Diagnostics in a Digital Age: Promises and Challenges

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Diagnostics in a Digital Age

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- **Context:**
  - **Diagnostics for infectious diseases**
  - **Developing world settings**
- **Disruptive innovation in the developing world**
- **Recent diagnostics innovation driven by:**
  - **HIV**
  - **Global health emergencies**
  - **Antimicrobial resistance**
- **Promises and challenges**
- **The way forward**

Disruptive Innovation in the Developing World: The Mobile Phone

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Disruptive Innovation in the Developing World: Unmanned Aerial Vehicles for Health

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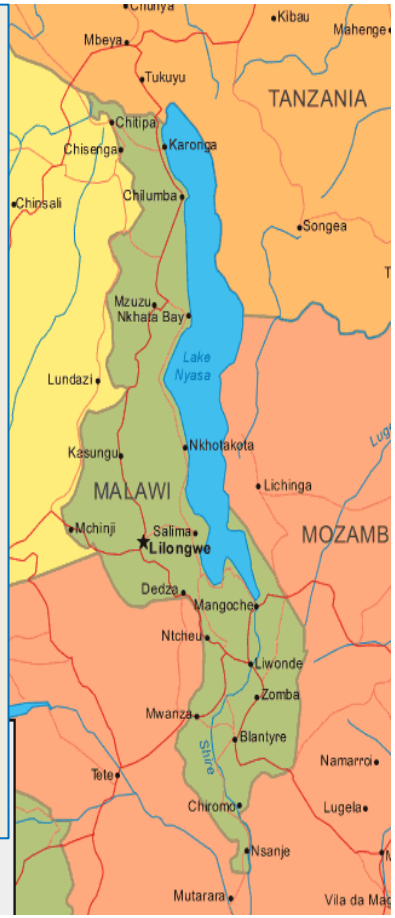
Cost: ~ $10,000
Payload : 5 lbs
Flight time: 30-60 min
Range: 20-60 miles

Operation: manual or pre-programmed for specific routes; need almost no room to land, and can even drop packages from a low hover; can deliver 100 HIV POC tests



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UNAIDS/WHO 2020 Targets for HIV

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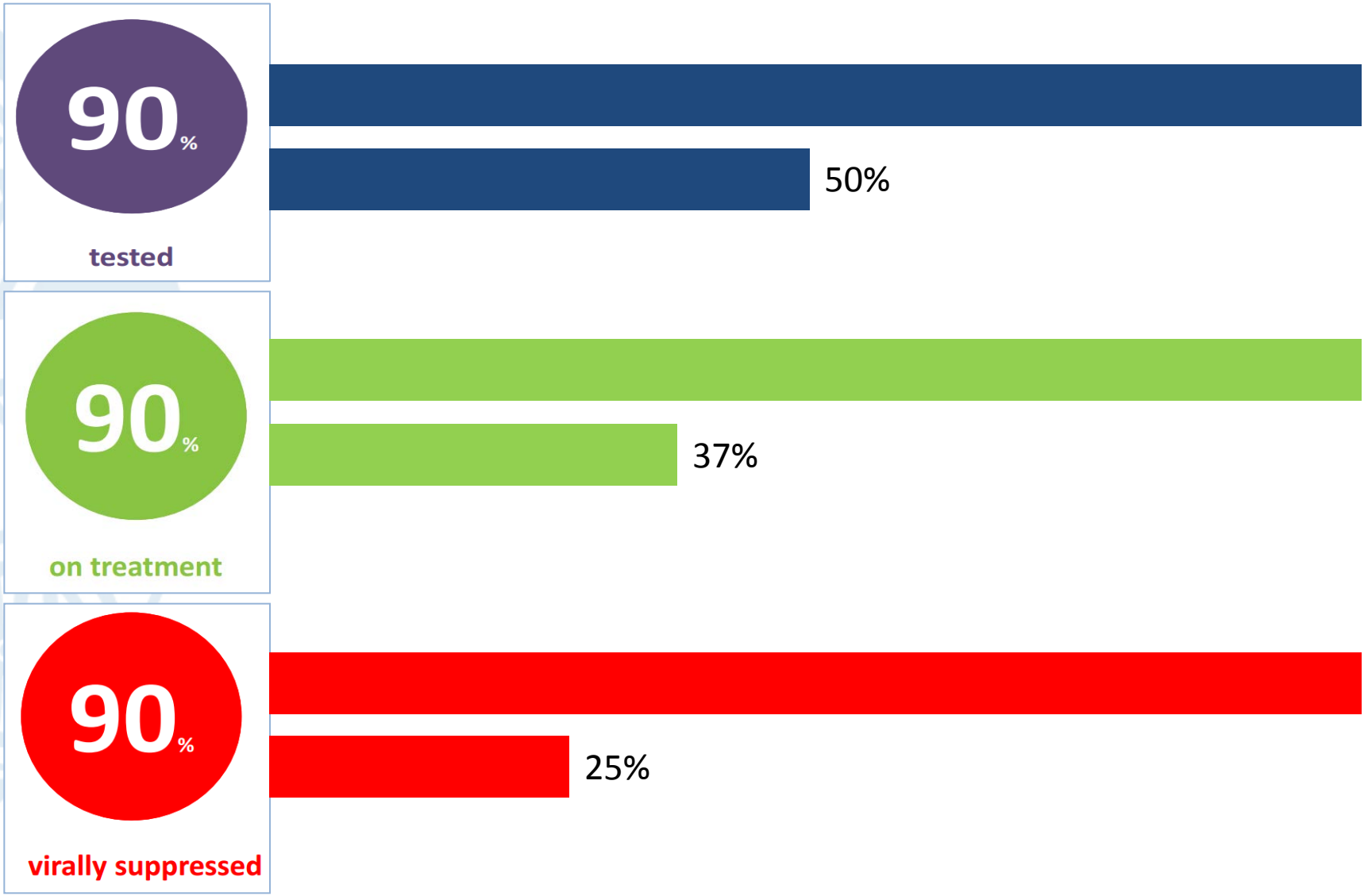

