Global perspectives of the AMR threat and the need for diagnostics: MSF's perspective

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And

Non-Malarial Febrile Illness (NMFI):

a.k.a. what to do when the test is negative

Malaria Diagnosis

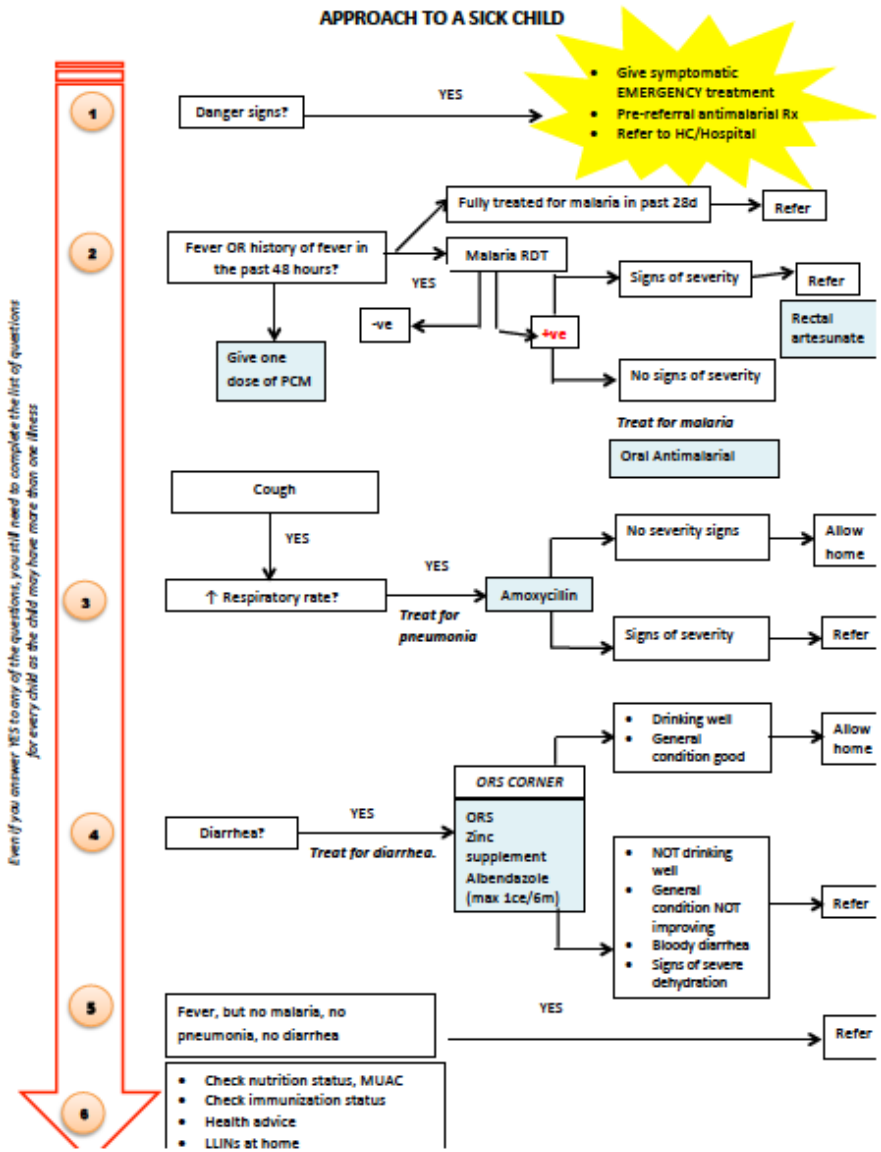
- Clinical diagnosis of malaria based on fever (*Pfeffer 2008)*:
  - *Low sensitivity: 75%*
  - *Low specificity: 41%*
- Differential diagnosis with RTI, UTI or severe conditions (pneumonia, sepsis, meningitis, typhoid: NMFI)
- Mainstays of diagnosis:
  - *microscopy ('gold standard' - thick and thin films)*
  - *Rapid Diagnostic tests (RDTs) - detect specific antigens (proteins) produced by malaria parasites*
- WHO "T3" initiative – test, treat, track

197 million
patients worldwide were tested for malaria by microscopic examination.

62%
of patients with suspected malaria in the WHO African Region received a diagnostic test in public health facilities.

