The POC Challenge

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www.idc-dx.org

The POC Diagnostics Challenge

- **Need for innovation: POC diagnostics**
  - Universal health care – leave no one behind
  - Epidemic preparedness
  - Antimicrobial resistance (AMR)

- **The Promise of Innovation**
  - Convergence of digital and point-of-care diagnostic technologies
  - Mobile phone technology for health
  - Host biomarker rapid POC tests

- **Accelerating access to quality-assured innovative diagnostics**

Sustainable Development Goals (SDGs): A Global Pledge to Leave No-One Behind

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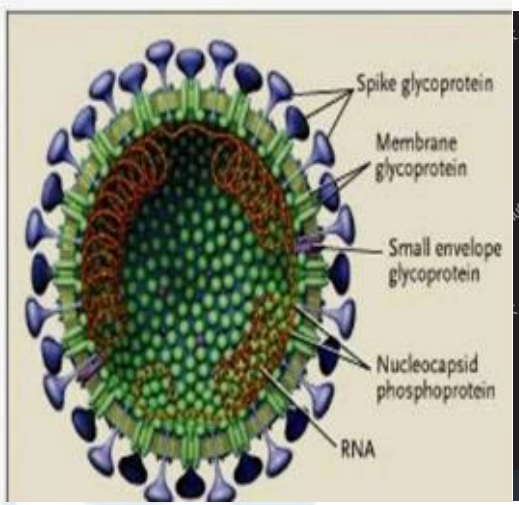
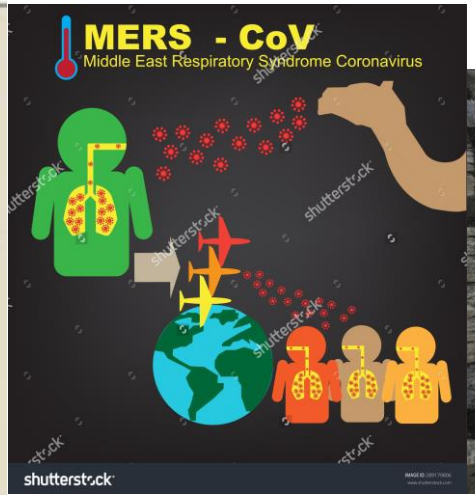
WHO Sustainable Development Goals.
http://www.who.int/sdg/targets/en/

Global Health Emergencies:
Viral epidemics - more frequent and severe





2003-4
SARS

Needed a new test

2012
MERS-CoV

Needed a new test

2013
EBV

Needed a faster NAT and more sensitive antigen test

2015-6
ZikaV

Needed a more sensitive antigen test and more specific antibody test

Rise of the Superbug!

- Public health officials from Nevada reported on a woman who died in September 2016 from an incurable infection of *Klebsiella pneumoniae*. Testing showed the superbug that had spread throughout her system is resistant to all 26 different antibiotics available in the US

- The woman had spent considerable time in India, where she broke her right femur and later developed a bone infection in her femur and her hip and was hospitalized a number of times over 2 years

- Dr. James Johnson, a professor of infectious diseases at the University of Minnesota and a specialist at the Minnesota VA Medical Center:

“People have asked me many times ‘How scared should we be?’ … ‘How close are we to the edge of the cliff?’ And I tell them: We’re already falling off the cliff. It’s happening. “

O'Neill Report May 2016

- In 2016, 700,000 people die from AMR (1 every 45 secs)
- If no action is taken, by 2050:
  - 10 million people will die from AMR (1 every 3 secs)
  - Global lost productivity will amount to US$100 trillion
  - Modern medicine as we know it can no longer be practiced - many infections will become incurable; routine surgery, childbirth, cancer therapy etc will become high risk

Overuse of Antibiotics for Respiratory Infections: Need for host biomarker assays