Global Health Emergencies: Call for Open Technology Platforms

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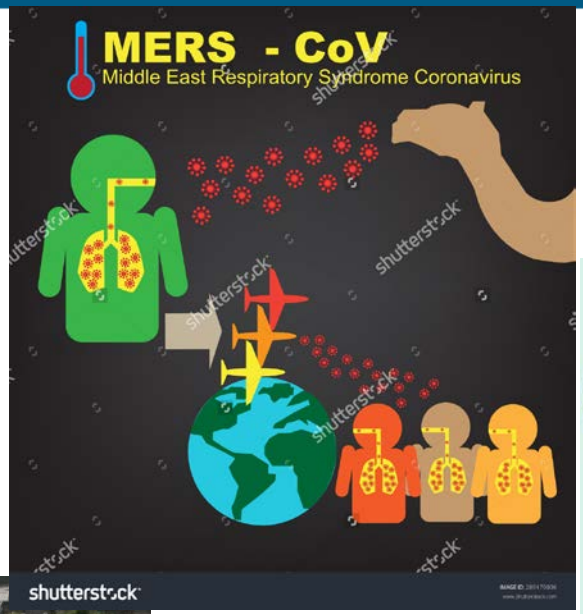

Source: J. Whitehorn

Antimicrobial Resistance: POC Tests

POC Test or test systems are needed to:

- improve the specificity of syndromic management leading to more targeted use of antibiotics
- detect and map AMR for surveillance and guiding treatment
- lower the cost of clinical trials for new drugs

Incentivising Test Development:

- The UK Longitude Prize £ 10 million
- The EC Horizon 2020 Prize: 1 million euros
- The US NIH AMR Prize of up to $ 20 million

The Ideal Diagnostic Test

A = Affordable

S = Sensitive

S = Specific

U = User-friendly

R = Rapid and robust

E = Equipment-free

D = Deliverable

✓ Accurate

✓ Fast/Simple

✓ Cheap

Pick 2 of 3!

Tests: Wish List

Site	Diagnostic test	Wish Tests
GP	POCT for: - Respiratory viruses (influenza, parainfluenza, adenovirus) - Diarrhoea (crypto, salmonella)	Bacterial vs viral infections
Pediatrics	POCT	Bacterial vs viral infections
Obstetrics	POCT for Group B strep, HSV	
A & E	Nasal swab for influenza; Blood for malaria RDT	Sepsis biomarkers
Travellers	VHF, malaria, dengue, rickettsia etc, depending on travel history	

