Update on Febrile Illness Rapid Diagnostic Tests Research & Development

Diagnostic Tests for Pneumonia & Other Severe Bacterial Diseases

Deborah Burgess, PhD
October 20, 2011

BILL & MELINDA GATES foundation

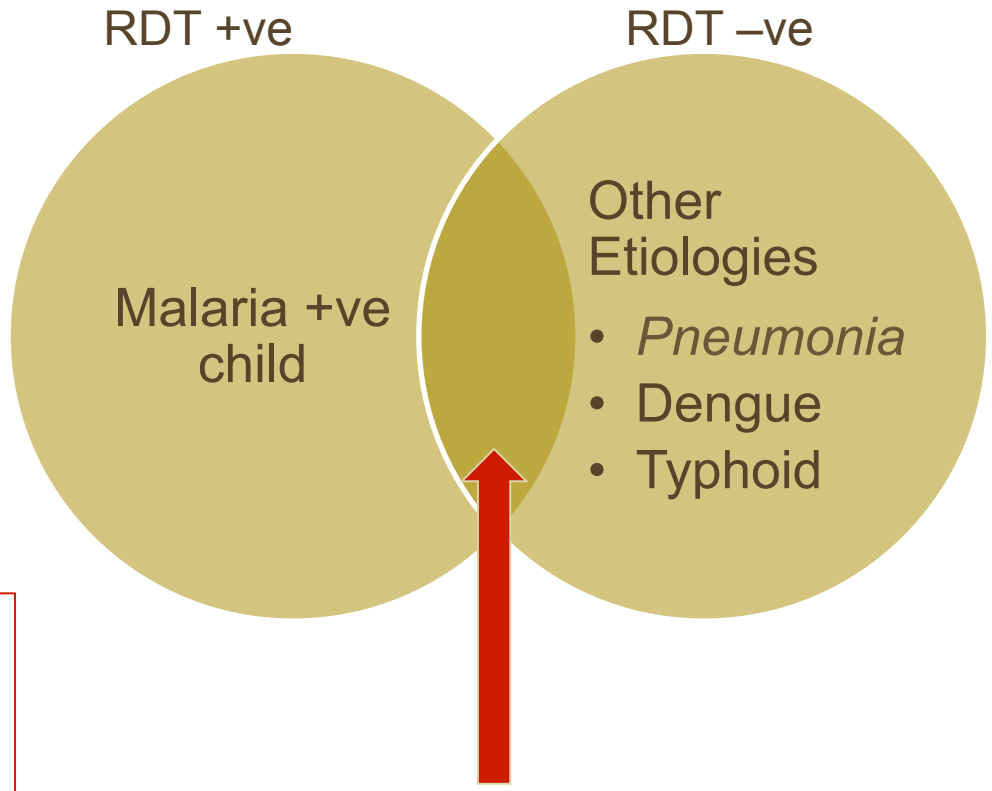
Presentation Outline

- Diagnosis of the febrile child
  - Multiple etiologies & challenges in diagnosis
- Diagnostic Opportunities
  - Differential diagnosis of malaria & pneumonia
  - Diagnosis of severe pneumonia & those likely to progress
- Translating biomarker research into test development

Febrile Illness: a diagnostic challenge

Sick child presenting with fever and/or difficulty breathing

Test with malaria RDT



In Uganda: 50% of all visits with a diagnosis of malaria are probably incorrect

In 64.6% of Ugandan children (n=186) with a diagnosis of pneumonia, a clinical diagnosis of malaria was also recorded

