Point-of-Care Diagnostics

Rosanna W Peeling
London School of Hygiene & Tropical Medicine
Director, International Diagnostics Centre

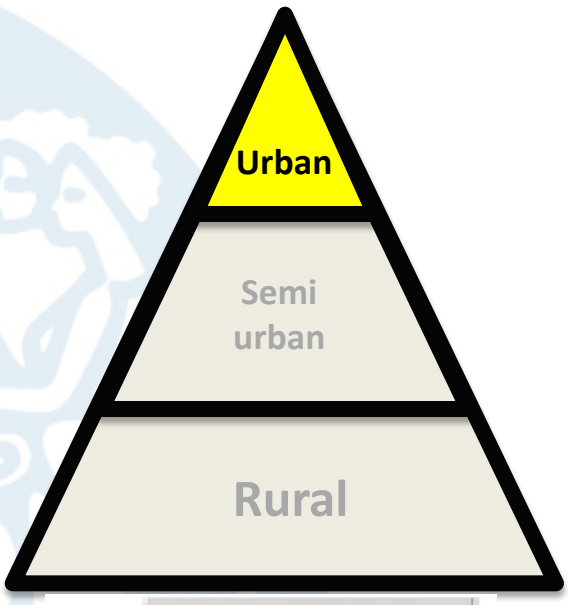
The International Diagnostics Centre

www.idx-dx.org

Plan of Presentation

1. Diagnostic technologies for different settings
2. Point-of-care tests to improve syndromic management
3. Technologies for the future

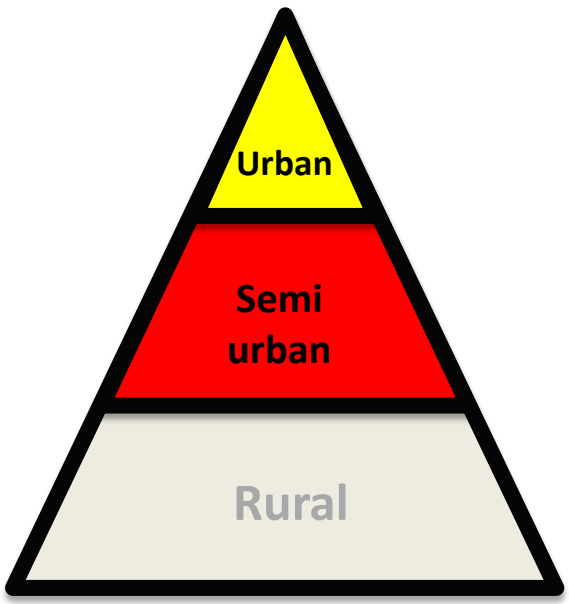
Diagnostics:
Access vs Accuracy vs Affordability