Diagnostics Methods:
Ease of Detection vs Confidence in Diagnosis

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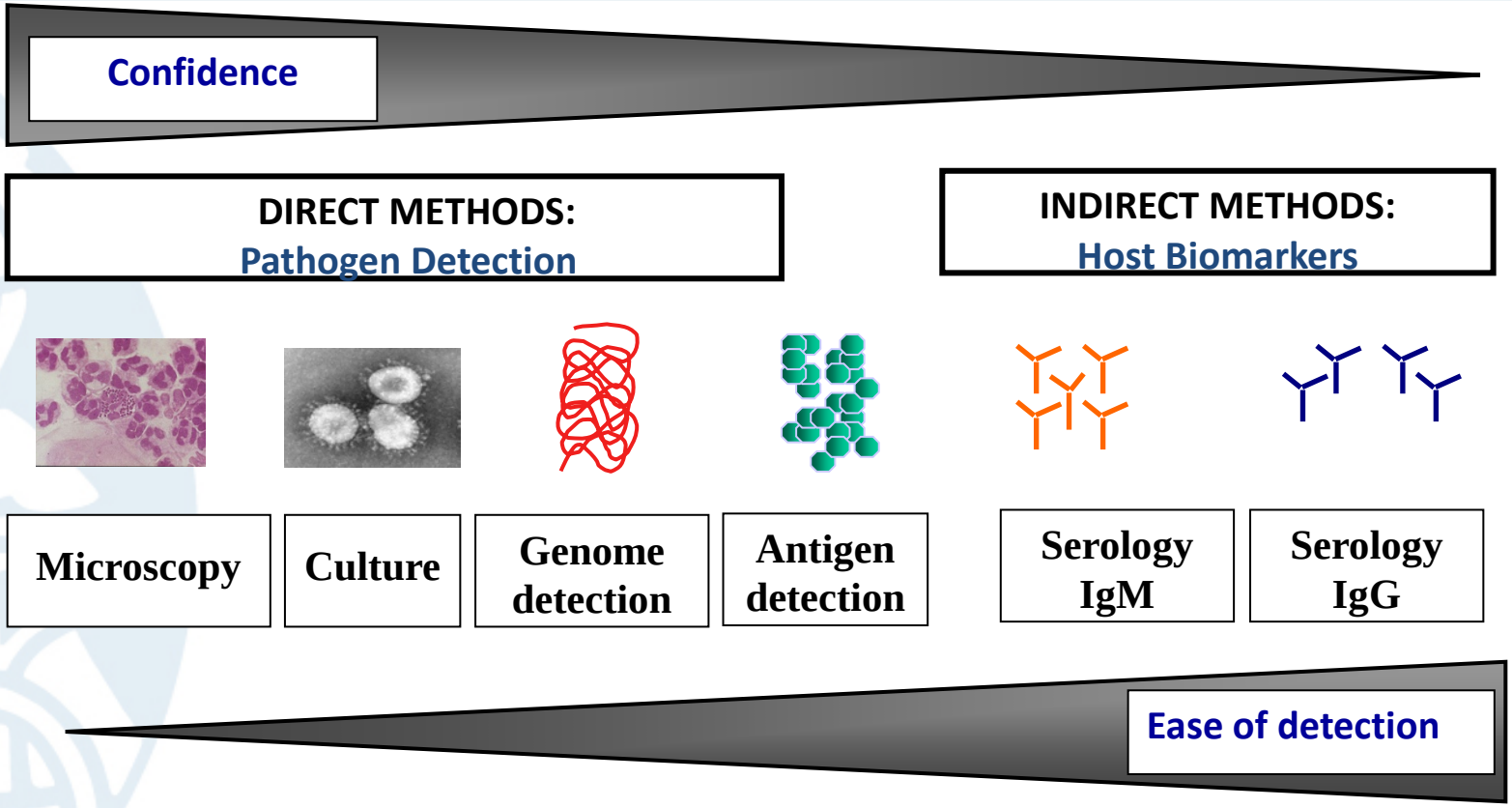

Time to Result:

Days/Hours → **Minutes**

Adapted with permission from J. Cardosa

HIV Early Infant Diagnosis and Viral Load Product Pipeline

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Sample in-answer out

SAMBA VL

DDU/Cambridge

Alere Q

Alere

Roche Liat™

Analyser

IQuum

EOSCAPE HIV™ Rapid RNA Assay System

Wave 80 Biosciences

Gene Xpert

Cepheid

LYNX Viral Load Platform

NWGHF

Truelab PCR

Molbio/bigTec

Cavidi AMP

RT CPA HIV-1

Viral Load

Ustar

Gene-RADAR

Nanobiosym

Viral Load Assay with BART

Lumora

2013

2014

2015

2016

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

UNITAID

Alere i: Point-of-care Molecular Platform

- **Principle:** nucleic acid amplification system (iNAAT) that uses a fluorescence-based molecular signal for detection

- **Applications:**
  - Approved: Influenza virus A and B (Europe)
  - In clinical trials: Ct/Ng
  - In development: Strep A, C. difficile, RSV

- **Operation:**
  - adapted for use by non-laboratory staff
  - time to result: 15min (only 2 min of “hands on” time)

- **Connectivity:**
  - cloud based data storage

Cepheid: A Multi-disease Random Access Real-time PCR Platform

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Omni:
- 9 in. tall
- 1 kg
- AC or battery operated
- controlled via dedicated mobile device
- wireless, web enabled
- USD 2,895

MTB/RIF, Flu A, B/RSV
MRSA, *C. difficile*, Norovirus
CT/Ng, HPV, Group B Strep
HIV Viral Load, early infant diagnosis
HCV

5	20	80	500-1000	Samples per shift

Roche: Cobas Liat RT-PCR System

STEP 1.
Add sample

STEP 2.
Scan barcode

STEP 3.
Insert tube

Done.
Results in ~30 minutes

- **Principle:** RT-PCR with an internal optical analyser that provides 6 independent optical detection channels for real-time detection and quantification of multiple targets
- **Applications:**
  - FDA and CE approved: Influenza virus A and B and Strep A
  - In development: HIV viral load, HCV
- **Operation:**
  - time to result: 15-20 min
  - AC or battery powered
  - Self checks and calibrations with Internal and volume controls
- **Connectivity:** to be confirmed

Molbio: Truelab Real Time micro PCR System

- **Principle:** nucleic acid amplification system that uses a fluorescence-based molecular signal for detection

- **Applications:**
  - Available: MTB, HBV, dengue, Chikungunya, Flu (H1N1), malaria
  - In development: Ct/Ng, HIV viral load

- **Operation:**
  - Sample prep: Trueprep MAG Prep Device and kits 20-25 min.
  - Take 6 ul of extract into reaction well of micro PCR chip
  - Insert chip into micro PCR analyser
  - Amplification with internal controls
  - Quantiative detection using fluorophores in 30 min.
  - time to result: 60 min