Source: APUA, 2010

Pneumonia: a global health problem

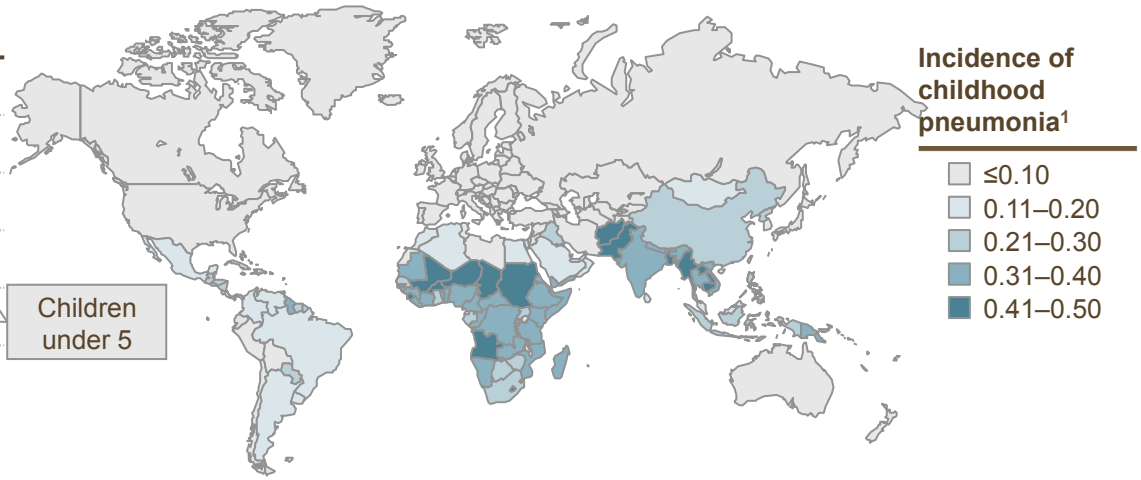
Overview:

- Vast majority of disease burden in developing world
- **Difficult to diagnose**
  - Affected tissue, lower lungs, not accessible to sampling
  - Blood culture, gold standard diagnostic method for invasive pneumonia, has low sensitivity (10-12%)
  - Carriage – presence of commensal (accidental) organisms
  - WHO Guidelines for pneumonia methods outdated (e.g. reading of X-rays)

Disease burden and geographic distribution

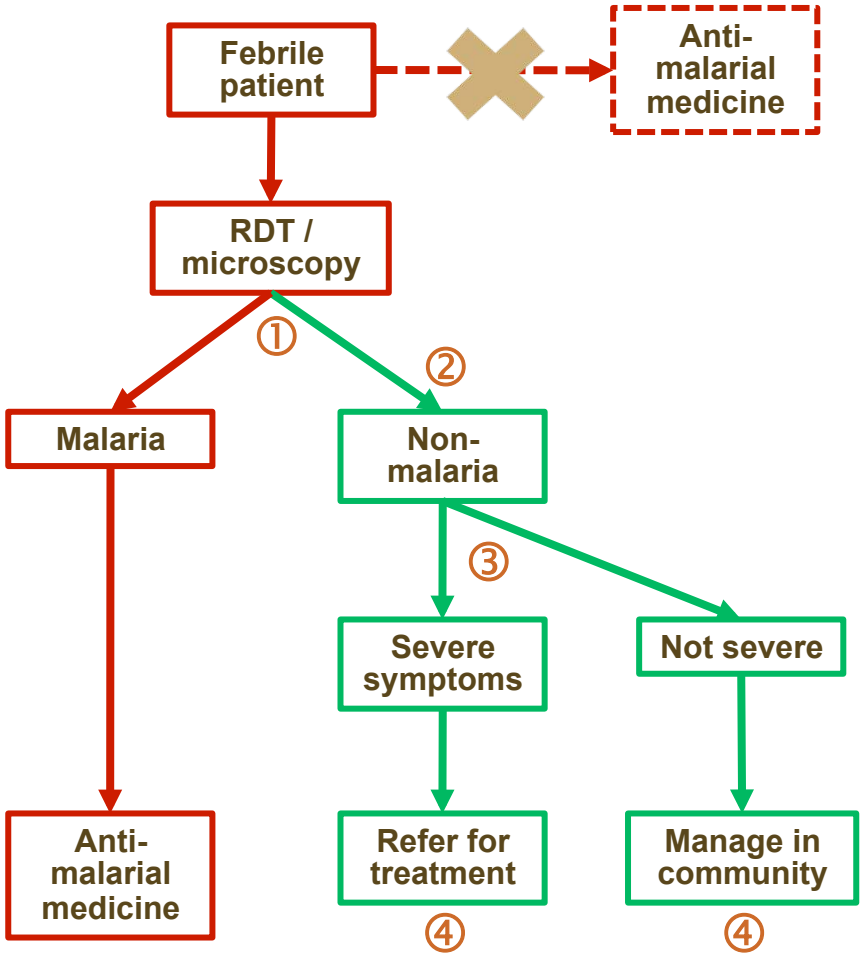
Global burden of disease (M)