World Malaria report 2016

Syndromic approach to fever management

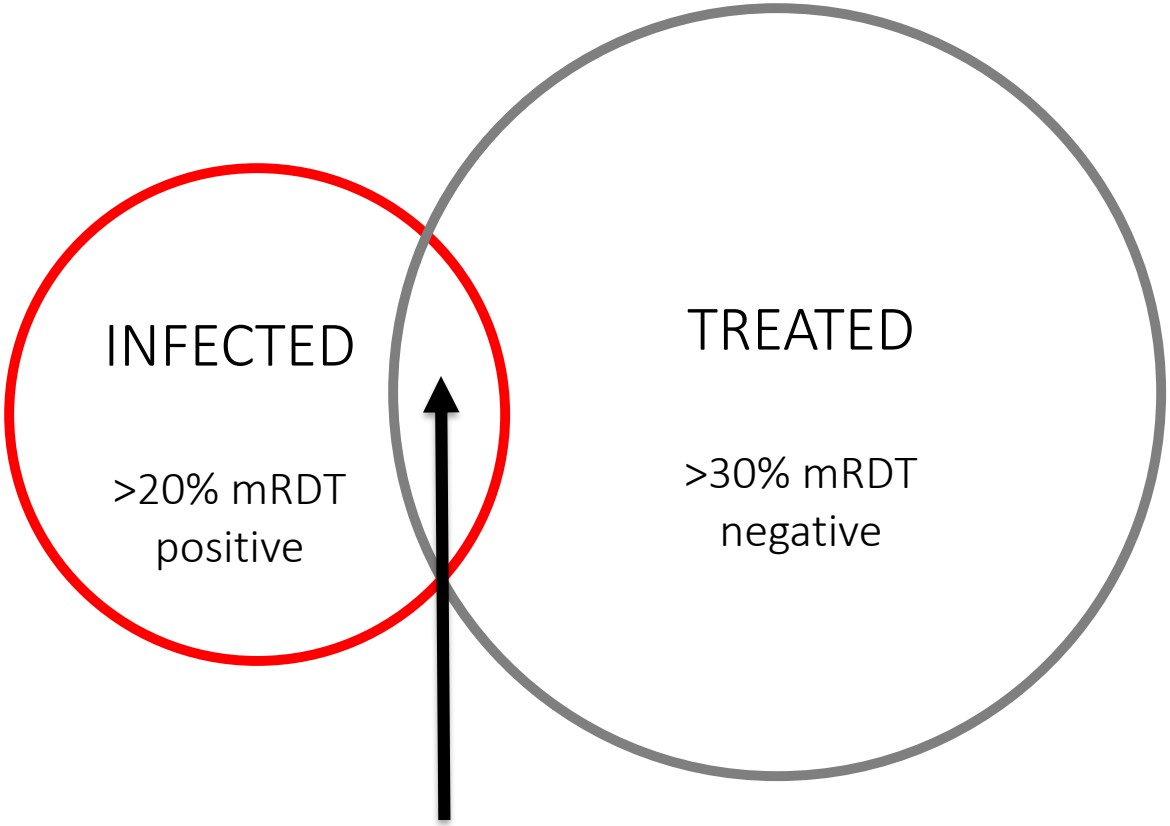


- Management of the three most common childhood illness
- Integrated Management of Childhood Illness (IMCI) and Integrated Community Case Management (ICCM)
- Shown to increase care seeking and lower cost of care
- Reduced wastage of ACTs: CHWs workers follow mRDT results