- **Connectivity:** not known

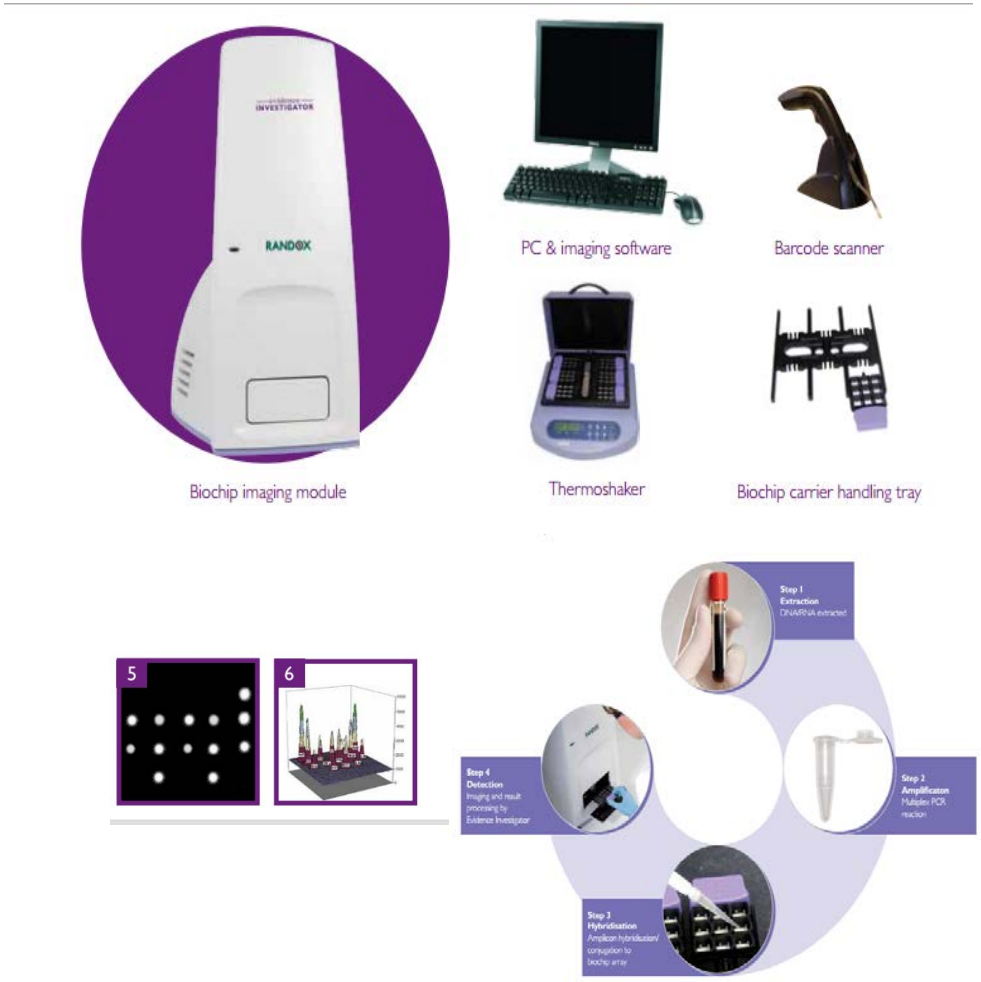
BioFire Film Array

- **Principle**: 2-stage nested multiplex PCR with reagents dried in a plastic pouch; tests 16 pathogens in a run
- **Applications**:
  - Respiratory panel*
  - Biothreat Panel
- **Operation**:
  - time to result: 60 min (only 2 min of "hands on" time)
- **Connectivity**:
  - Interoperable with global information grid

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

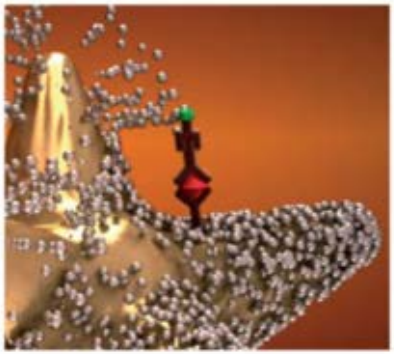
STI Multiplex Molecular BioChip Array

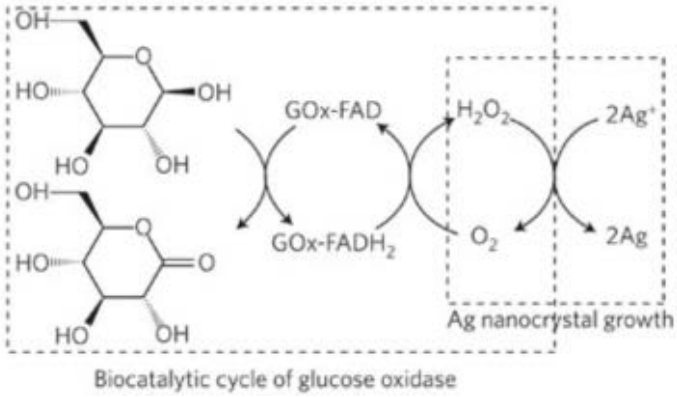
- *Chlamydia trachomatis*
- *Neisseria gonorrhoea*
- *Herpes simplex I*
- *Herpes simplex II*
- *Treponema pallidum*
- *Trichomonas vaginalis*
- *Mycoplasma hominis*
- *Mycoplasma genitalium*
- *Ureaplasma urealyticum*
- *Haemophilus ducreyi*