At risk	Global
Prevalence[1]	--
Incidence[1]	156 (10% severe)
DALYs[2]	94.5
Deaths[3]	1.8
Geographies bearing main impact[1]	• 97% cases in <5 years in developing world • >70% deaths in Sub-Saharan Africa, SE Asia



1. Incidence in children <5 years; Rudan, Epidemiology and etiology of childhood pneumonia; note: lower respiratory infections responsible for 4.2M deaths in all age groups worldwide according to WHO Global Burden of Disease 2004; 2. DALYs include all age groups; The Diagnostics Innovation Map, BIO Ventures for Global Health; 3. WHO-UNICEF, Global Action Plan for the Prevention and Control of Pneumonia, 2009; BCG analysis. 4. Per July 2011 Co-Chair meeting

Managing Fever, not Malaria



Progress

- Malaria RDTs reduce overuse of ACTs and delays in treating pneumonia

Challenges

- Pneumonia algorithms are intended to minimize the number of cases that go untreated. As a result, overtreatment is common

Potential Diagnostic Opportunities

1. Differentially diagnose pneumonia and malaria
2. Improve pneumonia diagnosis with breath rate counters, oximetry, digital stethoscopes or biomarker-based test
3. Test to identify severe cases, and those likely to progress
4. Bacterial infection test, to guide antibiotic use

Figure from: Malaria Diagnosis: WHO Guidelines and their implementation, David Bell, WHO Global Malaria Program

Diagnostic Opportunities

	Target	Benefits	Challenges	Ongoing R & D
①	**Differentially diagnose pneumonia and malaria**	▪ Positive pneumonia diagnosis ▪ Identify cases that need both antimalarial and antibiotic	▪ Only relevant in areas with malaria ▪ Improvement over malaria RDT may not justify added costs ▪ Technically challenging ▪ Modeling indicates test will have low health impact	▪ Specific Biomarker Analysis ▪ Biomarker Discovery ▪ Modeling health impact and cost effectiveness
②	**Improve pneumonia diagnosis with breath rate counters, oximetry, or digital stethoscopes**	▪ Improve pneumonia diagnosis ▪ High feasibility ▪ Relevant globally ▪ Tools generally useful in clinical setting & community based management of pneumonia	▪ May require changes to diagnostic algorithms	▪ Digital stethoscopes ▪ Digital analysis of cough sounds ▪ Cells phones with oximetry & respiratory rate applications
②	**Improve pneumonia diagnosis with biomarker-based test**	▪ Positive pneumonia diagnosis ▪ Relevant globally	▪ Likely to be more expensive than presumptive treatment ▪ Technically challenging	▪ Biomarker Discovery
③	**Test to identify severe cases, and those likely to progress**	▪ By targeting the most expensive treatments, likely to be cost-effective ▪ Relevant globally ▪ Model indicates test will have high impact	▪ Technically challenging ▪ Impact of diagnostic will be affected by healthcare provider behavior/willingness to use test	▪ Biomarker Discovery/ validation
④	**Bacterial pneumonia test, to guide antibiotic use**	▪ Reduce antibiotic overuse ▪ Relevant globally	▪ Likely to be more expensive than presumptive treatment	

