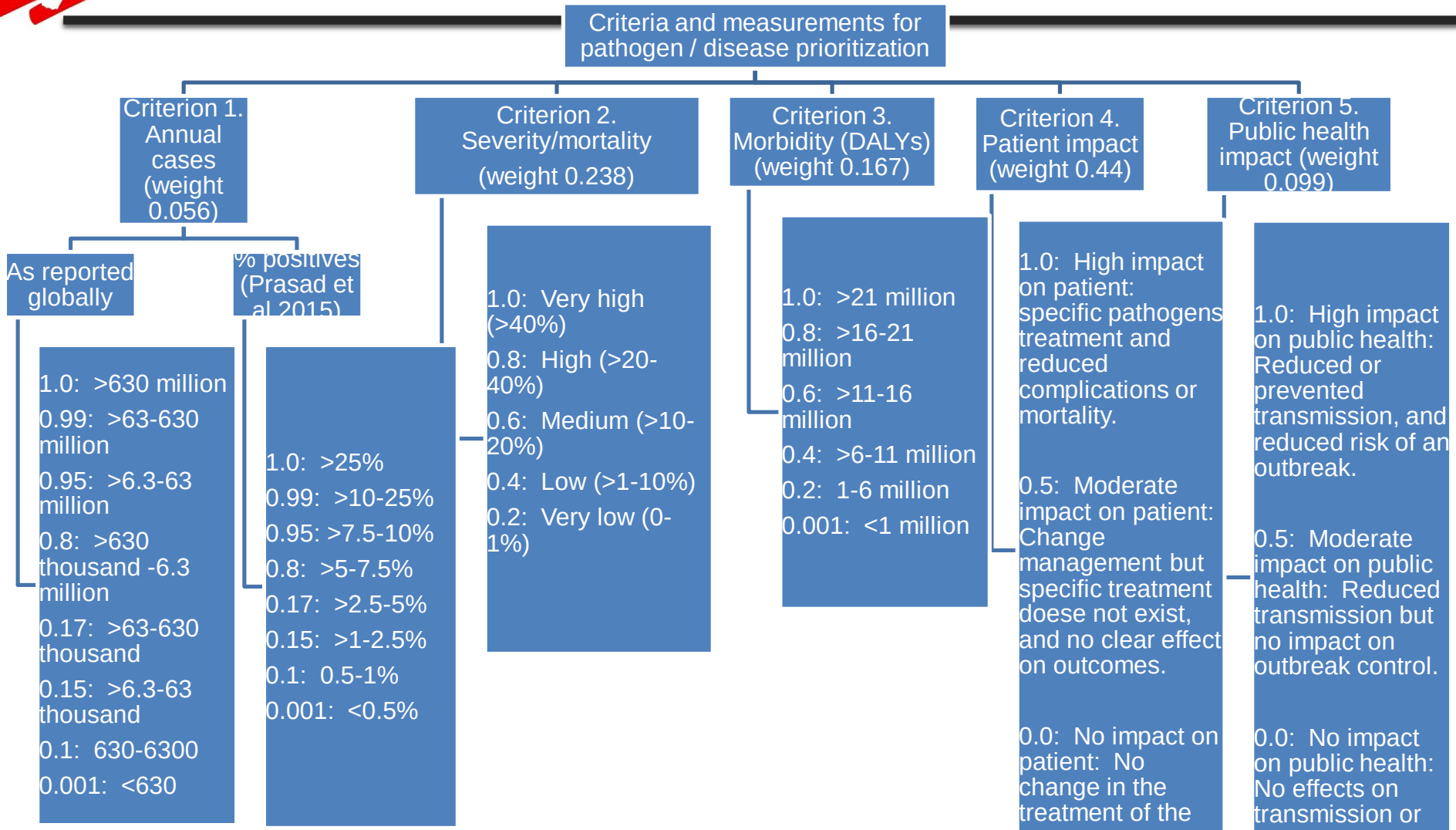
What is it?

"The Analytic Hierarchy Process (AHP), developed in the late 1970s, is one of the methods for multi-criteria decision making. The AHP disaggregates a complex decision problem into different hierarchical levels. The weight for each criterion and alternative are judged in pairwise comparisons and priorities are calculated by the Eigenvector method. "

Who used it?