Accurate ✓✓✓

Cheap ×

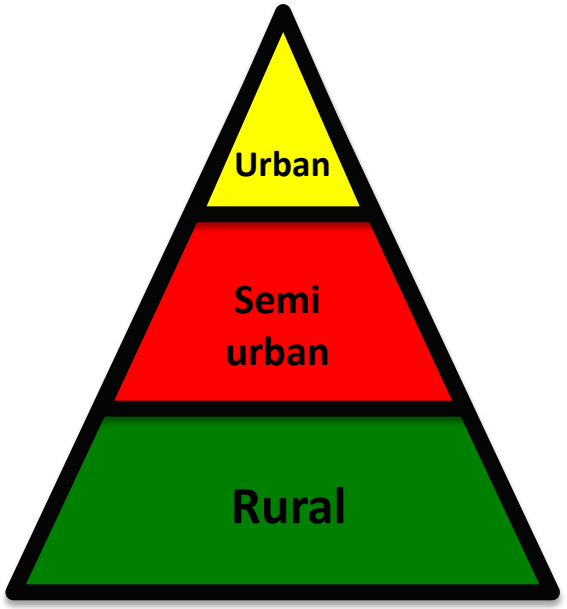
Fast/simple ×



Accurate ✓✓

Cheap ✓

Fast/simple ✓



Accurate ✓

Cheap ✓✓

Fast/simple ✓✓

Rapid vs Point-of-Care (POC) Tests

Courtesy Dr. Ray Waters

Senior K. Lancet ID 9: 467 2009

ASSURED Tests to Improve Global Health

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A = Affordable

S = Sensitive

S = Specific

U = User-friendly

R = Rapid and robust

E = Equipment-free

D = Deliverable

✓ Cheap

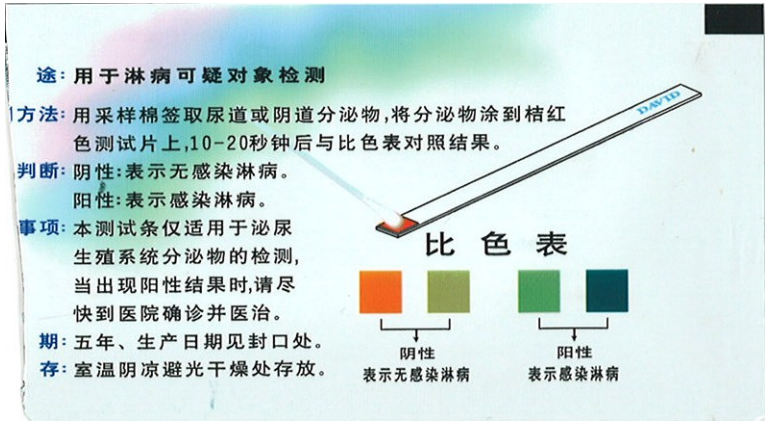
✓ Accurate

✓ Fast/Simple

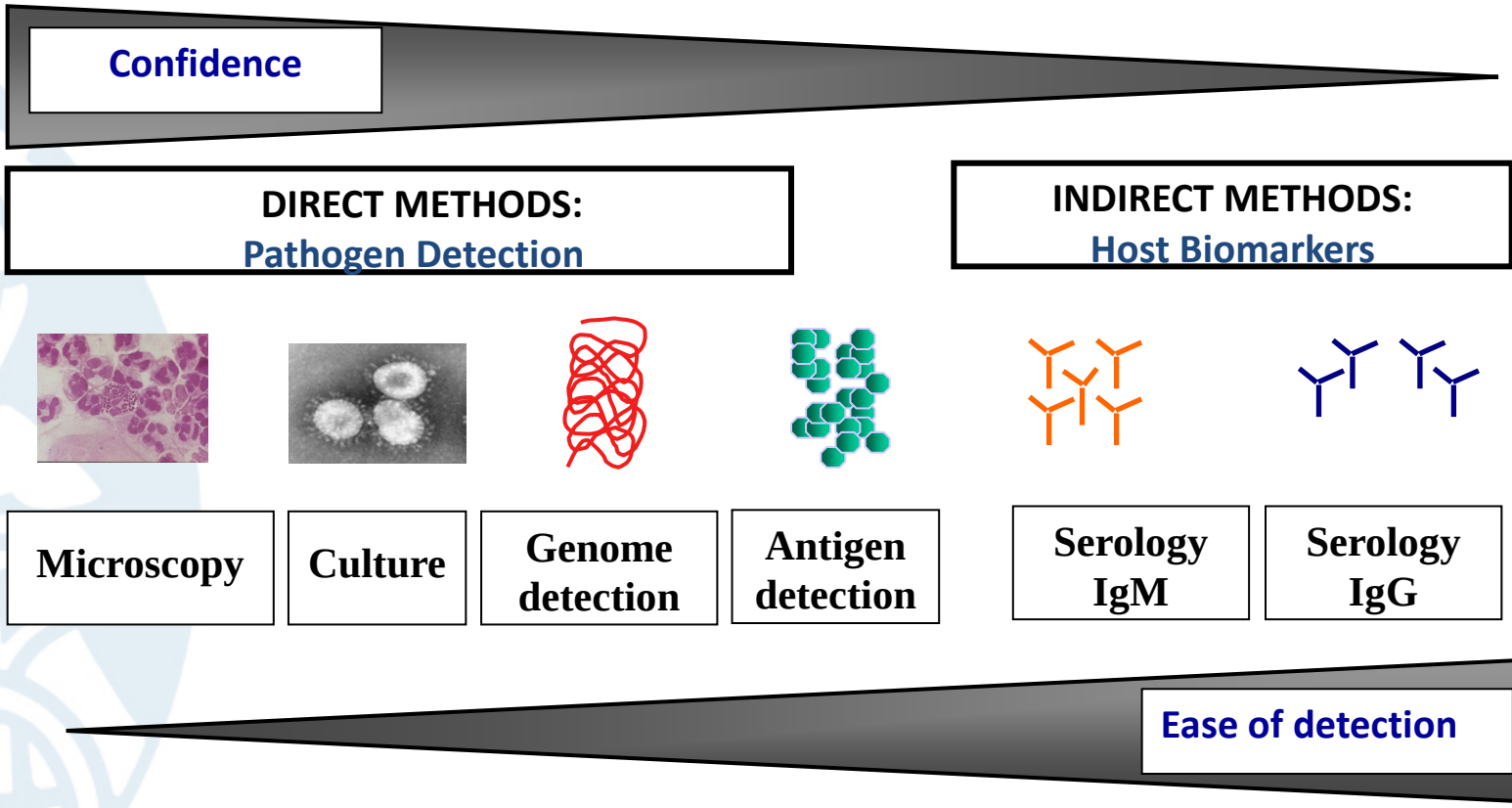
"Pick 2 of 3, you can't have them all."

Gonorrhoea Tests at Sex Shops

Quality of
Rapid STI Tests?



Diagnostics Methods:
Ease of Detection vs Confidence in Diagnosis



Adapted with permission from J. Cardosa

Product profile of HIV/Syphilis Dual Tests

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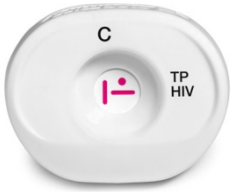
Standard Diagnostics, Inc.
BIOLINE HIV/Syphilis Duo



MedMira
Multiplo TP/HIV Antibody Test

Chembio
DPP® HIV-Syphilis Assay

Purpose/use setting	Screen for HIV and Syphilis in clinics	Screen for HIV and Syphilis in clinics	Screen for HIV and Syphilis in clinics
Specimen	Serum/Plasma/Whole Blood (10-20uL)	S/P/WB (1 drop, approx.30-40uL)	S/P/WB (1 drop, approx.30-40uL)
Test time	15-20min.	>20min + sample preparation	15-20min + sample preparation
#Operator steps	3	3	4
Performance	HIV: 100%/100% SYP : 100%/99.1%	99.8%/99.7% 94.4%/100%	99.1-100%/99.6-100% 95.7-100%/98.2-100%
Price($)	$1.50	$3.50	$2.50 - 3.00

FDA approves Oral HIV Tests for home use, July, 2012

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Aspirin? Check. Shampoo? Check. Free HIV Test — Check?

LWA / GETTY IMAGES

Source: time.com

Oct 22, 2013: European Parliament votes favourably for home use of IVDs

Performance of the oral HIV Test

Performance Measure*	Professional Use OraQuick Test Performance (2-sided 95% CI**)		Over-the-Counter OraQuick Test Performance (2-sided 95% CI**)	
	Minimum FDA Recommended Performance	**Evaluation Results**	**Minimum FDA Recommended Performance**	**Evaluation Results**
Sensitivity	**98%** (lower bound of the 2-sided 95% CI)	99.3% (**98.4** - 99.7%)	**95%** (lower bound of the 2-sided 95% CI)	92.98% (**86.64** – 96.92%)
Specificity	**98%** (lower bound of the 2-sided 95% CI)	99. 8% (**99.6** – 99.9%)	**95%** (lower bound of the 2-sided 95% CI)	99.98% (**99.90** – 100%)

* Compared to a blood based HIV test

**95%CI = 95% Confidence Interval

4th Generation HIV Tests

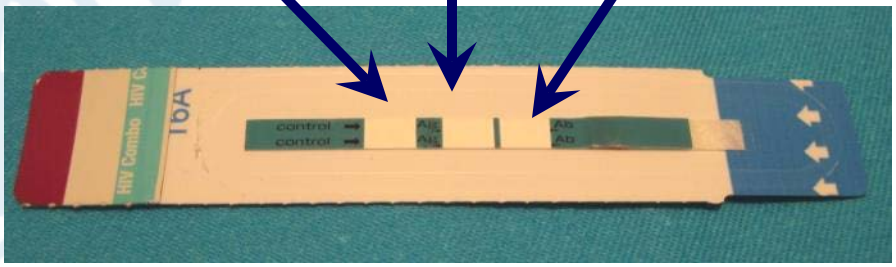
Abbott Architect Ag/Ab Combo

2010

Bio-Rad Ag/Ab Combo

2011

Control **Antigen** **Antibody**



Determine Combo Ag/Ab Rapid Test

2013

Detect HIV-1 p24 antigen and IgM and IgG antibodies against either HIV-1 or HIV-2

Insufficient data for rapid Ag/Ab test to recommend it as 1st test in algorithm

HIV Viral Load Product Pipeline

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Sample in-answer out

Alere Q

Alere

EOSCAPE HIV™ Rapid RNA Assay System

Wave 80 Biosciences

Truelab PCR

Molbio/bigTec

RT CPA HIV-1

Viral Load

Ustar

Gene-RADAR

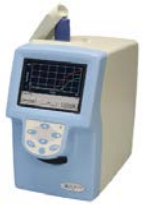
Nanobiosym

SAMBA VL

DDU/Cambridge

Liat™ Analyser

IQuum



Gene Xpert

Cepheid

Cavidi AMP

LYNX Viral Load Platform

NWGHF

Viral Load Assay with BART

Lumora

2013 2014 2015 2016

http://www.unitaid.eu/images/marketdynamics/publications/UNITAID-HIV_Diagnostic_Landscape-3rd_edition

UNITAID

Sample In, Answer Out: A Multi-disease Random Access Real-time PCR Platform

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MTB/RIF
MRSA
CT/Ng
HIV Viral Load
…..