① Differential Diagnosis of Malaria & Pneumonia

- **Pathogen specific biomarkers**
  - **C-polysaccharide BinaxNow lateral flow device**
    - High sensitivity in adults, low specificity in children due to carriage
  - **Latex Agglutinatex of respiratory samples (Slide Kit, bioMeriuex)**
    - Conflicting data, low sensitivity (30%) & high specificity in children
  - **Use of Pneumococcal Capsular Polysaccharide Antigen (PCPA)**
    - Single report using sputum indicated a 90% sensitivity & 79% specificity. (Wellstood)
    - PcpA is expressed in the lungs but not in the nasopharynx (Glover *et al*., 2008)
      - Studies evaluating serological response and diagnostic utility underway (University of Alabama)
- **Host Response Biomarkers**
  - **Evaluation of specific biomarkers**
    - Historically, extensive focus on CRP & PCT, especially in developed world settings
    - PCT – levels elevated during gram +ve and –ve infections, malaria, invasive fungi, legionella, not viruses, chlamydia
      - *Padrisa et al, 2010*, evaluated CRP & PCT levels in well characterized febrile patients in Mozambique
      - Unable to distinguish between invasive bacterial & viral pneumonia in presence of *P. falciparum* parasites
- **Biomarker Discovery….**

Padrisa et al., PLOS One, 5 (2010) Wellstood, (1992) Eur. J. Clin Infect Dis.

② Biomarker Discovery Efforts

- **Multiple ongoing efforts to identify appropriate biomarkers to distinguish**
  - Malaria from Pneumonia
  - Bacterial vs. Viral etiology
  - Degree of pneumonia or bacterial disease severity or likelihood of progression

- **Roger Weigand, Broad Institute**
  - Proteomic analysis of blood samples from well characterized febrile patients in Mozambique & Kenya
    - Objective to identify biomarker to differentiate viral vs. bacterial infection and/or malaria vs. pneumonia and indicator of disease severity
    - Outputs anticipated early 2012

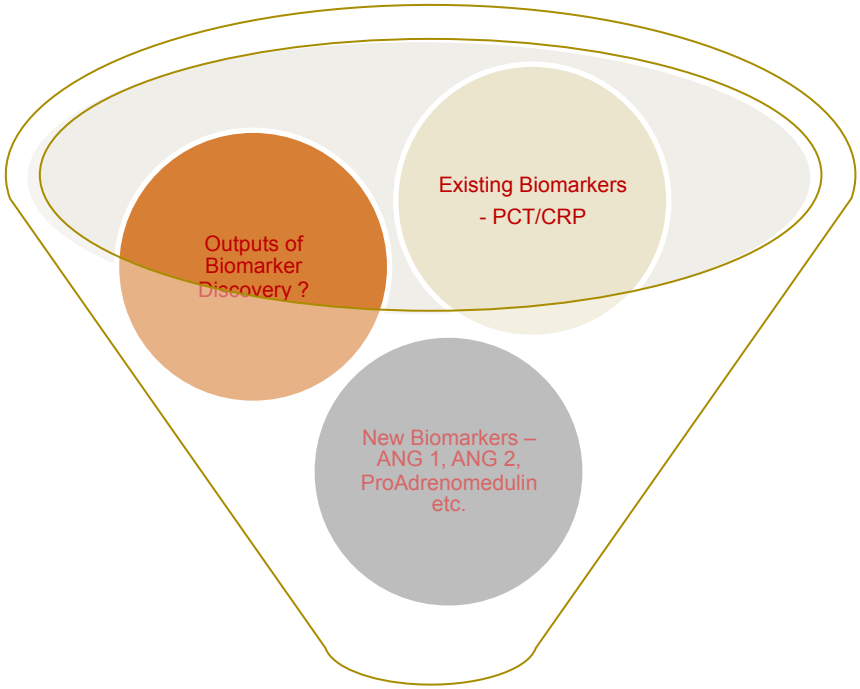
- **Geoff Ginsburg, Duke University**
  - Primate model to study course of pneumonia infection and profile of diagnostic markers over time