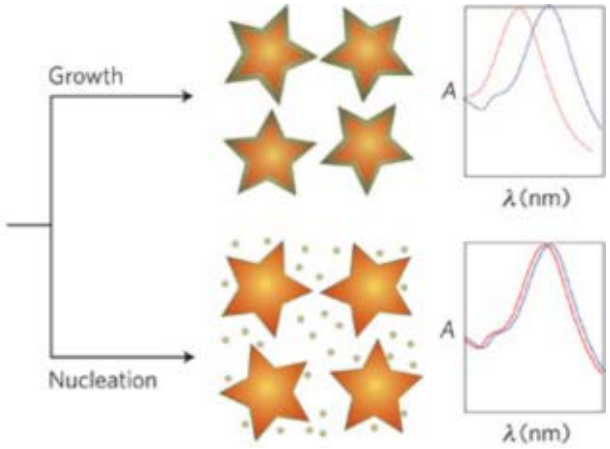
25 ul sample, 22 assays per biochip, 45 samples and 4 calibrators per run

Plasmonic Nanosensors





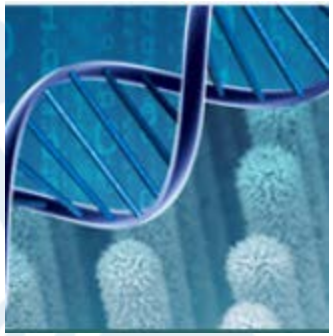
Biocatalytic cycle of glucose oxidase

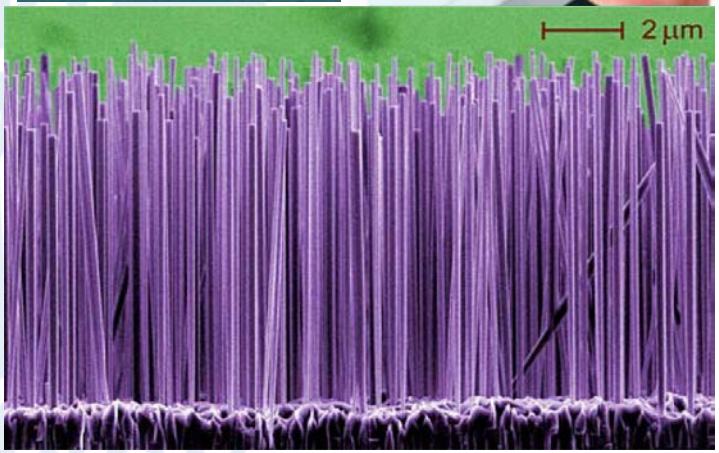


Molly Stevens (Imperial College)

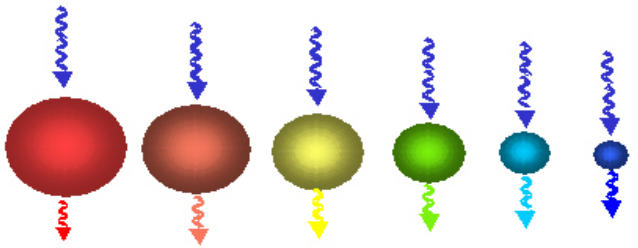
Rodriguez-Lorenzo et al *Nature Materials* **11**, 604–607 (2012)

Nanotechnologies: The potential for Signatures to identify infections

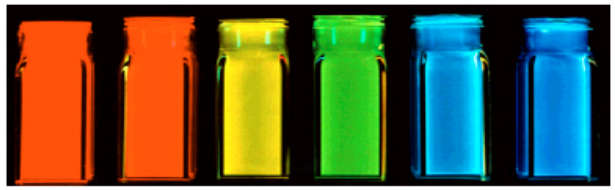




Nanowire technology:
From a finger-pricked sample of blood,
It is possible to detect in 20 min:
- malaria parasites
- distinguish malaria species
- malaria drug resistance



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



Felice Frankel

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

Nanodot technology: can create molecular barcodes with nanodots. These barcodes can represent molecular signatures and allow the system to detect pathogens and their resistance genes or host responses such as cytokines.

