Current Status of Rapid Diagnostic Tools Beyond Malaria

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Presentation Outline

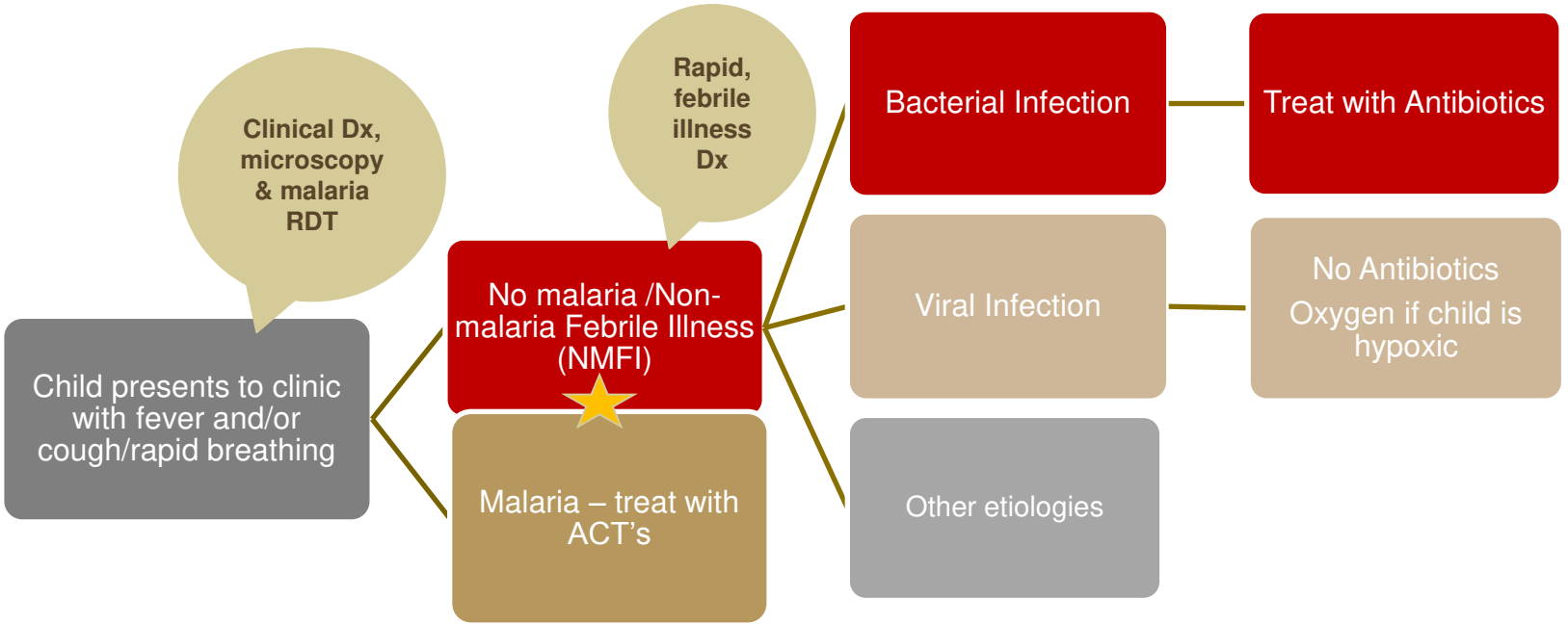
- **Understanding the etiology of fever beyond malaria**
- **Rapid diagnostic tools beyond malaria**
  - Brief overview of the diagnostic landscape
    - Pneumonia
    - Other pathogens associated with non-malarial fever
- **Prioritizing the need for specific diagnostic tools beyond malaria**

Why Consider RDT's Beyond Malaria?