- WHO prioritization of ABR bacteria for R&D for new antibiotics and for the Blueprint
- Japanese Public Health authority to prioritize emergency preparedness efforts/funding (Kadohira et al. 2015)
- as well as 69 published studies in health science between 2010-2015 (systematic review: Schmidt et al. 2015)

AHP



Original pathogen list from Prasad et al. PLoS ONE 2015
Etiology of severe febrile illness in low- and middle-income countries - A systematic review

Final Pathogen Prioritization List

Item	Rank	Change Antibiotics (CFTX or Amp+Gen)	Primarily a community-acquired or nosocomial pathogen, or both?
Typhoidal salmonella	1	Yes	Community-acquired
Streptococcus pneumoniae	2	No	Community-acquired
Staphylococcus aureus	3	Yes	Community-acquired
Non-typhoidal salmonella	4	Yes	Community-acquired
Escherichia coli	5	No	Community-acquired
Rickettsial spp	6	Yes	Community-acquired
Leptospira spp.	7	Yes	Community-acquired
Brucella spp	8	Yes	Community-acquired
Burkholderia pseudomallei	9	Yes	Community-acquired
Coxiella burnetii	10	Yes	Community-acquired
Neisseria meningitidis (serogroups A, B, C, W-135, Y, and X)	11	No	Community-acquired
Klebsiella spp	12	No	Community-acquired and nosocomial
Orientia tsutsugamushi	13	Yes	Community-acquired
Haemophilus influenzae	14	No	Community-acquired
Dengue virus 1, 2, and 3	15	Yes	Community-acquired
Histoplasma capsulatum	16	Yes	Community-acquired
Lassa fever	17	Yes	Community-acquired
Enterococcus faecalis	18	Yes	Community-acquired
Borrelia recurrentis	19	Yes	Community-acquired
Chikungunya virus	20	Yes	Community-acquired
Pseudomonas spp	21	Yes	Nosocomial
Acinetobacter baumannii	22	Yes	Nosocomial
Enterobacter spp	23	Yes	Nosocomial

Final Pathogen Prioritization List Compared to the Sub-lists

Almost perfect agreement | Substantial agreement | Moderate agreement | Fair agreement

Final Pathogen Prioritization List	Rank	Paediatrics (all)	Africa	Paediatrics Africa	Asia	Paediatrics (≥ 1 month to 4.9 years)	Paediatrics (≥ 5 years to 15 years)	Paediatrics Asia	Symptomatic HIV infection	Paediatrics (0 days to < 1 month)	Latin America
Typhoidal salmonella	1										
Streptococcus pneumoniae	2										
Staphylococcus aureus	3										
Non-typhoidal salmonella	4										
Escherichia coli	5										
Rickettsial spp	6										
Leptospira spp.	7										
Brucella spp	8										
Burkholderia pseudomallei	9										
Coxiella burnetii	10										
Neisseria meningitidis	11										
Klebsiella spp	12										
Orientia tsutsugamushi	13										
Haemophilus influenzae	14										
Dengue virus 1, 2, and 3	15										
Histoplasma capsulatum	16										
Lassa fever	17										
Enterococcus faecalis	18										
Borrelia recurrentis	19										
Chikungunya virus	20										
Pseudomonas spp	21										
Acinetobacter baumannii	22										
Enterobacter spp	23										

Data driven + expert input AHP process:

1. Literature review; 2. weighting of categories; 3. survey: KOLs,
   4. final SAC e.g. deprioritise HAIs

Sub-list interpretation

Almost perfect agreement
- Paediatrics (all)
- Africa
- Paediatrics Africa

Substantial agreement
- Asia
- Paediatrics (≥1 month to 4.9 years)
- Paediatrics (≥5 years to 15 years)
- Paediatrics Asia

Suggest that the application of the final pathogen prioritization list to any of these cohorts could be **beneficial** for improving patient clinical management outcomes.

Moderate agreement
- Symptomatic HIV infection
- Paediatrics (0 days to <1 month)

Fair agreement
- Latin America

Suggest that the application of the final pathogen prioritization list to any of these cohorts could be **less beneficial** for improving patient clinical management outcomes.

Further possible MAPDx panels

- Advanced HIV (IA+NAAT)
- ABR resistance genes (IA+/-NAAT)
- Further febrile illness panels (IA+NAAT) more specific for:
  - Africa region
  - Asia region
  - Latin America region
- Sepsis (NAAT)
- Outbreak (IA+NAAT)
- Vaccine preventable diseases (IA+NAAT)
- HIV gen Dx+Mg (IA,NAAT,C+H)
- Pregnancy (IA,NAAT,C+H)
- High income country panels:
  - STAT lab tests (C+H)
  - clinic patient Mg (IA,C+H)
- Paediatric Dx+Mg (IA,NAAT+H)
- Routine care (IA,NAAT,C+H)
- Hospital OCP+IPD (IA,NAAT,C+H)
- Respiratory tract (NAAT)
- Meningitis/enchephalitis (NAAT)
- MSF wish list - various (IA,NAAT+C)

Abbreviations:
IA immunoassay, NAAT nucleic acid amplification test, C chemistry, H haematology, Dx diagnosis, Mg management

Test panels were based on different combinations of the following refs:

- SWKS pathogen sub-list analysis
- Literature reviews
- WHO recommendations
- FIND Menu Expansion Report
- MSF Diagnostic Packages
- And other additional references

Why Multi-Analyte Detection?