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Promises:

- people-centred health care
- improved access to diagnostics for more evidence-based care
- open technology platforms requiring less capital investment and re-training
- automated surveillance through connectivity

Home Use Oral HIV Tests in the US, 2012

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

LWA / GETTY IMAGES

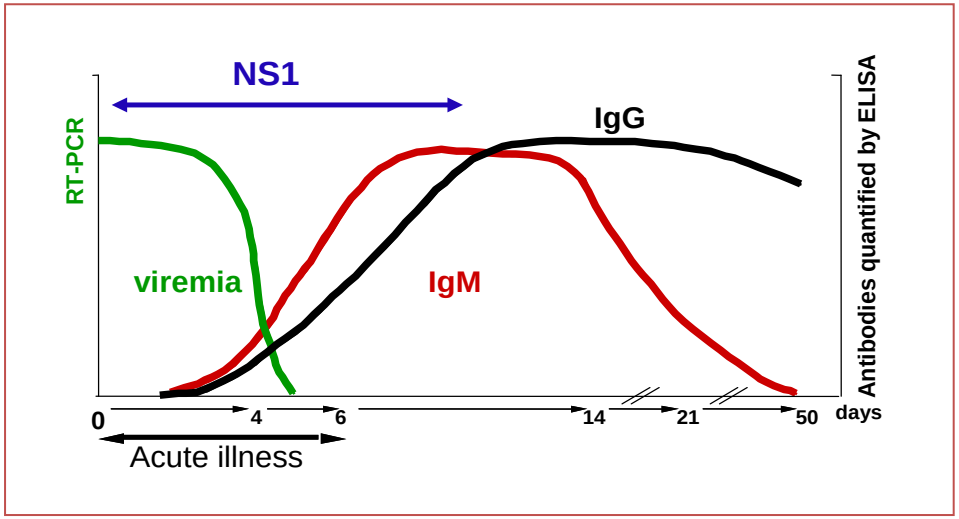
Source: time.com

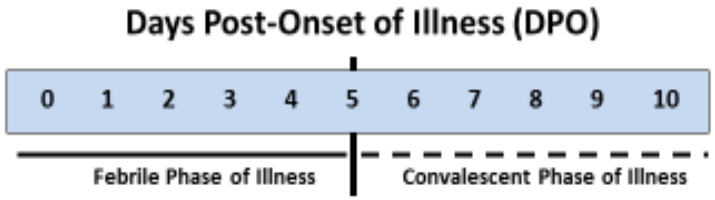
Wearable Biosensors

Reimagining the Future of the Diagnosis of Viral Infections

- 1,234 paired serum samples from laboratory confirmed dengue patients, archived between 2005-2011
- Accurately identified >90% of dengue cases from a single serum specimen collected during the first 10 days of illness by using either:
  - **DENV-RT-PCR + IgM ELISA**

  or
  - **NS1 antigen ELISA + IgM ELISA**





Specimen from suspected dengue case by DPO	IgM anti-DENV	RT-PCR or NS1	Percent Positive	Decision
0-3	-	+	79-90%	One-Test
4-7	+	+	95-100%	Two-Test
>7	+	-	93-100%	One-Test

Hunsperger et al JID Mar 2016

Early-Warning Sensing Systems for Infectious Diseases

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Patients & Public
- Better treatment, care & prevention

facebook

Mobile POC Diagnostics

Social Media

twitter

Health Protection Agency

NHS

BBC

Real Time Public Health Surveillance Systems
- Rapid interventions, prevention

Early-Warning Sensing Systems for Infectious Diseases in the UK

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NHS

Clinical Care

Helping patients gain faster access to care

Accurate Information
Electronic prescriptions

Public Health England

Public Health

Protecting the public
Monitor interventions

Prevention Programmes
Local information

Early Detection

Rapid Response

EPSRC
Engineering and Physical Sciences Research Council

i-sense

Connectivity Solutions for Rapid Point-of-care Tests

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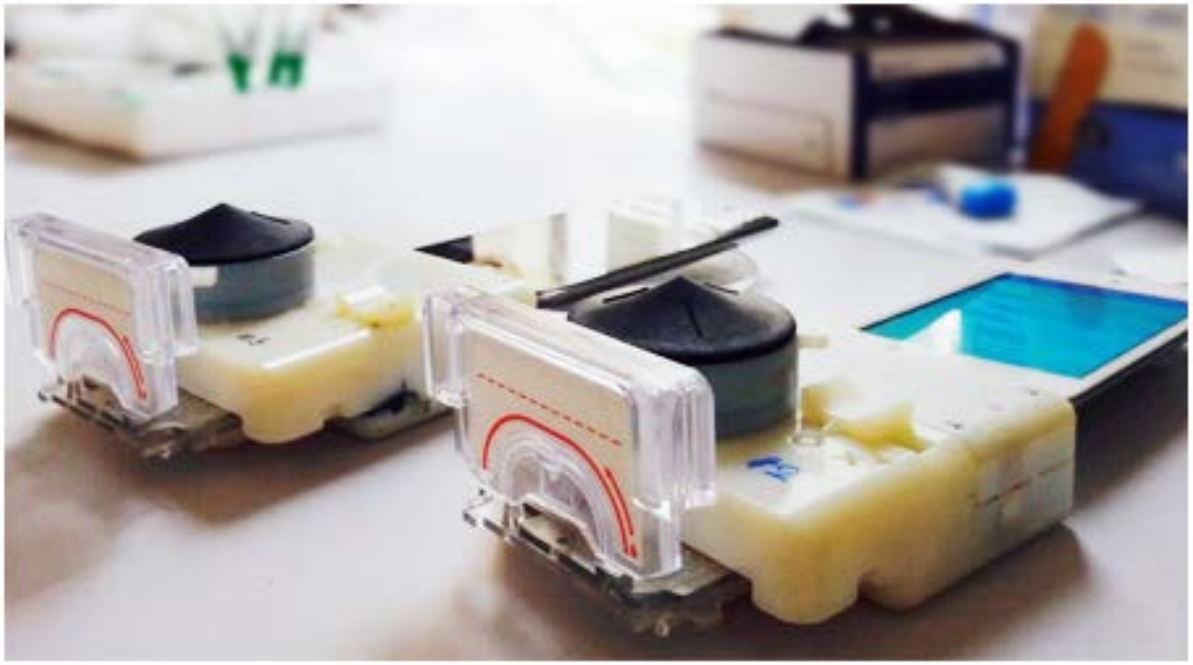
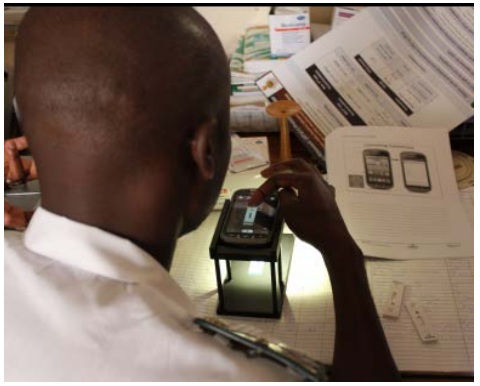
SHARE