5	20	80	Samples per shift	500-1000

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Malaria

Performance of Malaria RDTs

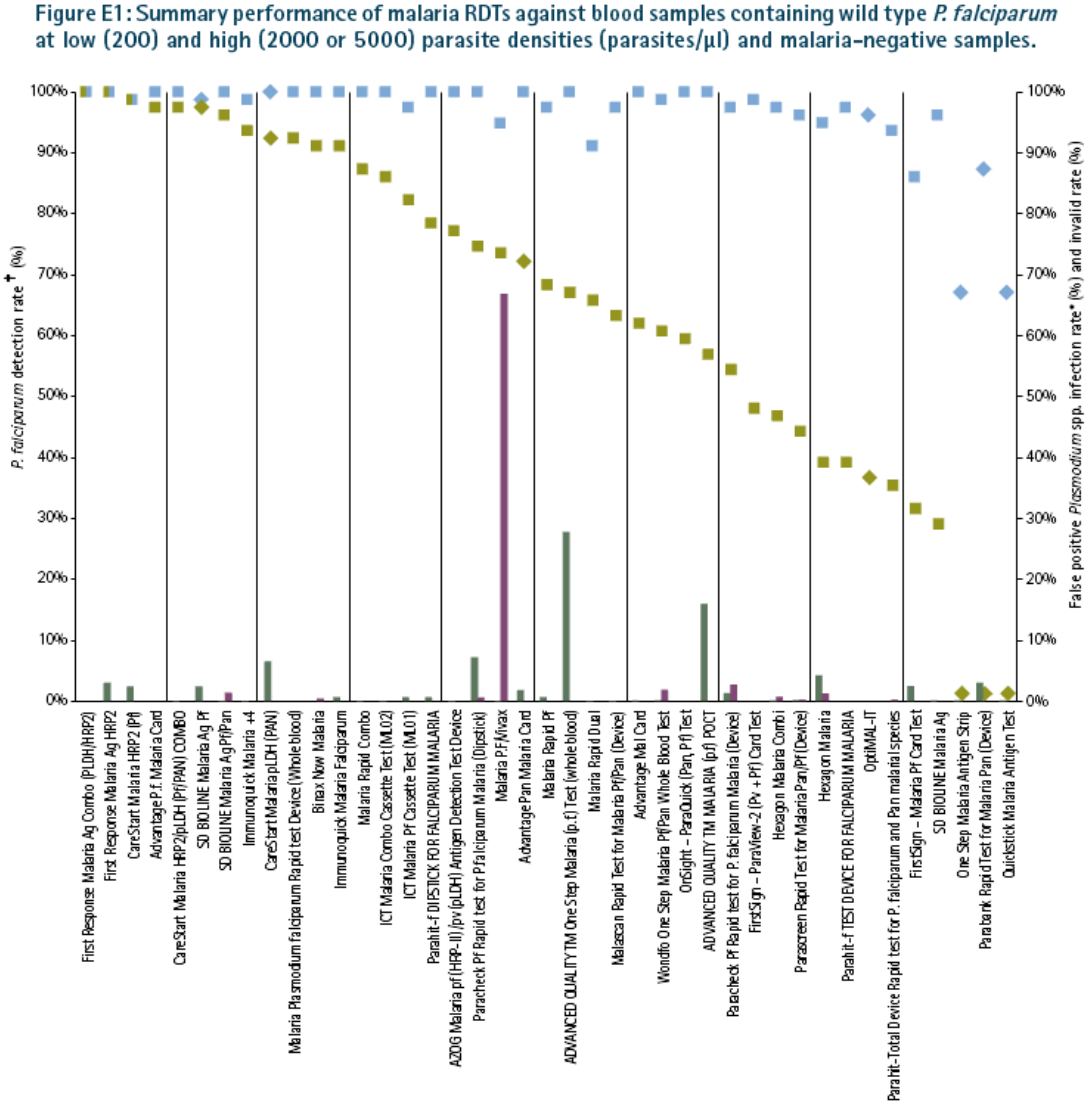
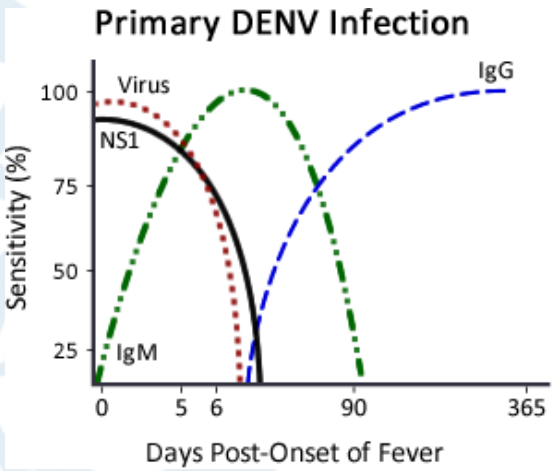


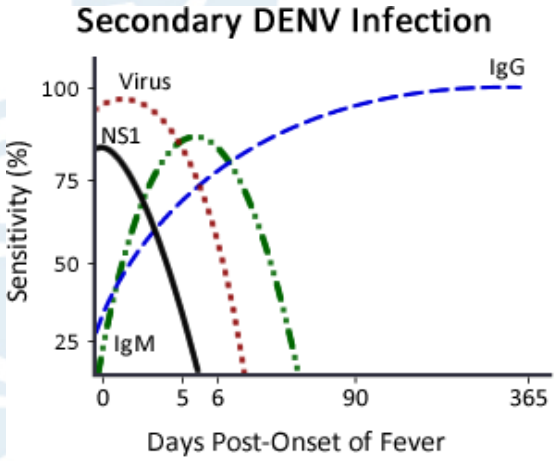
Figure E1: Summary performance of malaria RDTs against blood samples containing wild type *P. falciparum* at low (200) and high (2000 or 5000) parasite densities (parasites/µl) and malaria-negative samples.

- Malaria RDTs detect antigen In blood samples
- Biomarkers:
  Plasmodium falciparum: hrp2
  Plasmodium vivax: hrp2
  Pan Plasmodium: pDLH
- Tests: variable performance
- malaria parasites in some areas of south America missing hrp