(*Rao et al 2013 Trends in Parasitology)*

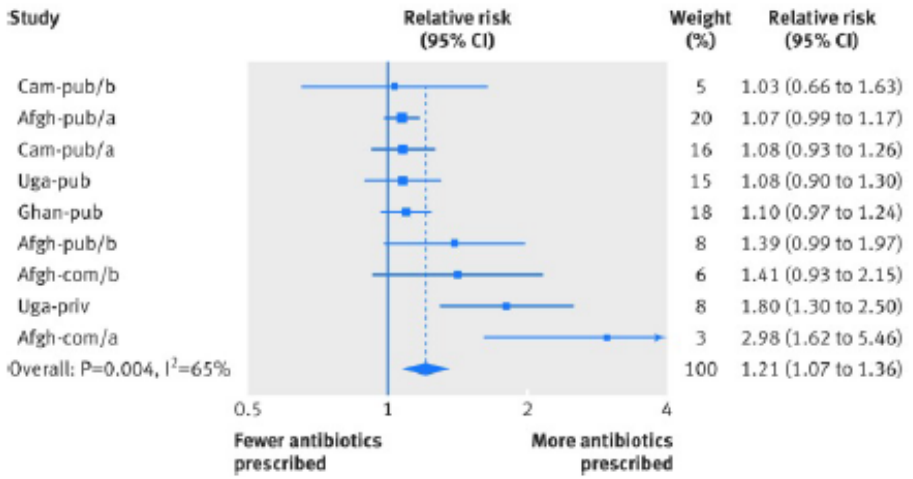
Over and under treatment of fever

- >75% prescribed an antimalarial or an antibiotic
- lower antimalarial prescriptions in mRDT negative pts offset by higher antibiotic prescription
- <25% received antipyretics



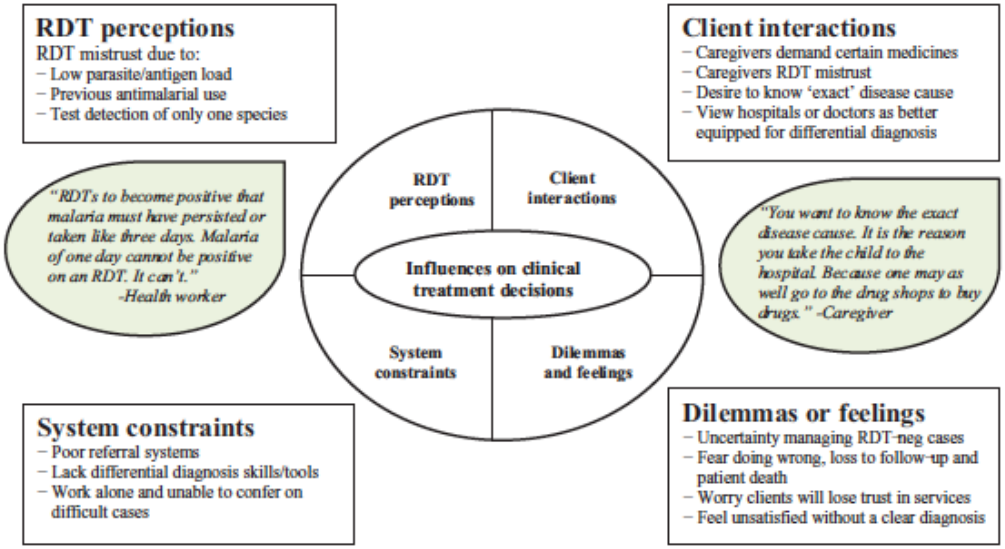
(Bruxvoort et al 2017 AJTMH)

Antibiotic over-prescription with a diagnostic-based approach



Hopkins et al BMJ 2017

- 69% of test negative patients prescribed antibiotics (21% higher than if no mRDT available)
- Patients with negative test received more antibiotic prescriptions than patients with positive mRDT: penicillins, tetracyclines, metronidazole, trimethoprim



Johansson et al GHA 2016

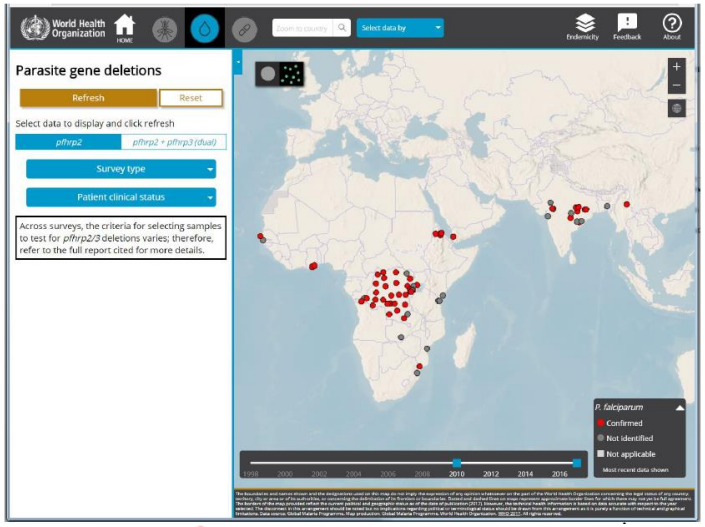
- 59% over-treatment with antibiotics when RDT negative
- Also 18% under-treatment – where antibiotics were recommended but not prescribed

Malaria false positives and false negatives ….