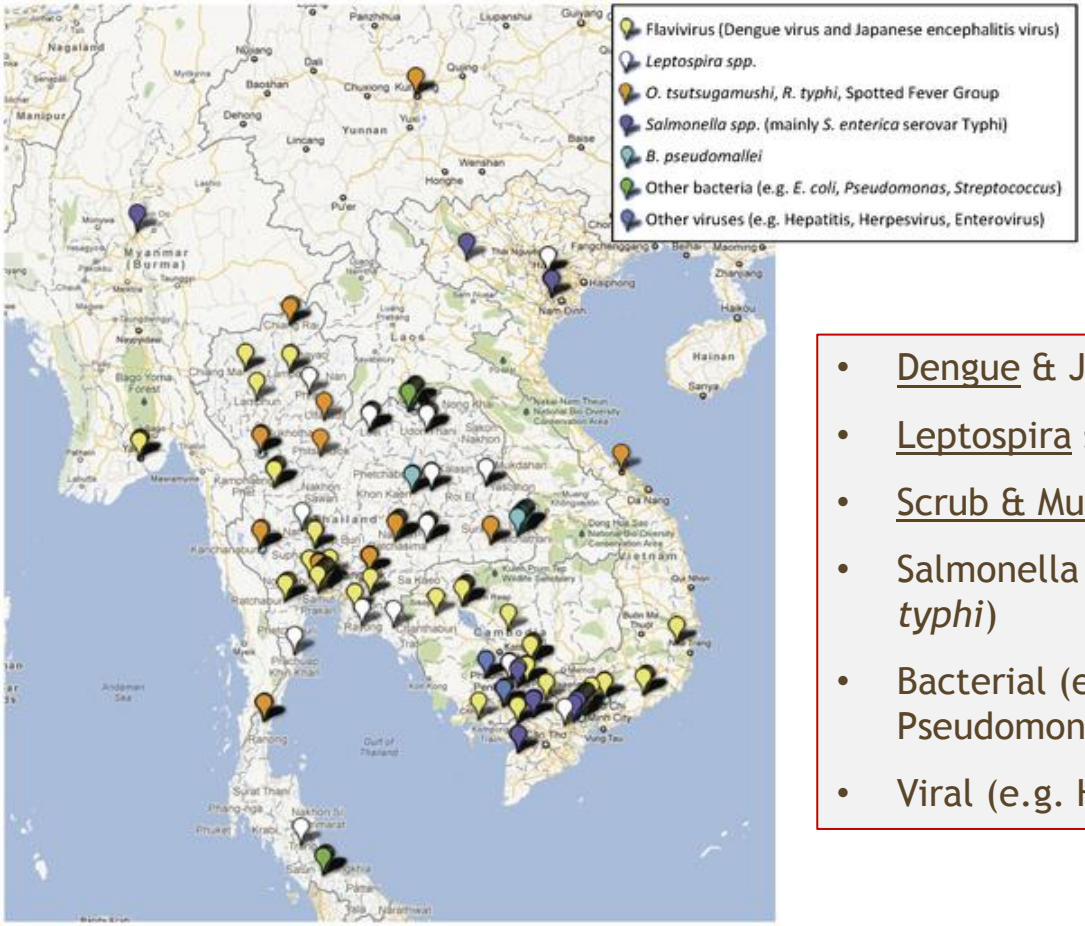
- Gething et al., (2007) estimated that 57% of the 182 million children presenting with fever to governments supported clinics in Africa do not have a malaria infection, and in some countries that proportion is greater than 90%
  - Highlights the potential benefits of a robust diagnostic for appropriate case management and drug stocking
- D'Acremont et al. (2010) demonstrated that malaria is cause of fever in only 9% of febrile children presenting to a clinic in Tanzania
- RDTs for non-malarial febrile illness should ideally meet the World Health Organization's ASSURED criteria
  - Affordable
  - Sensitive for the disease it is detecting
  - Specific
  - User friendly
  - Robust
  - Equipment free
  - Deliverable to those who need the test