Dengue

Performance of Dengue NS1 Tests



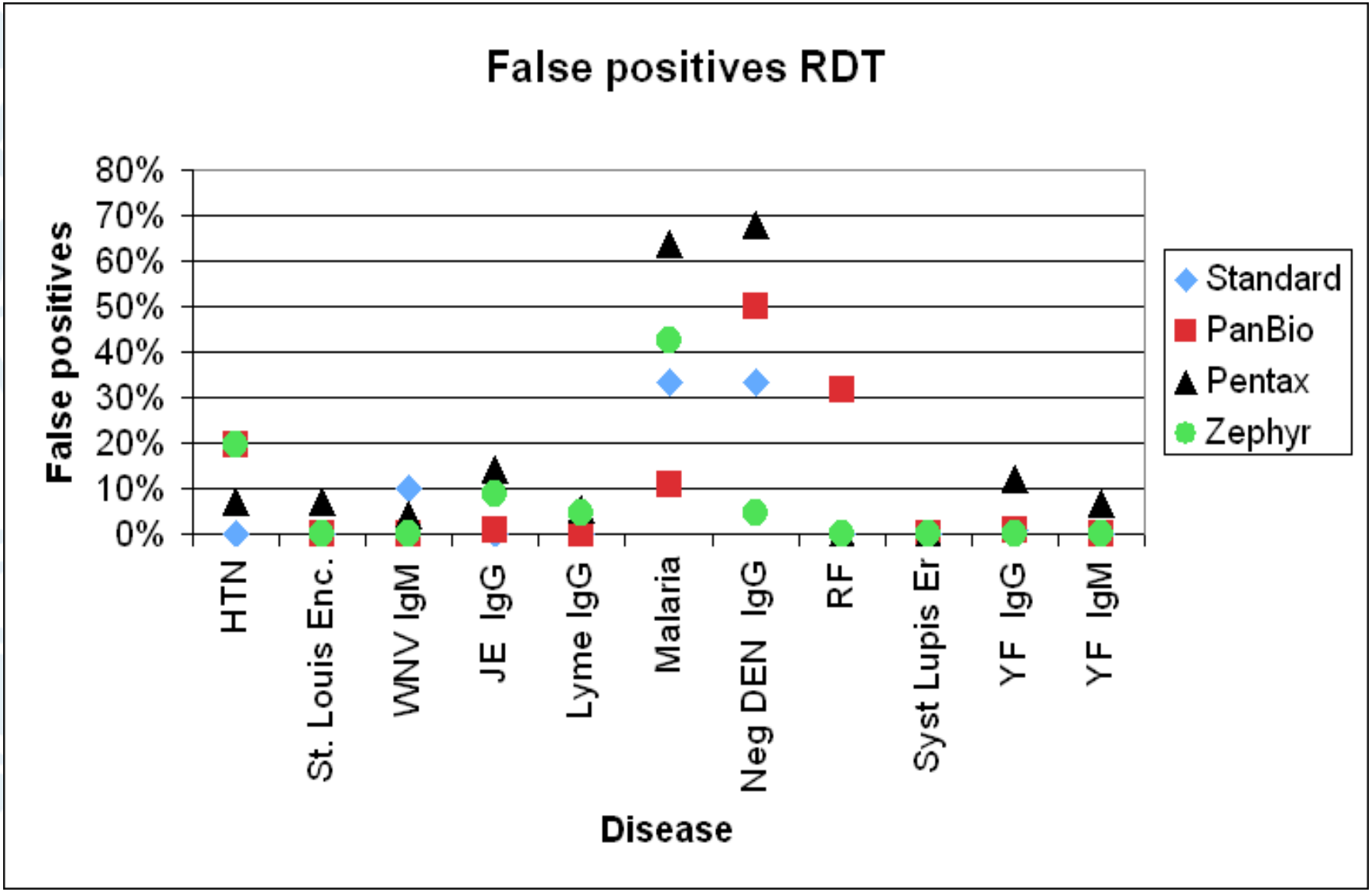


NS1 TESTS		Day 0-5	Day 6-14
	Company	Sensitivity*	Sensitivity**
ELISA	Bio-Rad	60%	29%
	Panbio	75%	19%
	SD	70%	31%
RDT	Bio-Rad	52%	19%
	CTK	40%	19%
	Panbio	60%	12%
	SD duo IgM/NS1	59%	59%

**Comparison to RT-PCR DENV positive samples,*
***Comparison to IgM seroconversion*

Hunsperger et al PLoS One 8:e3171 2014

Rapid Dengue IgM Tests: False Positive Results



Evaluation of Dengue Rapid IgM Tests

Test	Claimed Accuracy(%)		Accuracy (%)	
	Sens	Spec	Sens	Spec
Core	100	100	23	99
Diazyme	NS	NS	18	98
GlobaleMed	80	>99	63	69
Minerva	NS	NS	9	100
PanBio	70	100	65	98
Standard	93	100	22	99
Tulip	100	100	6	99

Blacksell et al. Clin Infect Dis 2006;42:1127

INFLUENZA

Influenza Virus Testing Methods

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Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Viral tissue cell culture (conventional; yields live virus)	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	No
Rapid cell culture (shell vials; cell mixtures; yields live virus)	A and B	As above	1-3 days	No
Immunofluorescence, Direct (DFA) or Indirect (IFA) Florescent Antibody Staining [antigen detection]	A and B	NP[4] swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hours	No
RT-PCR[5] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays [influenza viral RNA or nucleic acid detection]	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	Varies (Generally 60 minutes-8 hours)	No
Rapid Molecular Assay [influenza viral RNA or nucleic acid detection]	A and B	NP[4] swab, nasal aspirate, wash, swab	<30 minutes[7]	Yes/No[7]
Rapid Influenza Diagnostic Tests[6] (antigen detection)	A and B	NP[4] swab, (throat swab), nasal wash, nasal aspirate	<30 min.	Yes/No

Influenza Virus Testing Methods

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Method[1]	Types Detected	Acceptable Specimens[2]	Test Time	CLIA Waived[3]
Viral tissue cell culture (conventional; yields live virus)	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	No
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RT-PCR[5] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays [influenza viral RNA or nucleic acid detection]	A and B	NP[4] swab, throat swab, NP[2] or bronchial wash, nasal or endotracheal aspirate, sputum	Varies (Generally 60 minutes-8 hours)	No
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Rapid Influenza Diagnostic Tests[6] (antigen detection)	A and B	NP[4] swab, (throat swab), nasal wash, nasal aspirate	<30 min.	Yes/No

Rapid Influenza Tests

Procedure (Manufacturer/Distributor)	Influenza Virus Types Detected	Approved Specimens[2]	CLIA Waived[3]	Uses Analyzer Reader Device
BD Directigen™ EZ Flu A+B[4] (Becton-Dickinson & Co.)	A and B	NP[5] wash/aspirate/swab Throat swab	No	No
BD Veritor™ System for Rapid Detection of Flu A+B[4] (CLIA-waived), (Becton Dickinson & Co.)	A and B	NP[5] swab/ nasal swab	Yes	Yes
BD Veritor™ System for Rapid Detection of Flu A+B[4] (Moderately Complex), (Becton Dickinson & Co.)	A and B	NP[5] wash/aspirate	No	Yes
Binax NOW® Influenza A&B[4] Test (Alere Scarborough, Inc.)	A and B	NP[5] swab, Nasal wash/aspirate/swab	Yes	No
BioSign® Flu A+B[4] or OraSure QuickFlu Rapid A+B Test or Polymedco Poly stat Flu A&B Test or LifeSign LLC Status Flu A&B (Princeton BioMedtech Corp.)	A and B	NP[5] swab/aspirate/wash, nasal swab	No	No
ClearView Exact II Influenza A&B Test or Alere Influenza A&B Test (Alere Scarborough, Inc.)	A and B	Nasal swab	Yes	No
OSOM® Influenza A&B[4] Test (Sekisui Diagnostics)	A and B	Nasal swab	No	No
QuickVue® Influenza A/B Test[6] (Quidel Corp.)	A and B	Nasal wash/aspirate/swab	Yes	No
QuickVue® Influenza A+B Test[4] (Quidel Corp.)	A and B	NP[5] swab Nasal wash/aspirate/swab	Yes	No
RAMP Influenza A/B Assay or 3M™ Rapid Detection Flu A+B Test[4] (Response Biomedical Corp.)	A and B	NP[5] swab/aspirate Nasal wash/aspirate	No	Yes
SAS™ FluAlert A&B Test[4] (SA Scientific, Inc.)	A and B	Nasal wash/aspirate	No	No
SAS™ Influenza A Test[4] (SA Scientific, Inc.)	A only	Nasal wash/aspirate	Yes	No
SAS™ Influenza B Test[4,6] (SA Scientific, Inc.)	B only	Nasal wash/aspirate	Yes	No
Sofia® Analyzer and Influenza A+B FIA[4] (CLIA-waived) (Quidel Corp.)	A and B	NP[5] swab Nasal swab	Yes	Yes
Sofia® Analyzer and Influenza A+B FIA[4] (Quidel Corp.)	A and B	NP[5] aspirate/ wash	No	Yes
TRU FLU®[4] (Meridian Bioscience, Inc.)	A and B	NP[5] aspirate/swab Nasal wash/swab	No	No
XPECT™ Influenza A/B[4] (Remel Inc./Thermo Fisher Scientific)	A and B	Nasal wash/swab Throat swab	No	No