Rapid testing - time to negative *(Grandesso et al 2016 Malaria J)*

	Mbarara		Kazo	
	Median	**[95% CI]**	**Median**	**[95% CI]**
SD Bioline HPR2	35	[28 - 42]	42	[42 - NC]
CareStart HPR2	>42	[42 - NC]	42	[35 - NC]
CareStart pLDH	2	[2 - 2]	2	[2 - 3]

HRP2/3 deletions *(WHO Malaria threat map 2017)*



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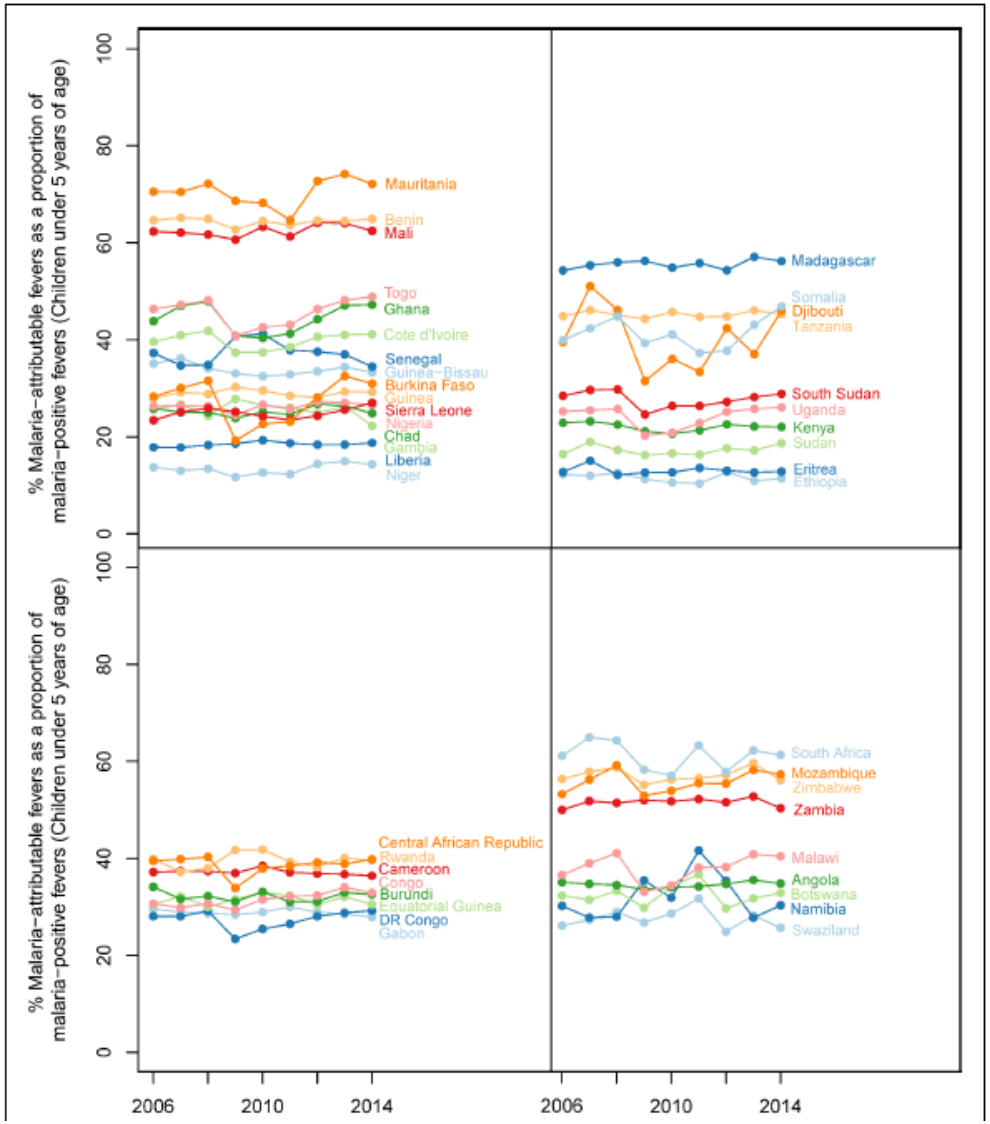

Even if there is a malaria infection – is it really malaria?