Peter W. Gething et al., (2010) Plos Med. 7(7); D'Acremont et al., 2010 ASTMH

Diagnosis of Fever beyond Malaria



Etiology studies will help inform what diagnostic tests are needed

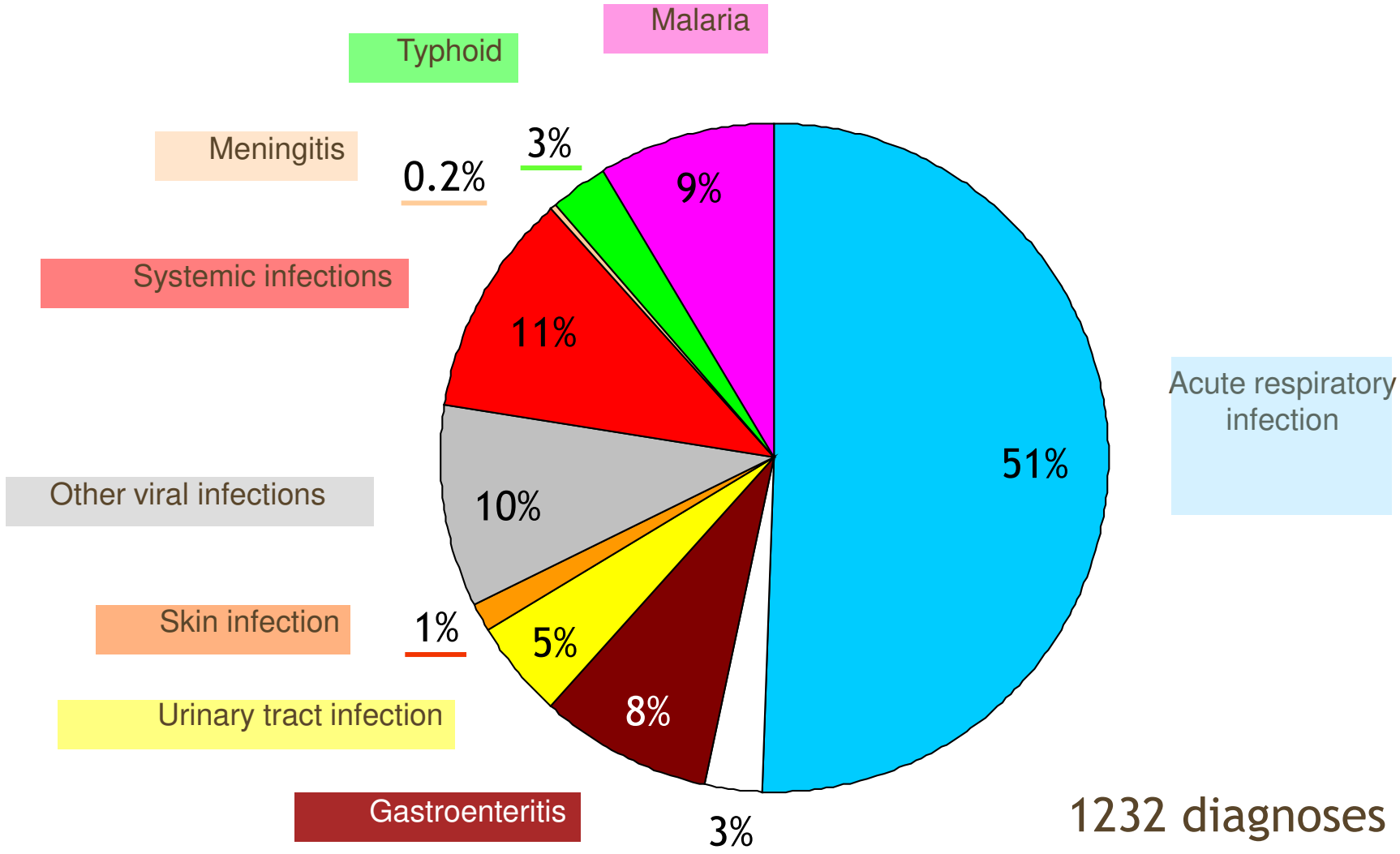


- Dengue & Japanese encephalitis virus
- Leptospira spp.
- Scrub & Murine Typhus
- Salmonella spp. (mainly *S. enterica serovar typhi*)
- Bacterial (e.g.. E. coli, Streptococcus, Pseudomonas)
- Viral (e.g. Hepatitis, Herpevirus, Enterovirus)