- **Several commercially available FDA approved rapid diagnostic tests (RDT) for Influenza (Table)**
- **Mainly antigen detection**
- **Time to result: 15min**
- **Low sensitivity: 10-70%**
- **High specificity: 90-95%**

Sofia Fluorescent Immunoassay Analyzer (Quidel, San Diego, CA, USA)

Roche: Liat Molecular Platform

STEP 1.
Add sample

STEP 2.
Scan barcode

STEP 3.
Insert tube

Done.
Results in ~30 minutes

IQuum (Boston) currently has FDA-approved Flu H1N1, A and B detection assays. The Liat Analyser has an internal optical system that provides 6 independent optical detection channels for real-time detection and quantification of multiple targets in each test. It can be powered by AC mains or by battery, allowing mobile use.

Molecular point-of-care tests for Influenza

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Alere i Influenza A&B test:

- **ONLY molecular platform that is FDA approved as a POCT**
- **Nucleic acid amplification system that uses a fluorescence-based molecular signal to detect influenza A and B.**
- **Time to result: 15min (only 2 min of "hands on" time)**
- **Adapted to be used by non-laboratory staff**
- **Results from a multicentre clinical evaluation (Bell et al 2014) indicate:**
  - **99.3% sensitivity and 98.1% specificity for Influenza A**
  - **97.6 sensitivity and 100% specificity for Influenza B**
- **Sensitivities of 73.2% and 82.3% have ben reported in other studies**

Alere i Influenza A&B (Alere, San Diego, CA, USA)

Molecular platforms with POC potential

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Table 1 Comparison of molecular platforms with point-of-care potential for detecting respiratory viruses.

System and panel	Benefits	Limitations
Alere i Influenza A&B	15 min run-time 2 min "hands on" time Simplicity	Moderate sensitivity for Influenza A Only influenza viruses detected
Biofire FilmArray Respiratory Panel	60 min run-time 2 min "hands on" time Wide range of viruses detected	Unable to process multiple samples simultaneously
Cepheid GeneXpert (Xpert Flu and Flu/RSV)	75 min run-time 2 min "hands on" time Modular system allows multiple simultaneous tests	Limited range of viruses detected

- Biofire panel: Flu A and B, Parainfluenza 1-3, RSV, adenovirus, human metapneumovirus, corona virus, rhinovirus, enterovirus (Mycoplasma pneumoniae, Bordetalla pertussis, and Chlamydophila pneumoniae)

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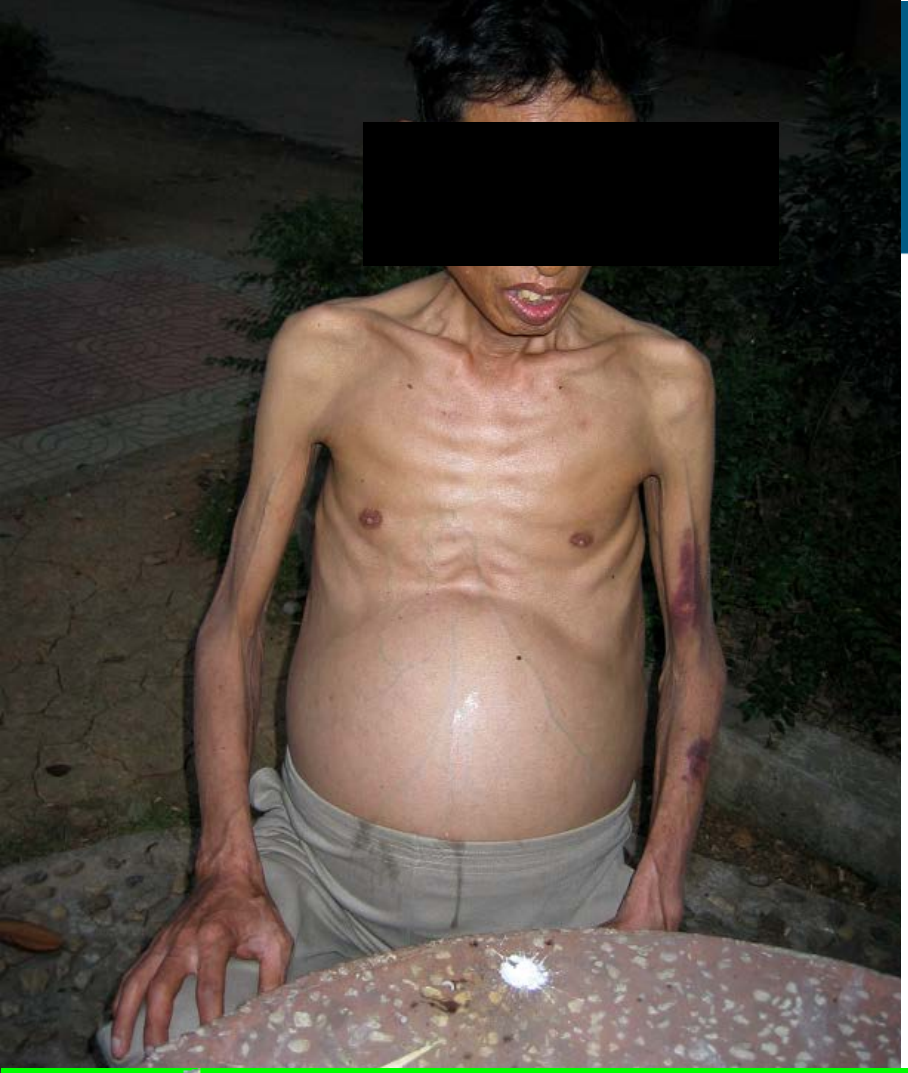
Neglected Tropical Diseases