- Infectious disease testing requires both NAAT and immunoassays for many pathogens of interest (e.g. yellow fever)
  - Ideally this can be performed simultaneously on the same test cartridge with the same patient sample
- Supports syndromic patient management with testing panels that are normally limited by analyte type (NAAT, antibody, antigen, cells, etc.)
- Simplifies the number of instruments, streamlines supply, and reduces maintenance and training costs

Patients Presenting w/ SFWS

Study	Country	Percentage with SFWS	Mortality Rate SFWS	Mortality Rate Non-SFWS
Chart Review	Liberia	9.7%	17.5%	6.5%
Chart Review	Nigeria	13.5%	16.7%	7.1%
Epicentre Study	Uganda	5%*	Not calculated	Not calculated
Epicentre Study	Mali	7%*	Not calculated	Not calculated

*the denominator includes surgical and trauma admissions, not included in the Liberia and Nigeria numbers

- 4th most significant cause of hospital admission after malaria, LRTI, non-bloody diarrhea
- Mostly prescribed Ceftriaxone, followed by Amp+Gen, and Amoxicillin PO

Results of Modelling of SFWS in SSA

PREDICTED IPD CASES YEAR 2014	Pop
TOTAL	878,966,426

Severe Febrile Illness IPD Admissions (per 1,000 people)					Severe Febrile Illness IPD Admissions Total				
Low95	Low68	Median	Up68	Up95	Low95	Low68	Median	Up68	Up95
0.6	6.8	18.4	31.1	44.3	492,324	5,993,249	16,200,337	27,321,779	38,947,507

Severe malaria cases *	Non-malarial cases (only severe malaria removed)
Median	Median
1,234,013	14,738,103

*Severe malaria admission data extracted from: F. Camponovo *et al. Incidence and admission rates for severe malaria and their impact on mortality in Africa.* Mal J. 2017: 16 (1)

Lead: Ursula Dalrymple, University of Oxford – Malaria Atlas Project

MSF Clinician Survey

Methodology

- Survey of MSF field clinicians (doctors, clinical officers, currently working or who have worked with MSF in the field in the past 2 years).
- 9 questions about their experiences treating patients that fit the definition of SFWS in MSF hospitals, diagnostic tools, management outcomes, and diagnostic needs.
- Survey sent to 595 clinicians – 193 (32.4%) from 26 countries responded.

MSF Clinician Survey: SFWS vs specialization

Overall, 67.2% of respondents had treated patients matching the definition of SFWS.

Specialization	Yes SFWS	No SFWS	Total	%
No reported specialization	68	27	95	72%
Pediatrics	22	2	24	92%
Emergency medicine	11	5	16	69%
Infectious diseases	5	1	6	83%
Obstetrician	5	6	11	45%
Family doctor	3	3	6	50%
Tropical Medicine	3	2	5	60%
Epidemiology	2	1	3	67%
Internal medicine	2	6	8	25%
Public health	2	1	3	67%
Anesthesia	1	2	3	33%
Surgery	0	7	7	0%

Empiric Antibiotics: Survey

Management	Responses	
a. Empirical broad-spectrum antibiotic treatment.	85.4%	158
b. Antimalarial drugs	52.4%	97
c. Antipyretics	67.5%	125
d. Other symptomatic treatment	40.5%	75
e. Observation without treatment	11.8%	22

Antibiotic	#	%
Ceftriaxone	55	61.0%
Ampicillin + Gentamicin	18	20.0%
Metronidazole IV	12	13.0%
Cloxacillin	4	4.0%
Doxycycline	1	1.0%

Survey Conclusions

- MSF clinicians are using guidelines and tools to guide their diagnoses, but they want new and improved guidelines.
- Using some lab & imaging tools.
- The use of some basic tests such as CBC or liver tests are limited.
- Access to blood culture is limited.
- Broad-spectrum antibiotic treatment is the most common treatment among SFWS patients, esp with Ceftriaxone.
- There is a need to improve guidelines and diagnostic tools in the field to move from syndromic to etiological diagnoses.