③ Identify Severe Cases of Pneumonia & those likely to progress

- **Biomarker Based Approaches**
  - **Pro-adrenomedullin, natriuretic peptides, endothelin-1 precursor peptides, copeptin and cortisol levels demonstrated to be promising predictors of progression (Chris-crain)**
    - Current studies limited to developed world Emergency Room settings
    - Most studies conducted by single group of investigators
    - Independent validation study using retrospective samples from the developed world required
  - **Angiopoietin 1 (ANG1) and Angiopoietin 2 (ANG2) and the ratio of ANG-1 to ANG-2**
    - Identify subjects having or at risk of developing an infectious disease state wherein endothelial cell integrity is compromised and the patient is at increased risk of developing a severe disease state
      - Angiopoietins are clinically informative prognostic biomarkers of morbidity and mortality in severe sepsis (Ricciuto et al.)
      - Retrospective and prospective evaluation of ANG1 and ANG 2 needed to determine their predictive and prognostic utility for serious bacterial infections and severe malaria in African children presenting for care
  - **Combinations of biomarkers are highly accurate at predicting outcome**
    - e.g.: 6 individual biomarkers for cerebral malaria
    - Logistic regression model predicted combined outcome under the ROC curve of 0.96 (with narrow CI's), considered excellent for a diagnostic test.
    - Biomarkers for febrile illness: ANG 1, ANG 2, PCT, Proadrenomedullin?

Chris-Crain (2007), BMC Infectious Diseases 7 (10) ; Ricciuto et al (2011) Crit Care Med 39 (4)

Translating Biomarker Research



Selection process

Retrospective & prospective evaluations using endemic samples

Combinations of biomarkers evaluated

Standardized Protocol

Potential selection of biomarkers for development of febrile illness RDT

Rapid, Point of Care Test for Febrile Illness: Performance Characteristics

***Intended Use*: Detection of a bacterial infection, indicative of pneumonia, and/or malaria infection**

***Target Population:* Febrile children presenting to a clinic or CHW* with fever**

***Test Platform:* Lateral Flow (like malaria RDT)**

***Sample Type:* Finger-stick sample of whole blood (10-15ul)**

***Total Test Time:* 10 minutes**

***Clinical Sensitivity:* 95% sensitivity**

***Clinical Specificity:* 85% specificity**

These values are based on the outputs a model. Input from the field on these numbers required.

***Reference Method:* Blood Culture, PCR**

***Shelf life:* >12 months at 40 degrees Celsius**

***Ease of Use:* 3 simple steps, clear visual read-out, minimal training: use by CHW's feasible**

***Cost:* TBD – not to exceed $0.60 ? (cost of malaria RDT. NB: Cost of oral antibiotics - $0.2)**

*CHW's – Community Health Workers

Rapid, low Cost, point of care, test for febrile illness

Child Presents with Fever

Existing Malaria RDTs

Malaria RDT +

Malaria RDT-

Control

Malaria positive

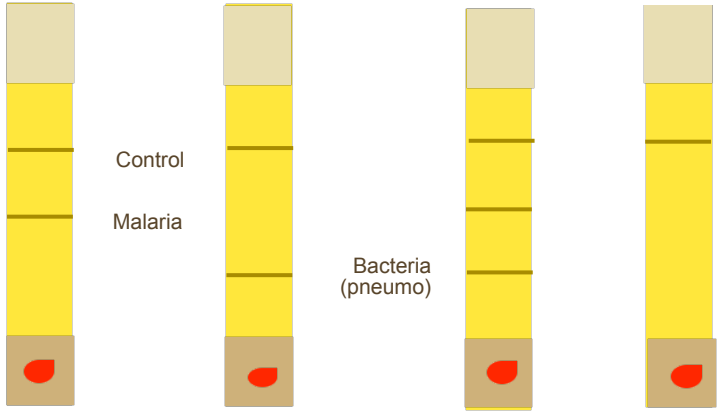
Test does not provide useful diagnostic information for those patients that are malaria RDT test negative