Schisto was eliminated in China 51 years ago

S.j. has re-emerged in higher risk areas of China

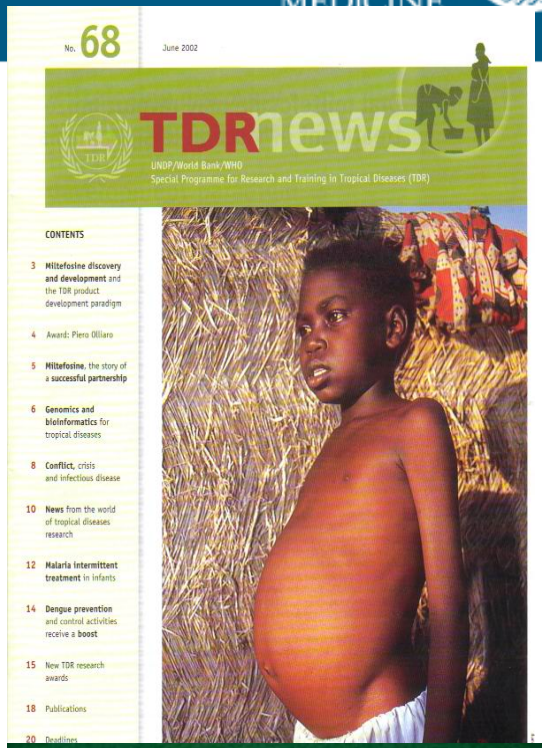
Visceral Leishmaniasis (Kala Azar or Black Fever)

Disease burden:
12 million new cases/year; 51,000 deaths

Cause:
Parasitic protozoa, genus *Leishmani,* through the bite of infected sand flies

Diagnostic Need:
- **simple tests for case detection**
- **test of cure**
- **less invasive specimens**

Current diagnostics:
- **Parasite culture (1-3 weeks)**
- **Microscopy of spleen or bone marrow aspirate, or lymph node biopsy**
- **Rapid test to detect serum antibody to rK39 antigen**



Human African Trypanosomiasis: Sleeping Sickness

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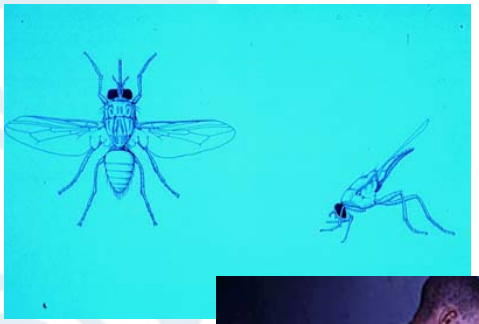
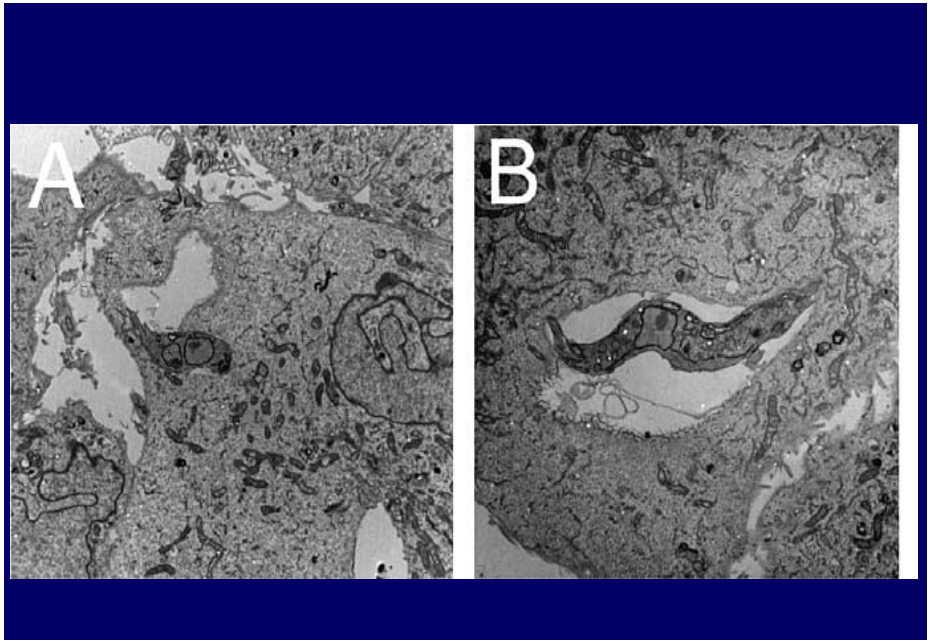
Caused by protozoan parasites, *Trypanosoma brucei rhodesiense* and *T. brucei gambiense, through t*he bite of infected tsetse flies

300,000 new cases/year; fatality rate = 70%





Human African Trypanosomiasis: need for a diagnostic for staging

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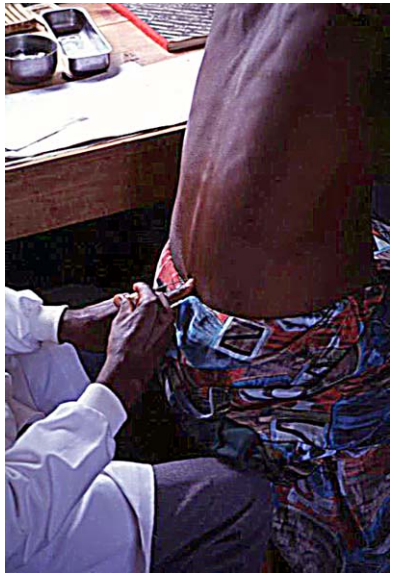
- **Treatment is toxic**
  - **Pentamidine for stage 1 (blood stage)**
  - **Melarsoprol/eflornithine for stage 2 (brain stage)**
- **Existing diagnostics:**
  - **microscopy**
  - **card indirect agglutination test**
  - **Staging: finding of trypanosomes and/ or wbc in the cerebrospinal fluid**
- **Diagnostic Need:**
  - **early detection to prevent progression**
  - **Non-invasive means of staging**



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MRSA

Nucleic acid amplification tests for MRSA

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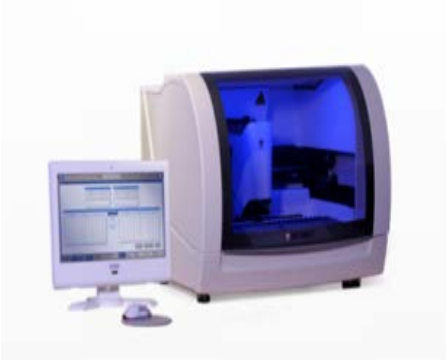
Test-type	Product	Manufacturer	Sensitivities	Specificities (95% CI)	Regulatory approval
Real Time-PCR	BD MAX™MRSA Assay	BD worldwide	93.0% (87.9%-96.0%)	95.9% (94.8%- 96.7%)	FDA
	BD GeneOhm MRSA ACP Assay	BD worldwide	92.0% (87.1%-95.4%)	94.6% (93%- 95.9%)	FDA
	Cobas® MRSA/SA Test	Roche Molecular Systems Inc.	93.8% (86.2%-98.0%)	92.6% (90.6% - 94.4%)	-
	GenoType MRSA	Hain Lifescience GmbH	91.7%	93.5%	-
	LightCycler® MRSA Advanced Test	Roche Molecular Systems Inc.	83.3% (77.0–88.5)	99.0% (98.2–99.5)	FDA
	NucliSENS easyQ®	Biomerieux, France	100%	97.3%	FDA
	Xpert® MRSA	Cepheid	86.3%	94.9%	FDA
	Prodesse ProGastro Cd assay	Hologic Gen-Probe Inc., USA	83.3% (70.0% -96.7%)	95.6% (93.1%-98.1%)	FDA
Multiplex	Xpert® MRSA/SA	Cepheid	98.1% (87.5%-100%)	99.6% (98.3%- 100%)	FDA
	BD GeneOhm's Staph SR assay	BD worldwide	94.3% (87.5%-100%)	97.8% (96.1%- 100%)	FDA
Nanoparticle Probe Technology	Verigene	Nanosphere, USA	95% agreement with VersaTREK Blood Culture System		FDA