- Contribution of *P. falciparum* malaria to malaria-positive febrile illness amongst African children
- 35.7% all self reported fevers are positive for malaria infection
- 18% of those (10% all fevers) are causally due to malaria

(Dalrymple et al 2017 eLife)

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Beyond malaria: causes of fever

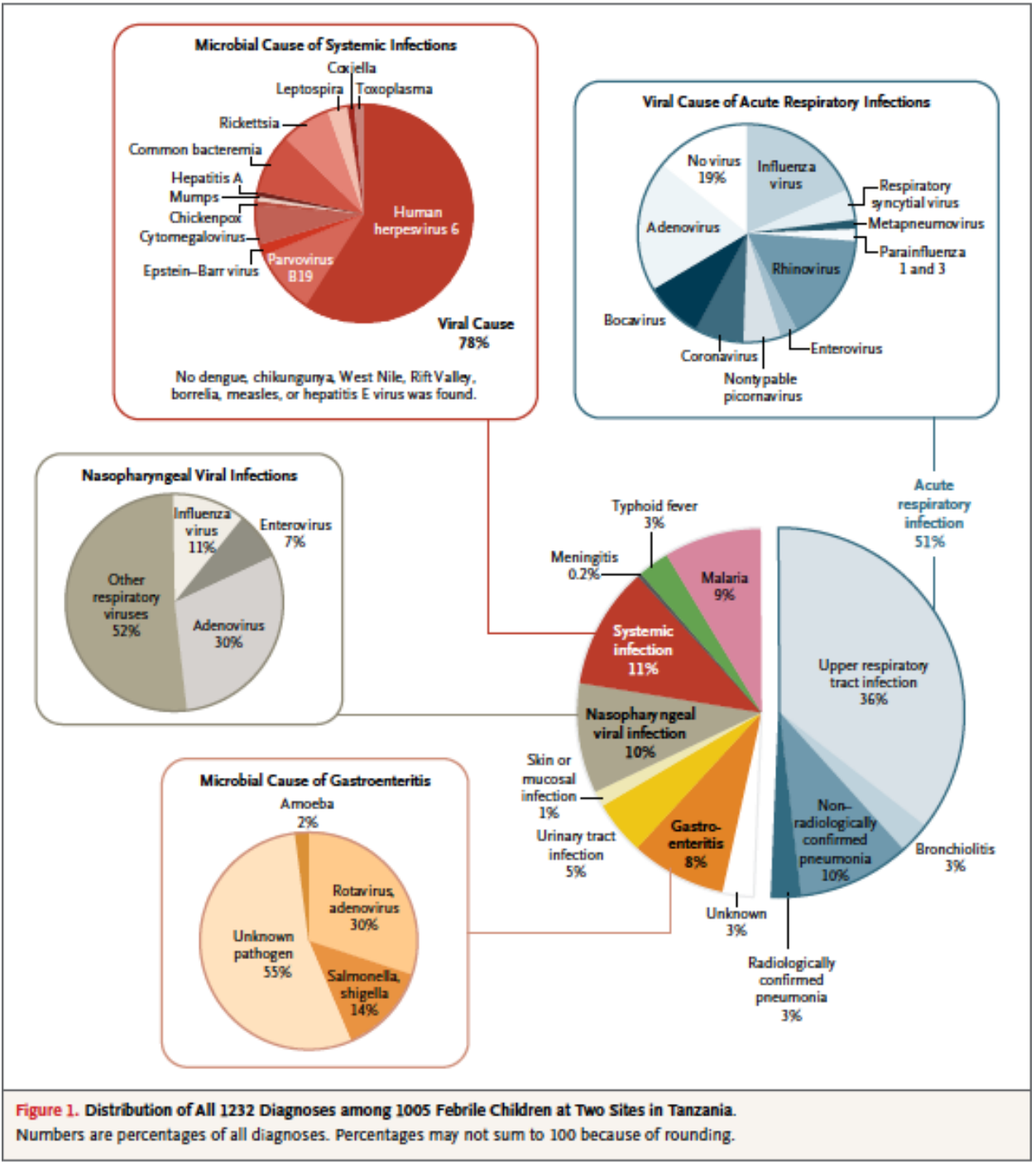
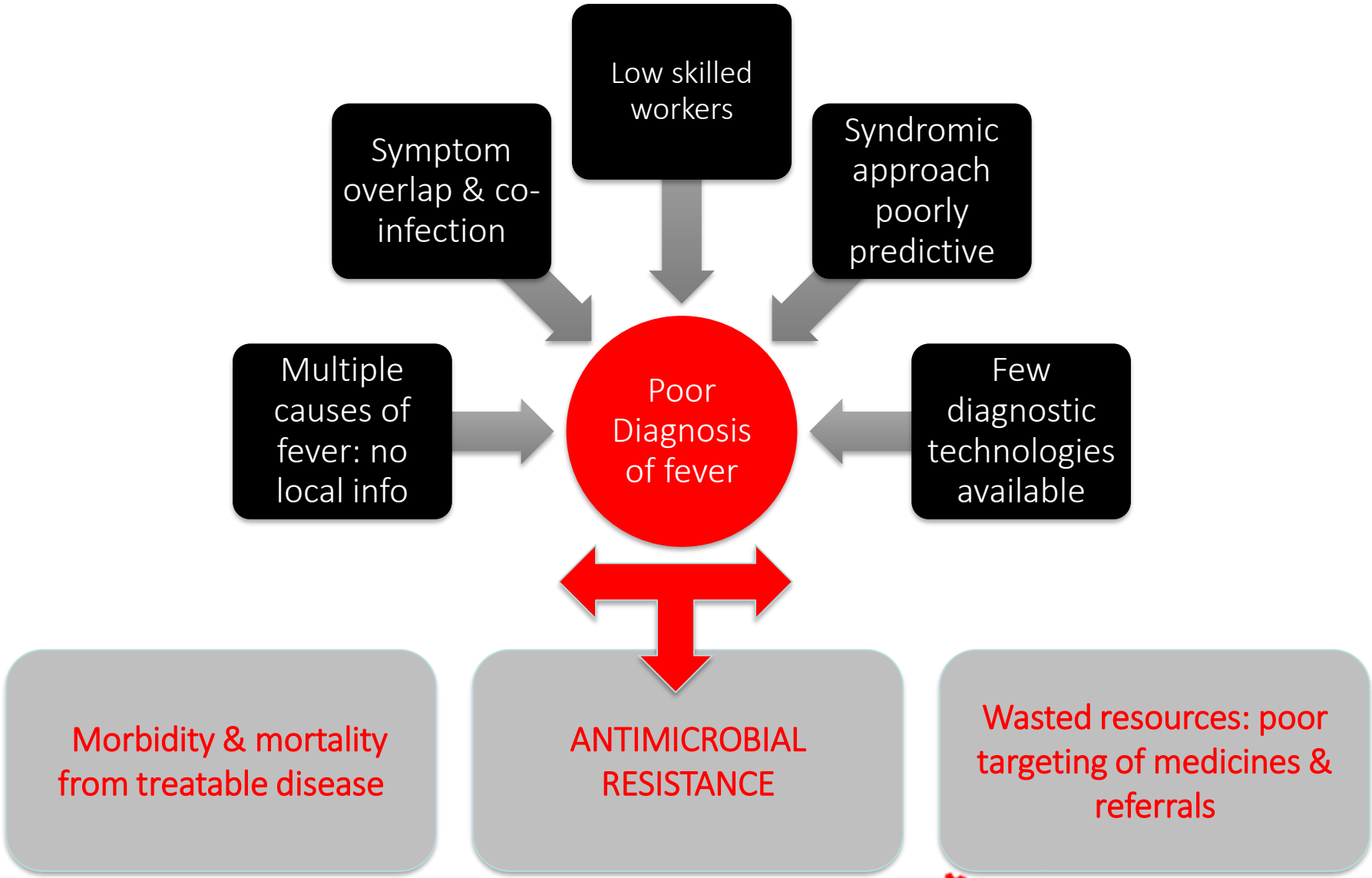


Figure 1. **Distribution of All 1232 Diagnoses among 1005 Febrile Children at Two Sites in Tanzania.**
Numbers are percentages of all diagnoses. Percentages may not sum to 100 because of rounding.