Malaria +ve

Bacterial Infection +

Malaria & Bacterial Infection +ve

No malaria or bacteria - viral infection



Control

Malaria

Bacteria (pneumo)

Treat with antimalarials

Treat with antibiotics

Treat with antimalarials & antibiotics

No treatment required

New , low cost point of care test for febrile illness

- **As easy to perform as malaria RDT**
- **Use 10ul of finger-stick blood sample**
- **Results in 10 minutes**
- **Measures levels of specific host response biomarkers associated with a bacterial infection**
- **Test also includes marker for malaria to test for both infections**

Summary

- Multiple biomarker reports in the literature
  - Limited studies in endemic settings
  - Poorly defined case definitions prevent comparisons across studies
  - Small sample sizes
  - Focused on testing specific biomarkers
- *On the horizon:*
- Identification of biomarkers to "potentially"
  - Differentiate bacterial vs. viral infections, to be used in combination with malaria RDTs
  - Identify children with greatest likelihood for a severe outcome and prioritize for treatment and/referral
- Availability of febrile illness RDT dependent on outputs of biomarker analyses

Thank You

BILL & MELINDA GATES *foundation*

Economic benefit: Grantee's modeling finds Pn RDT highly cost-effective, particularly for severe diagnosis

Research background	**Model reductions in malaria/pneumo burdens and cost-effectiveness of a diagnostic that improves 1) differential diagnosis of pneumonia v. malaria, and 2) differential diagnosis of severe pneumonia. Assumptions:** ▪ Initial point-of-care Dx priced at $1.00/test ▪ 50% reduction in test non-adherence when using RDT ▪ 95%/95% sensitivity/specificity (non-severe pneumo), 95%/99% (severe) ▪ Implemented in public health facilities, via scaled-up CHW program, or in both areas

Modeling results

	Type	Public health facilities only	Scaled-up CHW implementation	Combined facilities + CHW
Deaths averted	Malaria vs. non-severe pneumo	71.6K	150.5K	219K
	Pneumonia only (non-severe)	40.5K	87.7K	
	Severe Pneumo only	169K	113K	
Cost-effectiveness ($/ICER)	Malaria/Pneumonia	CS	CS	$70/DALY averted
	Severe Pneumo	$5/DALY	$80/DALY	$43/DALY

WHO treatment guidelines for pneumonia

For child between 1-3 years, weighing 10 - <14kg, in low-HIV setting

Condition	Medicine	Form/strength[1,2]	Regimen[1]	Cost per unit[2]	Cost per regimen
Non-severe pneumo (bacterial)	Oral amoxicillin	250mg tab	1.5 tab, 2x/day x 3 days	$0.02	**$0.18**
	Oral cotrimoxazole	TMP 80+SMX 400mg	1 tab, 2x/day x 3 days	$0.008	**$0.05**
		TMP 20+SMX 100 mg	3 tab, 2x/day x 3 days	$0.001	**$0.02**
Severe pneumo	Oral amoxicillin	250mg tab	1.5 tab, 2x/ day x 3 days	$0.02	**$0.18**
Very severe pneumo	Oxygen	Cylinder	As needed	*Unknown*	
	Ampicillin + gentamicin	500 mg, at 50mg/kg	3mL, e6 hours x 1 day	$0.13	**$0.52**
		40 mg/ml (2ml vial), at 7.5mg / kg	1-1.5 vials, 1x/ day x 10 days	$0.06	**$0.60**
Viral infection (non-severe); pain	Paracetamol	100mg tab	Every 6 hours as needed	$0.001	**Variable**
		500mg tab		$0.004	**Variable**

1. WHO IMCI guidelines as of 2010. 2. AFRO Essential Medicines Price Indicator, September 2007,