Acestor N, Cooksey R, Newton PN, Ménard D, et al. (2012) Mapping the Aetiology of Non-Malarial Febrile Illness in Southeast Asia through a Systematic Review—Terra Incognita Impairing Treatment Policies. PLoS ONE 7(9): e44269. doi:10.1371/journal.pone.0044269

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0044269

Etiologies of fever in 1005 Tanzanian children



1232 diagnoses

D'Acremont *et al*, ASTMH 2010

Using rapid diagnostic tests to select ACTs or Antibiotics – *Malaria vs. Bacterial Pneumonia*

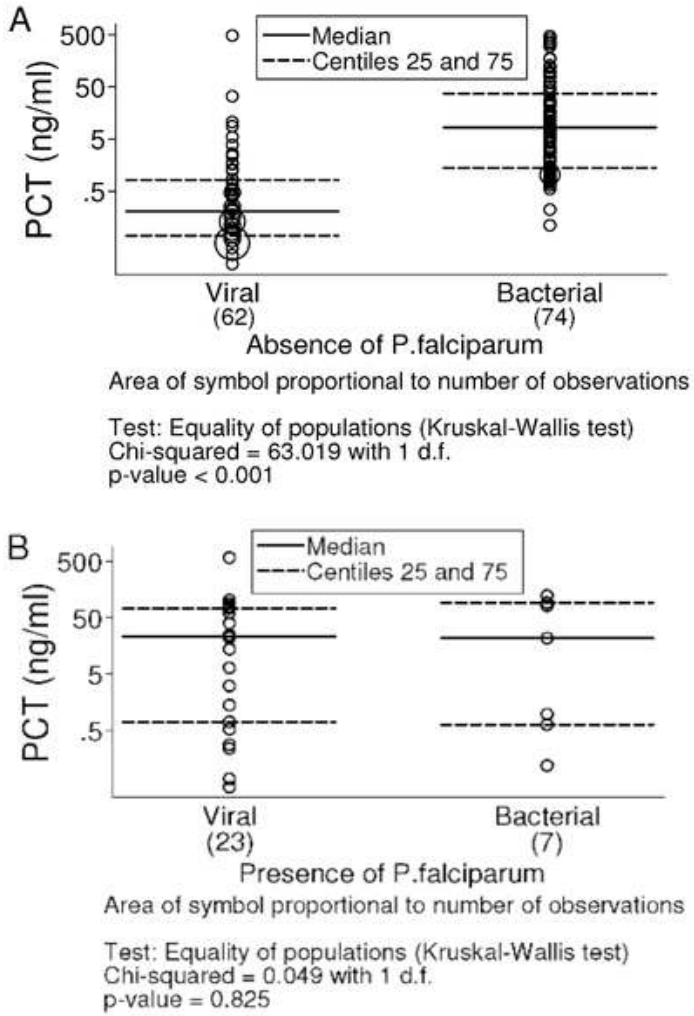
- **Molecular approaches exist but are technically too sophisticated for our populations of interest**

- **Host response biomarkers**

- *Existing Markers*
  - Potential to add a second reaction line to existing mRDTs - cost implication unknown
    - Historically, extensive focus on CRP & PCT, especially in developed world settings
      - Meta-analysis (Simon et al., 2004): Sensitivity of PCT vs. CRP = 92% vs. 86%, with comparable specificities
    - PCT – levels elevated during gram +ve and –ve infections, malaria, invasive fungi, legionella, NOT viruses, chlamydia. **Malaria presents major caveat**
      - Use mRDTs to provide specificity for malaria
    - PCT – potentially good marker of sepsis (95% sensitivity, 97.3% specificity (Kim & Han , 2010)
- *Promising Biomarker Research*
  - Oxford University (Climent Casal Pascal) – biomarker to differentiate bacterial vs. viral etiologies in pneumonia with promising sensitivity and specificity *(unable to discuss more at this time)*
  - Prognostic marker of severity – use to refer children to secondary level care for IV antibiotics and/oxygen