- 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)


Low skilled workers
Symptom overlap & co-infection
Syndromic approach poorly predictive
Multiple causes of fever: no local info
Poor Diagnosis of fever
Few diagnostic technologies available
Morbidity & mortality from treatable disease
ANTIMICROBIAL RESISTANCE
Wasted resources: poor targeting of medicines & referrals

MSF perspective on rapid diagnostics: 1st reduce morbidity & mortality and 2nd stopping unnecessary use of antibiotics

- Tests should be for clinical impact i.e. improve patient management
- Conundrum: proportion of patients benefiting from antibiotic therapy increases with disease severity and thus health system level i.e.

  primary care level < outpatient < inpatient
- BUT in order to increase access to care to a population – treatment is expanded at a peripheral level (where antibiotics are widely prescribed) which creates a huge drug pressure that can drives resistance
- Diagnostics can help avoid inappropriate treatment (albeit need accompanying guidance)
- Enforcement of drug regulations, IPC + stewardship important, but also need RDTs to move away from empirical diagnosis
- “Ultimately what we want are high quality, affordable rapid diagnostics that can be rolled out as widely as possible.”

What do we need?

1. **Bacteria/non-bacteria** - especially in the context of co-infection: host biomarker(s)
2. **Triage** for referral to hospital: host biomarker(s)
3. **Pathogen identification** (to use more narrow spectrum Antibiotics, currently only malaria in widespread use)
4. **Resistance or sensitivity** tests (to use 1st line Antibiotics or not)

Community:

- Potential for highest impact especially bacteria vs non-bacterial given large numbers
- Need to be of high specificity: ≈25% seek care for fever at health facility > ≈10% will be sent to OPD of a hospital > ≈10% will be admitted with severe disease – to identify this group at an early stage any test must be highly specific
- Specific TPPs need to based on prevalence of disease at this level

Hospital:

- Most studies in this context rather than at community level
- Impact of tests here more on mortality than resistance (low numbers of patients)

Biomarker test: to distinguish bacteria from non-bacteria

We know what we want: published expert consensus TPP including:

- Target population: non-severely ill, non-malaria
- Target setting: community health centres, informal health settings
- Staff training: <2 days
- SE: >90%; SP: >80%
- Works in challenging environments:
  - time-to-result <10 min (but maximally <2 hrs)
  - storage conditions 0–40°C, 90% non-condensing humidity, minimal shelf life 12 months
  - operational conditions 5–40°C, 90% non-condensing humidity
  - minimal sample collection needs (50–100µL, capillary blood)

(*Dittrich et al 2016 PLoS ONE*)

Challenges of biomarker tests for fever management in LMICs

- New biomarker tests not validated in LMICs
- Few studies for CRP and PCT indicate they are influenced by co-morbidities (HIV, malaria, parasites, malnutrition (*Page et al 2013 Paediatrics*)
- Lack of reference tests (definitive microbiological diagnosis) for comparative analysis
- Lack of regulatory clarity (clear guidance from regulatory bodies on biomarker tests)
- Lack of compatibility of clinical trial needs with intended use cases (e.g. “Total febrile population (including neonates) presenting with fever”)

(Escadafal et al 2017 Diagnostics)

Improving development and deployment of RDTs in LMICs

- Enhance profile of diagnostics globally and nationally
- Fix market failures (by ending the reliance on the expectation of high prices and monopolies to pay for innovation; thus better ensure public return in R&D public investment through national and global R&D funding mechanisms as committed by governments already in UN political declaration)
- Promote locally driven, patient-focused development
- Have a more coherent regulatory environment
- Develop deployment packages (within a programme)
- Strengthen quality assurance systems
- Engage with private sector (large part of the market, not just public sector)
- Boost local R&D and manufacturing (at least for higher volume tests)
- Develop more flexible diagnostic tools (differential (multiplex), upgradable, open systems)
- Support surveillance

(Academy of Medical Sciences 2016 Improving the development and deployment of RDTs in LMICs. Workshop report)