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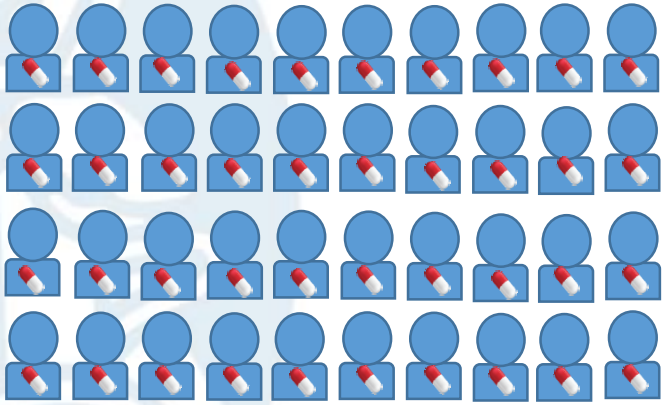
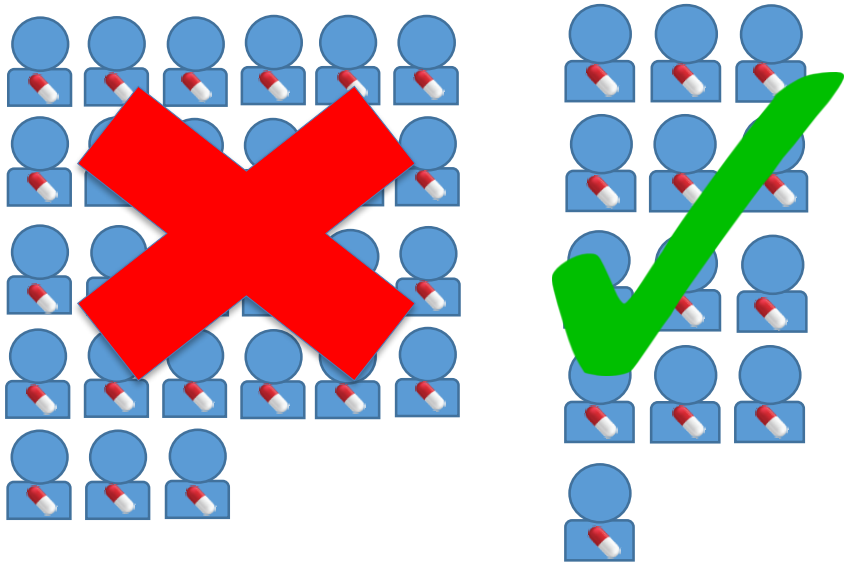
In the US each year, approx. 40 million people are given antibiotics each year for respiratory issues.



A study by Shapiro et al found that 27 million of these 40 million people are given antibiotics unnecessarily.



Overuse of antibiotics greatly increases the risk of antibiotic resistance

A rapid test to distinguish between bacterial and viral infections can reduce inappropriate use of antibiotics

Ref: Shapiro et al. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-9. J Antimicrobial Chemother 2013.

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  - Antimicrobial resistance (AMR)

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Explosion in Near-Patient Molecular Technologies