Simon et al., (2004) Clin Inf Dis 39 (2) 206-217; Kim KE & Han JY (2010). Korean J. Lab Med 30 (2) 153-9
Prilutsky et al., (2011) Anal Chem 83 4258-4265

Distribution of procalcitonin (PCT) concentrations in viral and invasive bacterial infections



Díez-Padrisa N, Bassat Q, Machevo S, Quintó L, et al. (2010) Procalcitonin and C-Reactive Protein for Invasive Bacterial Pneumonia Diagnosis among Children in Mozambique, a Malaria-Endemic Area. PLoS ONE 5(10): e13226. doi:10.1371/journal.pone.0013226

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0013226

Beyond RDTs, other tools could help improve malaria vs. pneumonia differential diagnosis….

- **Improve clinical algorithm**
  - Improved respiratory rate timer (also increases in malaria)
    - Automated on cell phone device
      - Combined with pulse oximetry
        - Pulse oximetry is sensitive & specific measure of hypoxemia – important in identifying those children needing referral to secondary level care
  - Chest auscultation (*in development*)
    - Use of stethoscope like device capable of distinguishing between pneumonia, other respiratory infections & wheeze

Diagnostic Tests for Bacteria

Disease	Disease / Diagnostic	Diagnostic Performance
Typhoid (*Salmonella enterica serovar typhi*)	- Gold standard used, blood culture, only has 50-60% sensitivity - Bacteria is sequested in lymphocytes - Rapid serological tests available but reported performance from multiple studies is poor K Keddy et al.,(2011) Bull. WHO 89: 640-647	- TyphiDot: 75% sensitive 60.7% specific PPV=54.3%, NPV=77.8% - Tubex: 73% sensitive, 69% specific PPV = 54.1%, NPV = 83.6% - Widal: 87.3% sensitive, 6.9% specific PPV = 20%, NPV=67.1%
Streptococcus pneumoniae	- Difficult to access sample deep in lung - Challenge of disease vs carriage - Gold standard of blood culture only positive in 10-15% of cases	- Binax Rapid Diagnostic Test • False results in children (specificity as low as 13% reported) • Looking at new antigens (e.g. PcpA) - Laboratory based approaches using urine are in development
Klebsiella pneumoniae	- Gram negative bacterium - Causes pneumonia but also UTI's & septicemia (important in neonatal infections)	- No Commercially available rapid test - Development of serological test in Malaysia using Capsular Polysaccharide Antigen • Only 76% sensitive based on 86 samples - PCR based tests under development
Moraxella Catarrhalis	- Gram negative bacteria, class acinetobacter - Common cause of otitis media, sinusitis and conjunctivitis in children , respiratory infection in adults https://catalog.hardydiagnostics.com/cp_prod/.../**CatScreen**.htm	- CatScreen™ (Hardy Dx) - rapid test for detection of the enzyme butyrate esterase in bacteria from culture

Diagnostic Tests for Viruses

Disease	Disease / Diagnostic	Diagnostic Performance
Dengue	- Estimated 50-100 million cases/ year - Rapid antigen based test (NS1) for early detection of Dengue (Alere Dx) - Rapid serological based tests - Gold standard of RT-PCR used Fry et al., (2011). PLoS Negl Trop Dis 5 (6) 10: 137	- Sensitivity 62.9% (95% CI 62.8% - 75.6%) - Specificity 96.7% (95% CI: 82.8 – 99%) - **If NSI test is used in combination with anti-glycoprotein E IgG & IgM serology sensitivity increases to 93%** - Multiple companies – PanBio, InBios
Japanese Encephalitis	- Estimated 500,000 cases and 10,000 deaths per/year - Commercially available ELISA based tests - Gold standard – platelet reduction neutralization James Robinson et al., (2010). Am J Trop Med Hyg 83 (5) 1146-1155	*Panbio:* Sensitivity - 33% (CI 24-44 %) Specificity - 98.8% (CI 97- 99%) PPV 86%, NPV = 97% *Inbios JE Detect* Sensitivity - 56% (CI 44-67%) Specificity - 96.9% (CI 95-98%) PPV 76%, NPV - 93% *Xcyton JEV Chex* Sensitivity - 19% (CI 12-28%) Specificity - 97.2% CI (95-98%) PPV 59%, NPV 95%
Rotavirus	- Multiple rapid diagnostic products for use with stool sample/swab for detection of group A rotavirus – all perform very well - Worldwide > 450K children under five die/year - Vaccine available	*IP-ROTA V* Sensitivity 97.2%, Specificity 100% *Dipstick Eiken Rota* Sensitivity 95.8%, Specificity 93.3% *Rota-Adeno* Sensitivity 88.7%, Specificity 100%