Potential to improve case management and reduce antibiotic prescription

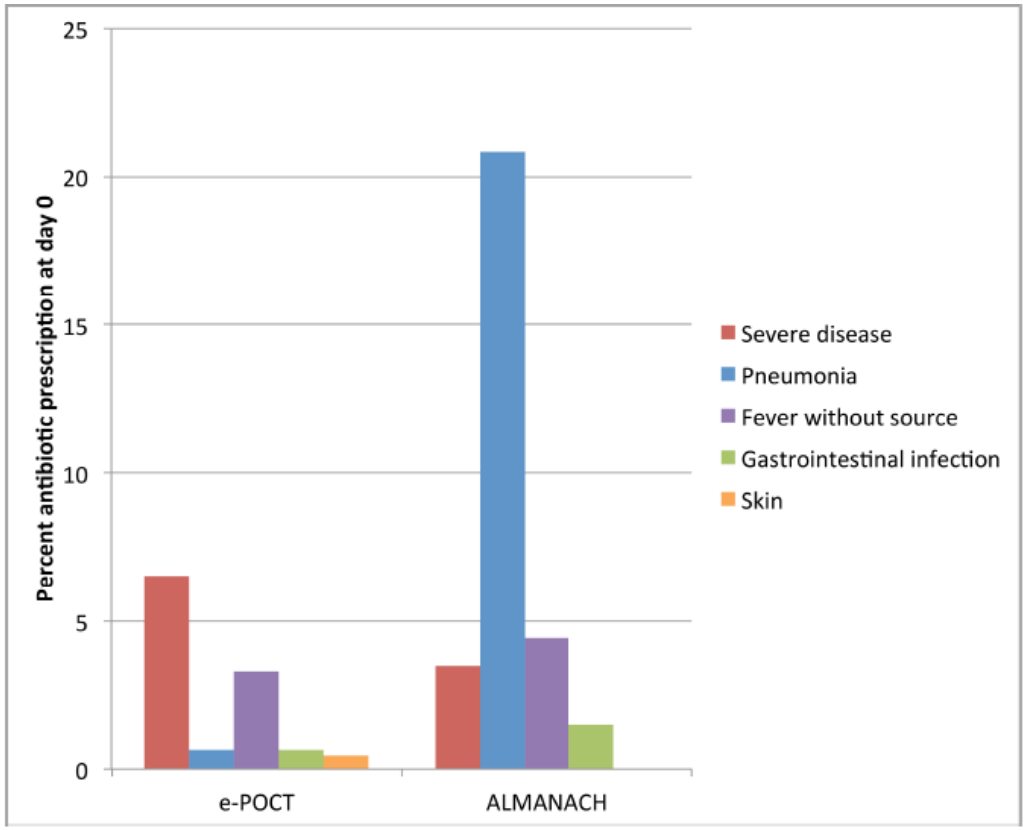


Fig 6. Percent of patients with antibiotic prescription at day 0 according to reason for antibiotic prescription and study arm. For e-POCT and ALMANACH, antibiotic prescription was determined by the algorithm classification.

- e-POCT: IMCI e-algorithm plus POCTs: CRP, PCT, glucometer vs standard e-algorithm (ALMANACH) vs routine care
- Compared to routine care: 49% reduction in RR clinical failure and decreased antibiotic prescription from 94.9% to 11.5%
- Compared to ALMANACH: 43% reduction in RR clinical failure and decreased proportion of antibiotic prescription 11.5% vs 29.7%
- e-POCT: most common indication was severe disease *vs* ALMANACH was non-severe respiratory disease

Keitel et al 2017 PLoS Med

Checklist for strategic priorities …..

A global health problem?	Is this a highly prevalent disease or medical issue associated with significant levels of death, morbidity, disability and suffering	✓
A humanitarian dimension?	Does it affect people in MSF/humanitarian contexts? Is there an equity dimension i.e. do the poorest or most vulnerable suffer disproportionally?	✓
Neglected dimension?	Does global focus on this topic neglect MSF/humanitarian settings?	✓
Potential for change?	Are there feasible ways for MSF to improve outcomes?	✓
Wider impact?	Can this have impact beyond the immediate sites MSF works in e.g. national and global health policy and practice?	✓

Thank you

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