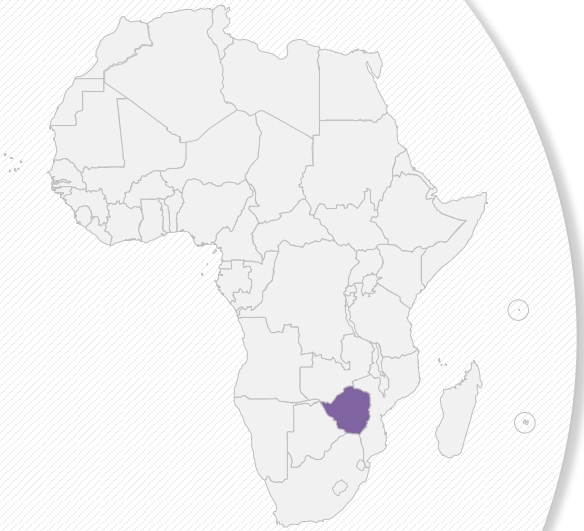


Smartphone dongles performed a point-of-care HIV and syphilis test in Rwanda from finger prick whole blood in 15 minutes, operated by health care workers trained on a software app.

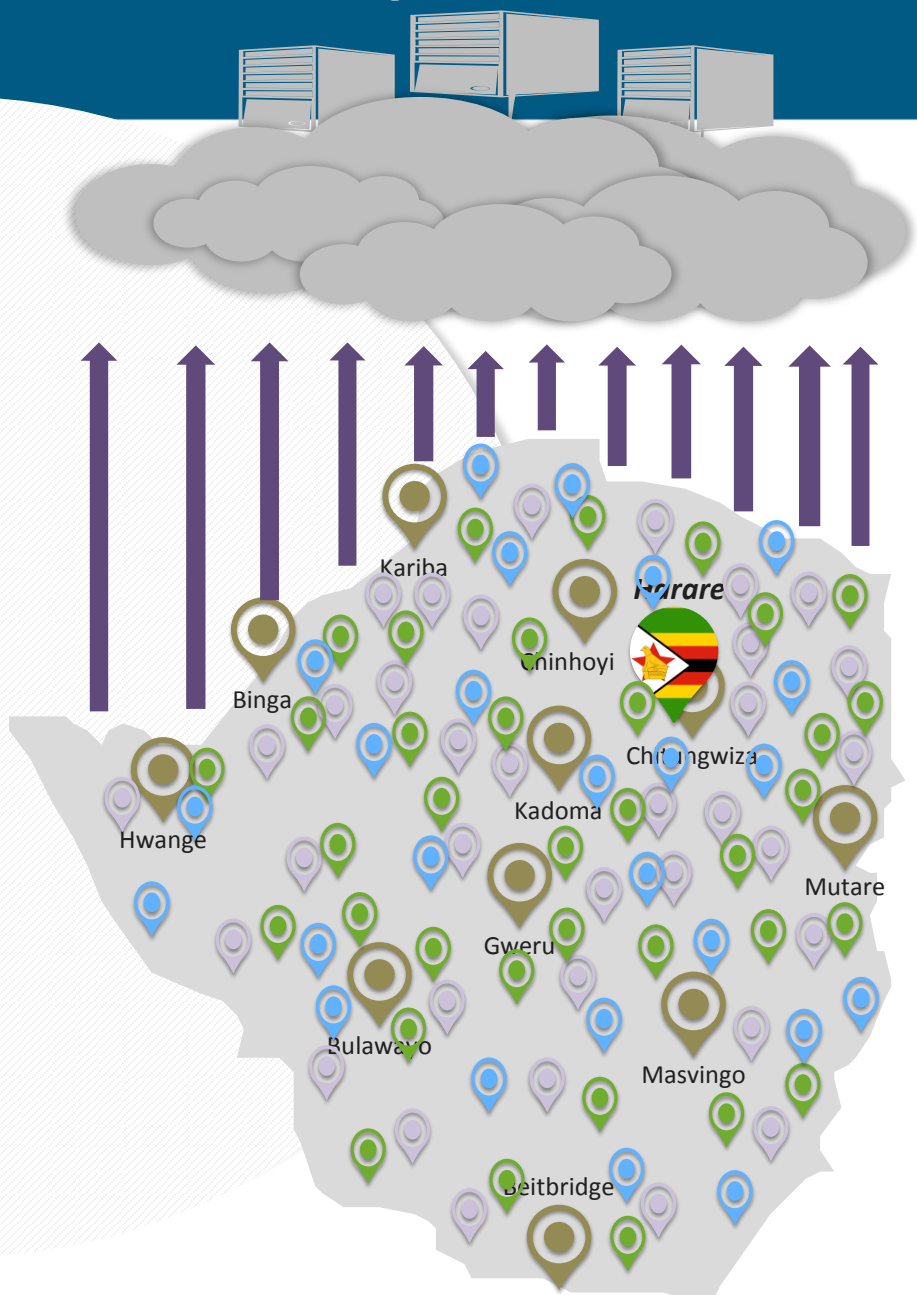
—Image courtesy of Samiksha Nayak for Columbia Engineering