Diagnostic Tests for Other Bacteria & Protozoa

Disease	Disease / Diagnostic	Diagnostic Performance
Scrub Typhus (*Orientia tsusugamushi*)	Important febrile pathogens in Asian region - Scrub Typhus - Gram negative alpha- Proteobacterium - Multiple commercially available RDTs – performance varies between product/study - Weil Felix Test is standard serological test – but notoriously unreliable Blacksell et al., (2010) Am J Trop Med Hyg 83 (2) 385-388	- *IgM based ICT - (PanBio)* Sensitivity 39.1 (95%CI-34.1-44.2%) Specificity 99.5% (95%CI=98.7%-99.9%) - Murine Typhus (Ricketssia typhi) *- Immunoblot Assay* Sensitivity 54.6% (95%CI 49.1-60.0%) Specificity 94.1% (95%CI 92.0-95.7%) *InBios – has IgM test as well as IgG for Scrub Typhus*
Ameoba – *Entameoba histolytica*	- Real time PCR most sensitive method for diagnosis - Rapid point of care test for detection of antigen in stool - Gold standard - ELISA Megan Leo et al., (2006) J. Clin Micro 44(12) 4569-4571	- *TechLab Inc (Blacksburg, VA)* Antigen based test Sensitivity 97% Specificity 100% - *Rapid serological test* Sensitivity 89-100% Specificity 95%
Leptospirosis	- Zoonotic infection caused by spirochete - Current gold standard, microscopic agglutination test (MAT) Mary D. Baiani et. al (2003). J. Clin Micro. 41 (2) 803-803	- *IgM dipstick (Royal Tropical Institute)* Sensitivity 93.2% Specificity 89.6% - *Igm Dot - ELISA dipstick test (Intregrated Dx, Baltimore)* Sensitivity 92.5% Specificity 98.8%

Other Diseases of Concern / Consideration

- **Hepatitis**
  - Hepatitis B – multiple rapid diagnostics tests for HBsAg
  - Hepatitis A – Anti-Hepatitis A virus IgM rapid test – 100% sensitivity & specificity (IVI, Korea)
  - Hepatitis C – OraQuick® HCV Rapid Antibody Test - Sensitivity > 99% , Specificity 99.9%
  - Hepatitis E – Assure HEV IgM rapid test - 93% sensitivity, 99.7% specificity
- **Enterovirus –** few serology tests, but mainly molecular
- **Cytomegalovirus** – IgM & IgG rapid test
- **RSV** – Binax Now RSV
- **Meningitis –** rapid IgM dipstick – 33% sensitivity, 99% specificity
- **African Trypanosomias (HAT)**
  - Antigen detection test – FIND & Standard Diagnostics (Korea)

Summary

- **Many pathogens contribute to non-malarial febrile illness**
  - Rapid diagnostic tests exist for some of these pathogens
    - Variable performance data based on robustness of evaluation
- **What are the critical rapid diagnostic tests needed?**
  - Informing drug treatment decisions
    - Determine spectrum of organisms susceptible to a particular antibiotic and/or need for alternative treatment regimen
    - Prioritize based on prevalence and disease severity
  - Cost a key factor - diagnostic could exceed cost of treatment
  - Willingness of multiple constituents to accept results of additional test result
- **Looking to the future – multiplex rapid diagnostic platform vs. multiple rapid tests**
  - Malaria, dengue, bacterial/viral, severity marker…….

Thank You

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