- Results available in 2 h
- excellent sensitivity and specificity for MRSA screening
- Pooled sensitivity 92.5% (95% CI: 87.4-95.9)
- More costly than culture methods

Nanosphere's Verigene

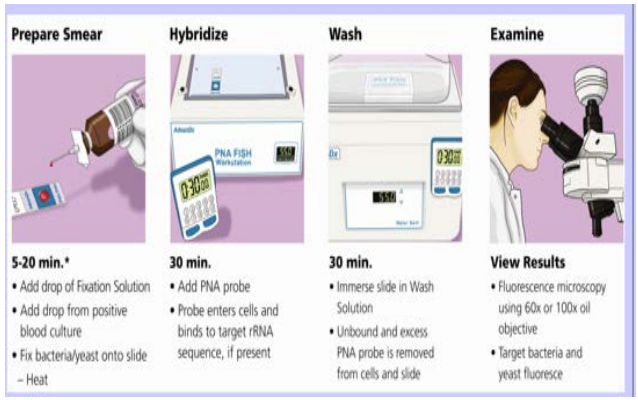


BD MAX™MRSA Assay

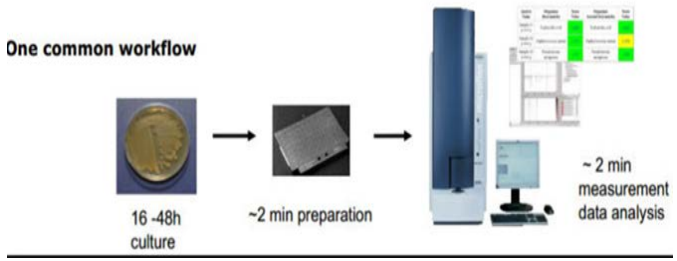
Rapid Molecular Methods For Organism Identification

Alere™ PBP2a Culture Colony Test

Peptide Nucleic Acid Fluorescent In Situ Hybridization



MALDI-TOF MS

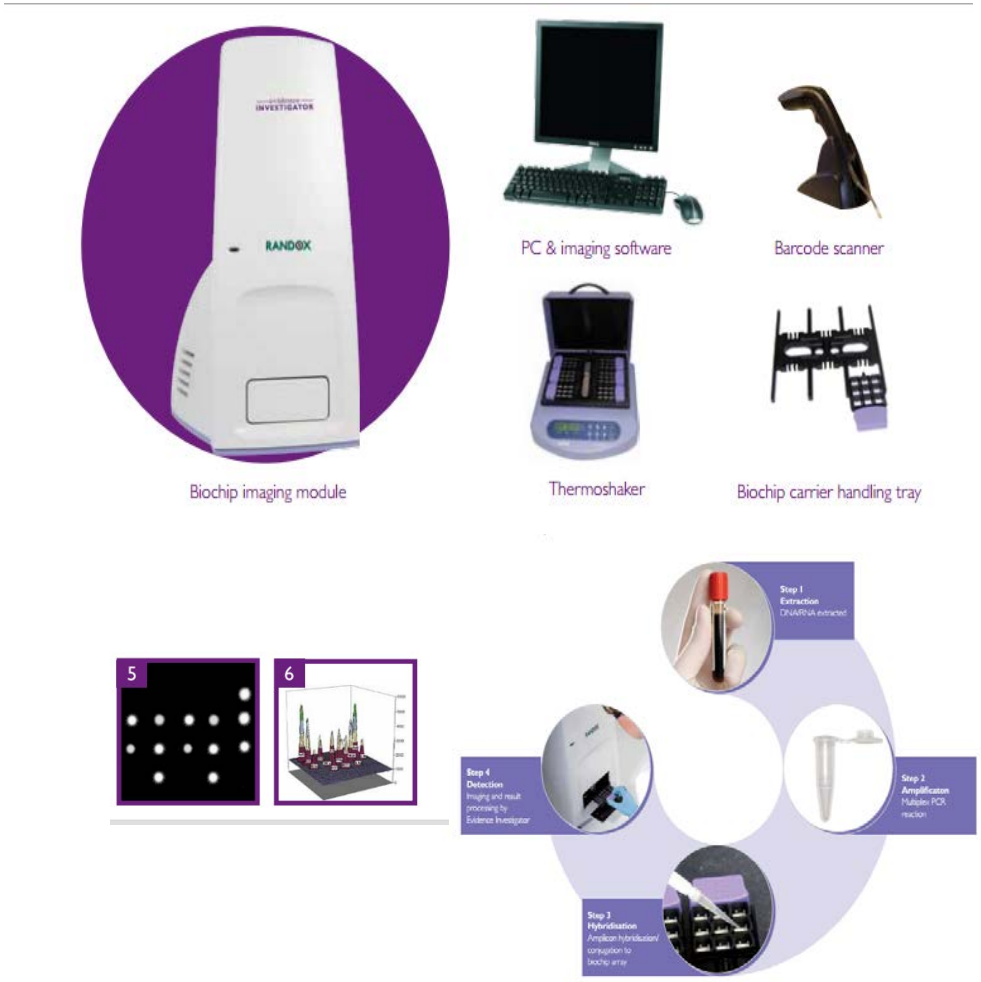


Causative agents of diarrheal diseases

Agent	Nonbloody diarrhea	Bloody diarrhea
Bacterium	• Enterotoxigenic *Escherichia coli* (traveller's diarrhea) • *Vibrio parahaemolyticus* • *Shigella* spp • *Salmonella* spp • *Yersinia* spp	• *Aeromonas* spp • *Campylobacter* spp • *E. coli* producing Shiga-like toxin (e.g., *E. coli* O157:H7 and other strains) • *Shigella* spp • *Salmonella* spp • *Yersinia* spp
Virus	• Norovirus • Rotavirus • Adenovirus • Astrovirus	
Parasite	• *Giardia lambia* • *Cryptosporidum* • *Isospora* or *Cyclospora* spp	• *Entamoeba histolytica*
Toxin	• *Clostridium difficile* • *Staphylococcus aureus* • *Bacillus cereus* • *Clostridium perfringens*	