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PositiveID


STATDiagnostica


Great Basin


Cepheid


BioCartis


IdahoTechnologies


BioFire


Alere


Veredus


Epistem


iCubate


Osmetech


Curetis


Roche


Enigma


Gentura


Atlas Genetics


Molbio


Rheonix


QuantumDx


Spartan


Fluidigm


Qiagen


Micronics

A Connected Diagnostic System from Labs to Phone-based diagnostic technologies

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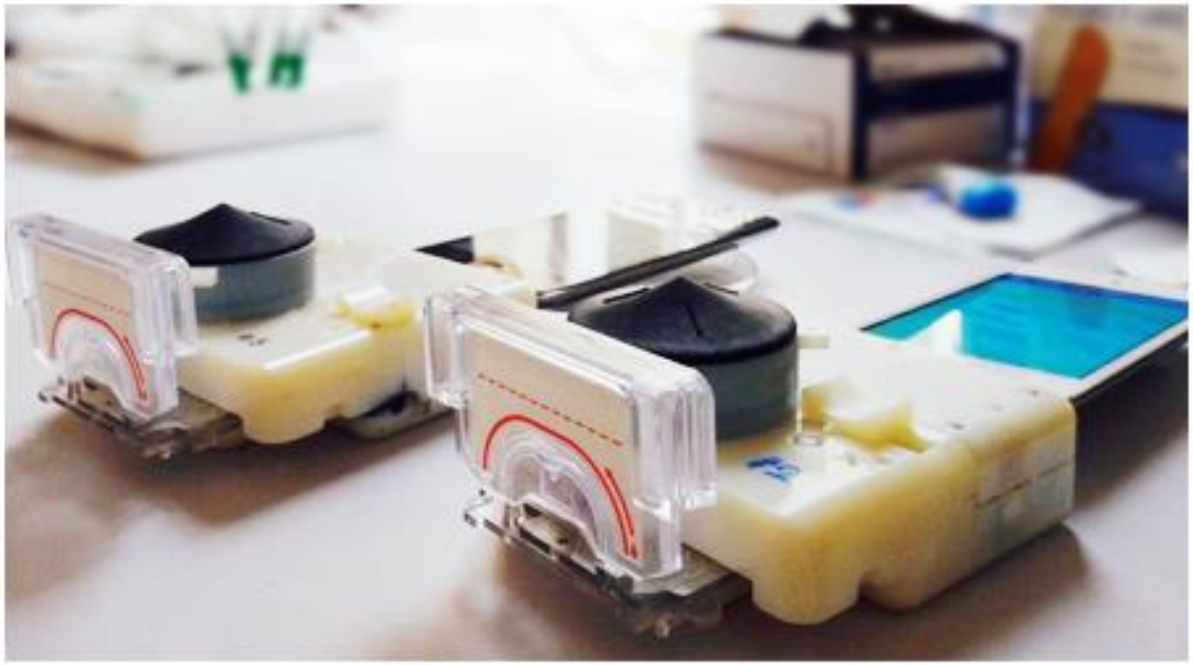
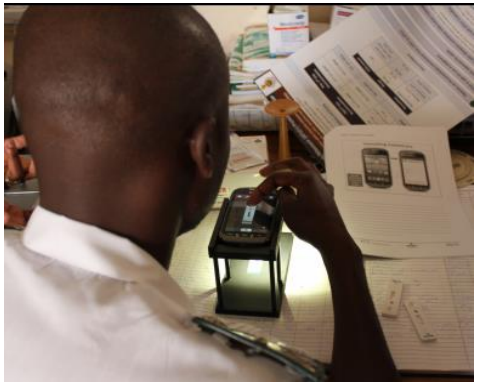
SHARE