Epicentre Studies: Background

- 2 studies on prevalence of bacteremia and pathogenic causes in children hospitalized with fever (Koutiala, Mali; Mbarara, Uganda)
  - Malaria smear microscopy, blood (and CSF) culture performed on site
  - 1 ml whole blood in citrate tubes frozen – used to search for other bacterial and viral pathogens in blood culture negatives

Results

- Uganda:
  - Most frequent overall: *S. aureus* > *S. pneumoniae*
  - Generally, diversity of bacteria isolated from patients with SFWS
- Mali:
  - Most frequent overall: non-typhi *Salmonella* >*S. pneumoniae*
  - While patients with malaria were mostly co-infected with NTS and patients with LRTI mostly infected with *S. pneumoniae* & *Haemophilus* spp, there was a diversity of bacteria isolated from patients with SFWS.
- Both: molecular testing didn't really reveal additional pathogens

What is the clinical value?

	First Line antibiotics	Changed Ceftriaxone	Changed ampicillin+Gen	Oubreak detection
Typhoidal salmonella	Ceftriaxone IV	No	Yes	Yes
Streptococcus pneumoniae	Ceftriaxone IV	No	No	No
Staphylococcus aureus	Cloxacillin IV	Yes	Yes	No
Non-typhoidal salmonella	Ceftriaxone IV	No	Yes	Yes
Escherichia coli	Ceftriaxone IV	No	No	No
Neisseria meningitidis	Ceftriaxone IV	No	No	Yes
Rickettsial spp	Doxycycline PO or Azithromycin	Yes	Yes	No
Klebsiella spp	Ceftriaxone IV	No	No	No
Leptospira spp.	Ceftriaxone IV	No	Yes	Yes
Brucella spp	Doxycycline PO or streptomycin	Yes	No	No
Orientia tsutsugamushi	Doxycycline PO or axithromycin	Yes	Yes	No
Haemophilus influenzae	Ceftriaxone IV	No	No	No
Burkholderia pseudomallei	Ceftazidime and Sulfamethoxazole	Yes	Yes	No
Pseudomonas spp	Piperacillin-tazobactam or ticarcillin-clavulanate	Yes	Yes	No
Acinetobacter baumannii	Imipenem	Yes	Yes	No
Dengue virus 1, 2, and 3	Routine antibiotics not recommended	Yes	Yes	Yes
Coxiella burnetii	Doxycycline PO	Yes	Yes	No
Histoplasma capsulatum	Liposomal amphotericin B or itraconazole	Yes	Yes	No
Lassa fever	Rivabirin	Yes	Yes	Yes
Enterococcus faecalis	Ampicillin + gentamycin	Yes	No	No
Enterobacter spp	Carbapenem	Yes	Yes	No
Borrelia recurrentis	Penicillin G.	Yes	No	No
Chikungunya virus	Routine antibiotics not recommended	Yes	Yes	Yes

Clinical value

- For 19 / 23 pathogens prioritized: treatment would change from empirical to more specific etiological management.
- Specific detection of some pathogens such as *Neisseria meningitidis* or Leptospira will help in the detection of outbreaks and facilitate implementing other measures such as vaccination.
- Detection of viral agents such as dengue or chikungunya will facilitate better management and supportive treatment, which should improve clinical outcome.
- Generates local surveillance data.
- No info on pre-test probability (prevalence) thus impedes correct test result interpretation.
- All negative result requires further diagnostic work-up and/or will still result in empirical Tx.

Diagnostic Gaps

Current/Pipeline	Gaps
Single analyte tests (immunoassays)	RDTs exist but most not quality assured and with unknown or poor performance; not capable of nucleic acid amplification
Single analyte tests (molecular)	High prices, not adequately robust, some pathogens require molecular and serological detection for definitive Dx
Lack of comprehensive multiplexing, low sensitivity	Current multiplexes lack tests adapted to epidemiology of LMICs; not adequate for differential diagnosis of SFWS; low sample volume a problem for bacterial detection
Closed systems	Test menus locked in, preventing flexibility or adaptation

The laboratory-based tests available for the identification of the pathogenic causes of febrile illnesses and their antibiotic resistances/sensitivities are not easily implemented in RLS.

Projects with access to bacteriology in MSF programs = paucity compared to need

Many thanks!

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  - MSF operational centers and field sites
  - MSF Epicentre
  - Project advisory and steering committees
  - FIND Diagnostics