STI Multiplex Molecular BioChip Array

- *Chlamydia trachomatis*
- *Neisseria gonorrhoea*
- *Herpes simplex I*
- *Herpes simplex II*
- *Treponema pallidum*
- *Trichomonas vaginalis*
- *Mycoplasma hominis*
- *Mycoplasma genitalium*
- *Ureaplasma urealyticum*
- *Haemophilus ducreyi*

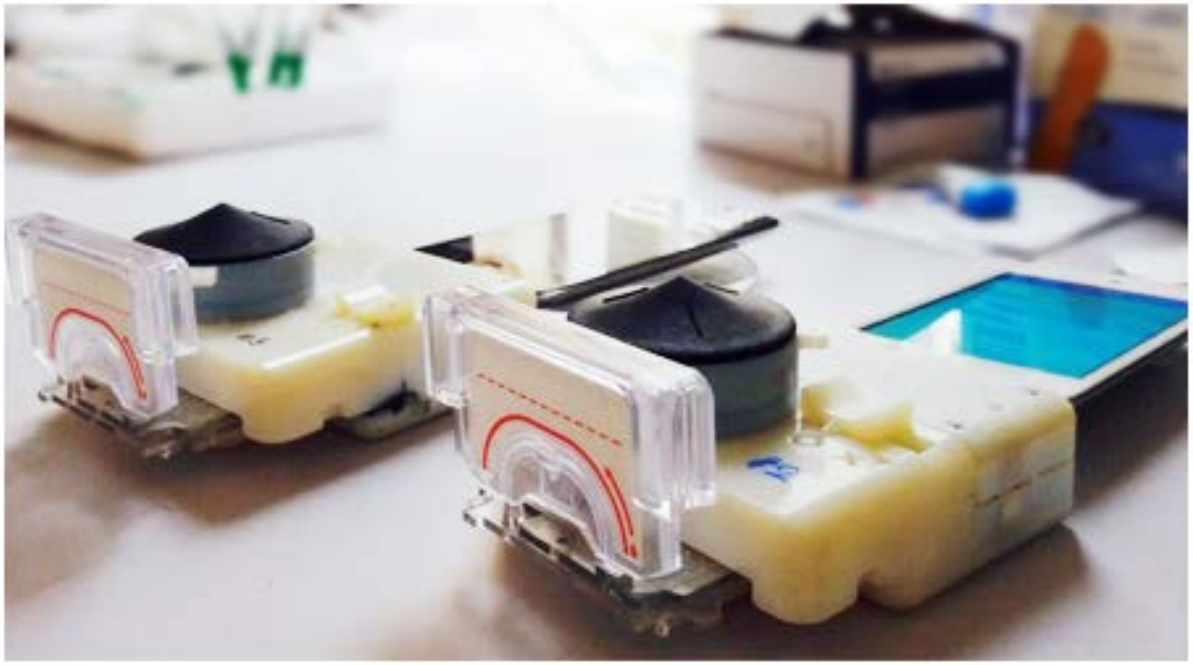


25 ul sample, 22 assays per biochip, 45 samples and 4 calibrators per run

Connectivity Solutions for Rapid Point-of-care Tests

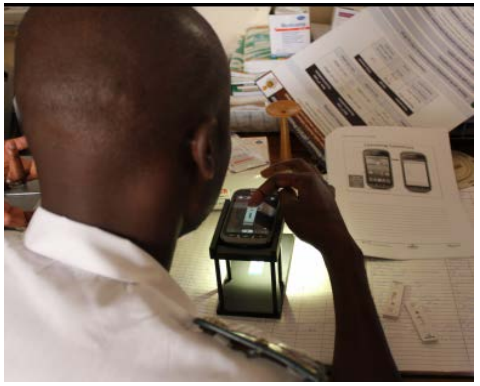
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

SHARE

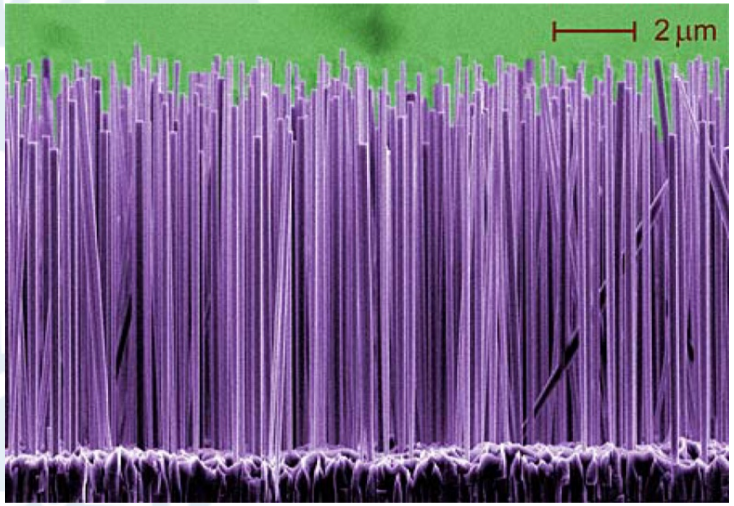


Smartphone dongles performed a point-of-care HIV and syphilis test in Rwanda from finger prick whole blood in 15 minutes, operated by health care workers trained on a software app.

—Image courtesy of Samiksha Nayak for Columbia Engineering



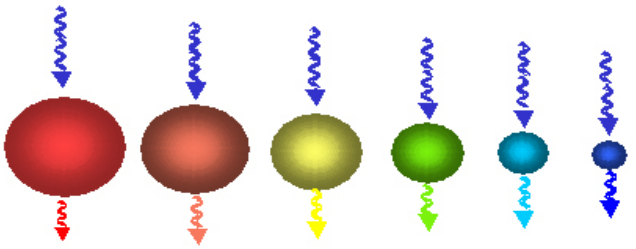
Nanotechnologies



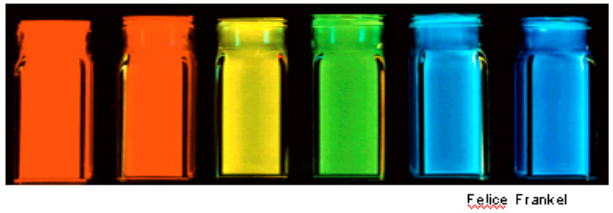
Nanowire technology:

From a finger-pricked sample of blood, this device can detect in 20 min:
- malaria parasites
- distinguish malaria species
- malaria drug resistance

Nanodot technology:



Nanocrystals absorb light then re-emit the light in a different color – the size of the nanocrystal (at the Angstrom scale) determines the color



Six different quantum dot solutions are shown excited with a long wave UV lamp

Summary

- **POCTs can increase access but often at the expense of accuracy and affordability**

- **Connectivity solutions linking data from diagnostic laboratories and POC test readers and devices provide opportunities for:**
  - **automated surveillance systems,**
  - **monitoring quality of tests and testing,**
  - **increasing the efficiency of health care systems,**
  - **improving patient outcomes**

- **System-wide solutions are necessary to provide the IT infrastructure within which diagnostic test data can provide early warning for infectious disease outbreaks, and timely information for disease control and elimination**


Thank you