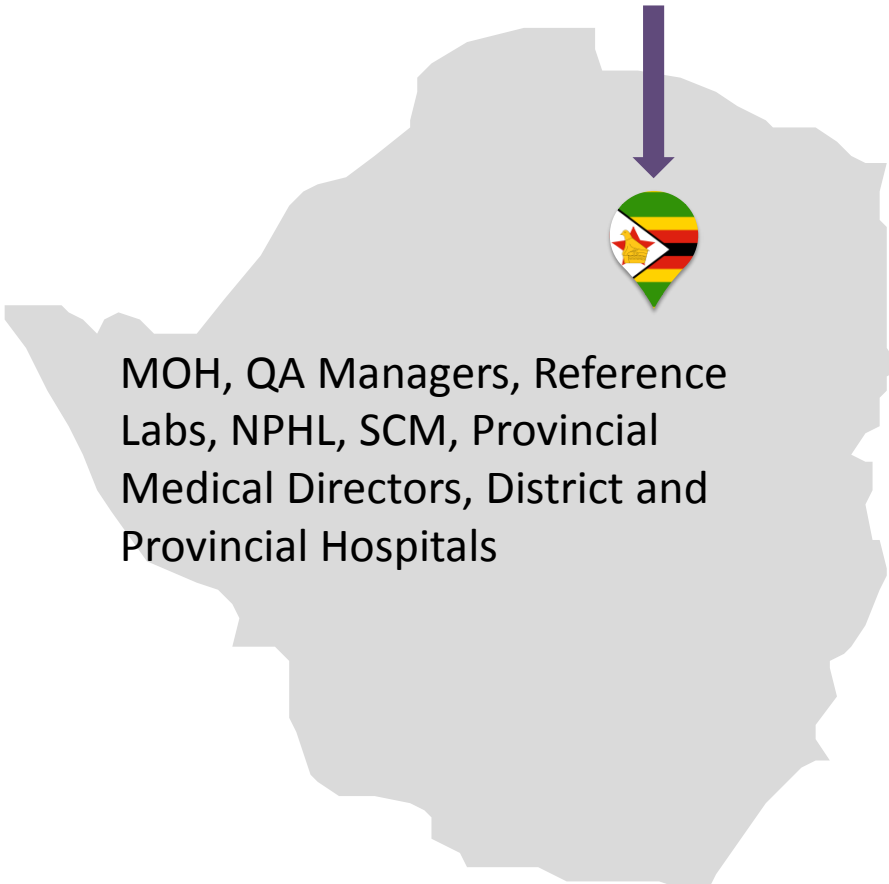


Traditional centralized testing model in Zimbabwe



Connectivity Pilot in Zimbabwe





MOH, QA Managers, Reference Labs, NPHL, SCM, Provincial Medical Directors, District and Provincial Hospitals

The Challenges:

- technological innovations not accompanied by innovation in service delivery
- need to modify patient pathways – more difficult to make changes to health care systems
- data governance

Medical Device Connectivity Ecosystem

- strive to capture all the data feeds which either directly or indirectly impact patient care
  - electronic patient management systems
  - treatment decisions
  - Early warning or public health alerts

- couple these data feeds with:
  - supply chain management systems
  - resources allocation

- Enable government health planners, private and public funding organizations to seamlessly access either patient identified or de-identified data depending upon need but rules needs to be established for data access

The Way Forward

- New sample in-answer out nucleic acid amplification technologies offer improved performance over antigen detection POCTs and the potential to test for multiple pathogens using a single specimen

- Connectivity solutions linking data from diagnostic laboratories and POC test readers/devices provide opportunities for automated surveillance systems

- Promises of diagnostics in a digital age include more patient- centred care, improved access to diagnostics for more evidence-based care, and automated surveillance through data connectivity

- The challenges include modifying care pathways and data governance

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