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



Smartphone enabled diagnostic technologies

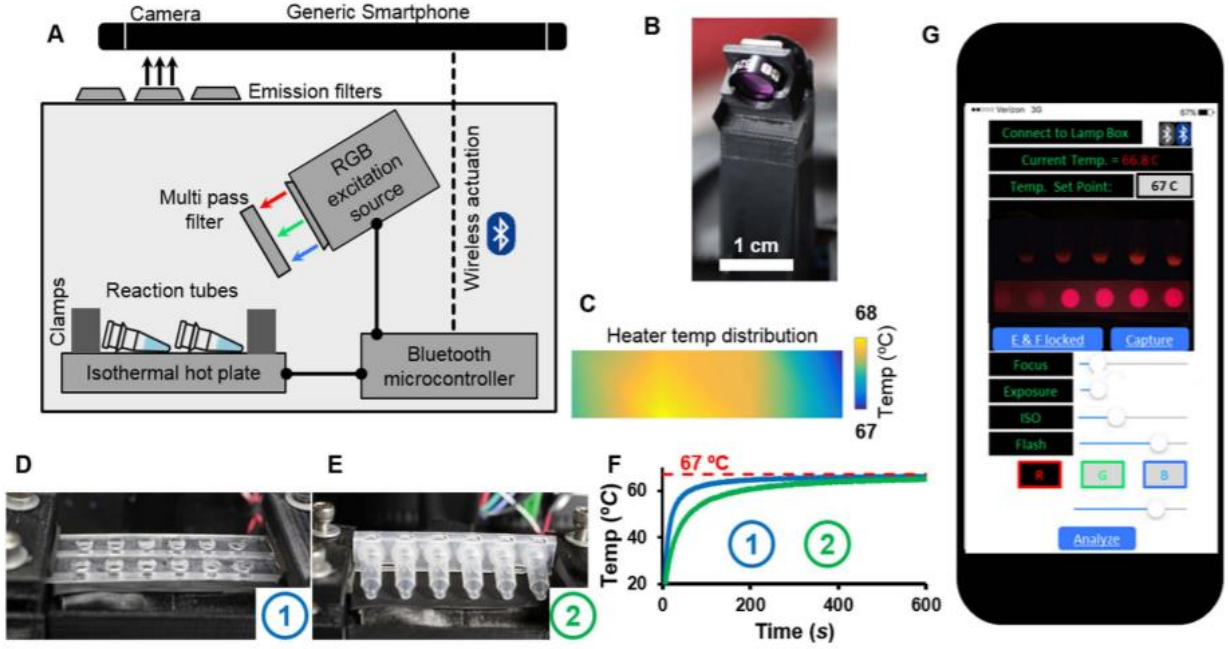


Figure 3. Smartphone enabled ZIKV detection. (**A**) Schematic of the RT-LAMP detection setup depicting the isothermal heater with reaction tubes, LED excitation source and Bluetooth microcontroller (Arduino Uno). (**B**) A 3 watt RGB LED coupled with an RGB multi band pass filter ensures a narrow excitation source for the assay reagents. (**C**) The isothermal heater provides a uniform surface temperature distribution within a 1 °C variation. The heaters can be loaded with either (**D**) off the shelf PCR polypropylene tubes or (**E**) custom made laser-cut reaction wells. (**F**) Thermal management and heat ramp rates are greatly improved with custom laser-cut wells. (**G**) The smartphone app wirelessly actuates the isothermal heater and RGB LED excitation source to enable real time monitoring and changing of the heater temperature along with illumination of the samples with appropriate excitation light source. The illuminated reagents are captured by the smartphone camera equipped with an interchangeable emission filter and the images are analyzed subsequently.

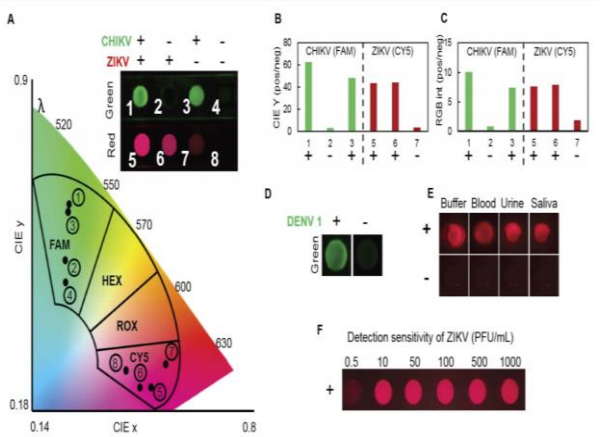
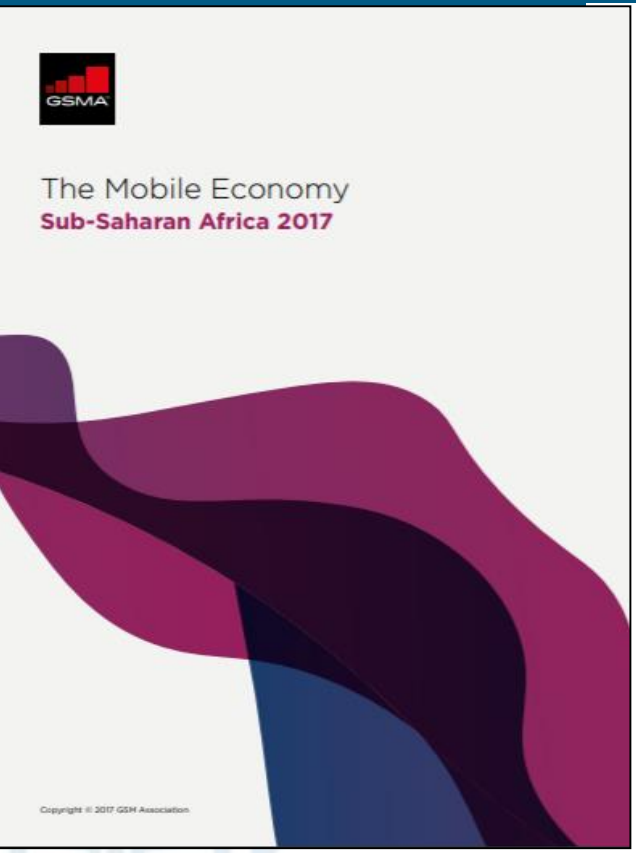
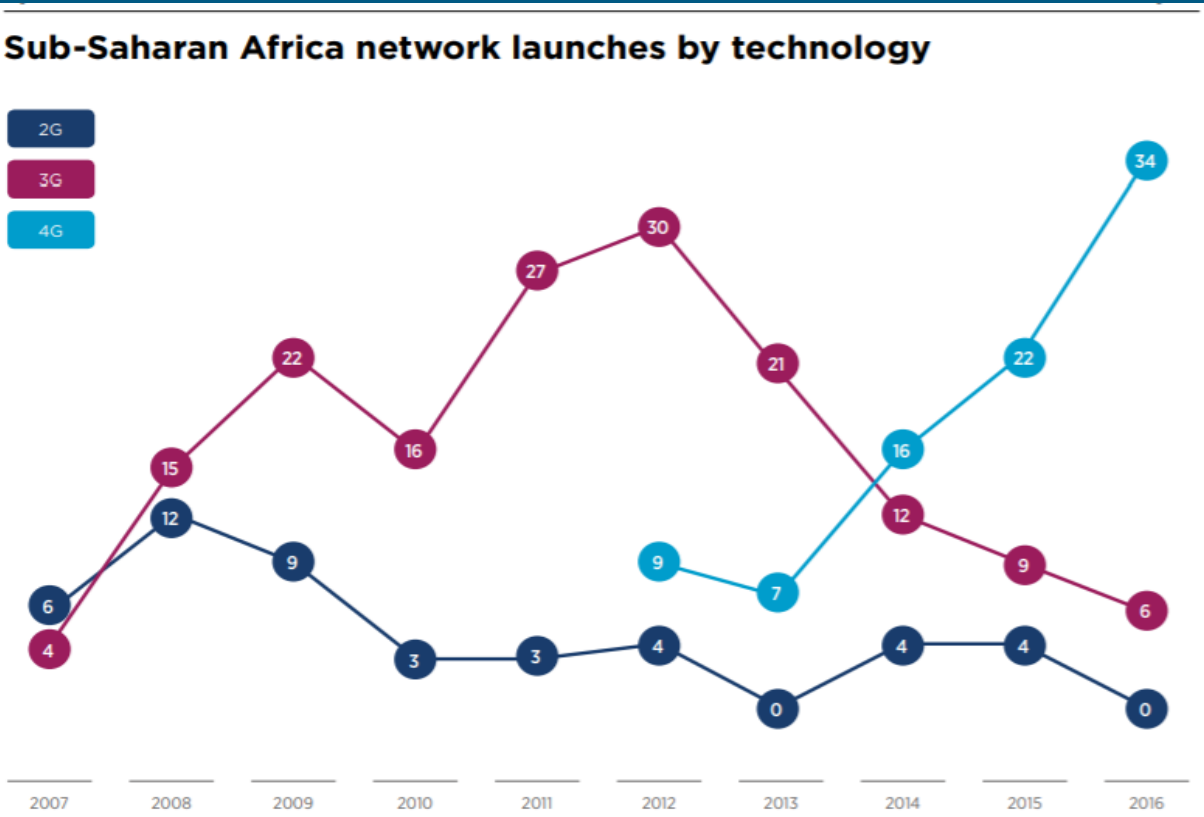


Figure 4. Mobile application for color sensitive multiplexed assay detection. (**A**) Duplex detection of ZIKV/

Priye, A. et al. A smartphone-based diagnostic platform for rapid detection of Zika, chikungunya, and dengue viruses. Sci. Rep. 7, 44778; doi: 10.1038/srep44778 (2017).

Africa CDC: Can we leapfrog public health practice by building connected diagnostic systems?





- At the end of 2016, there were 420 million unique mobile subscribers in Sub-Saharan Africa, equivalent to a penetration rate of 43%.
- Phone adoption in Africa continues to grow faster than any other region of the world

Harnessing Nanotechnology, Telecomms and Big Data for Global Health

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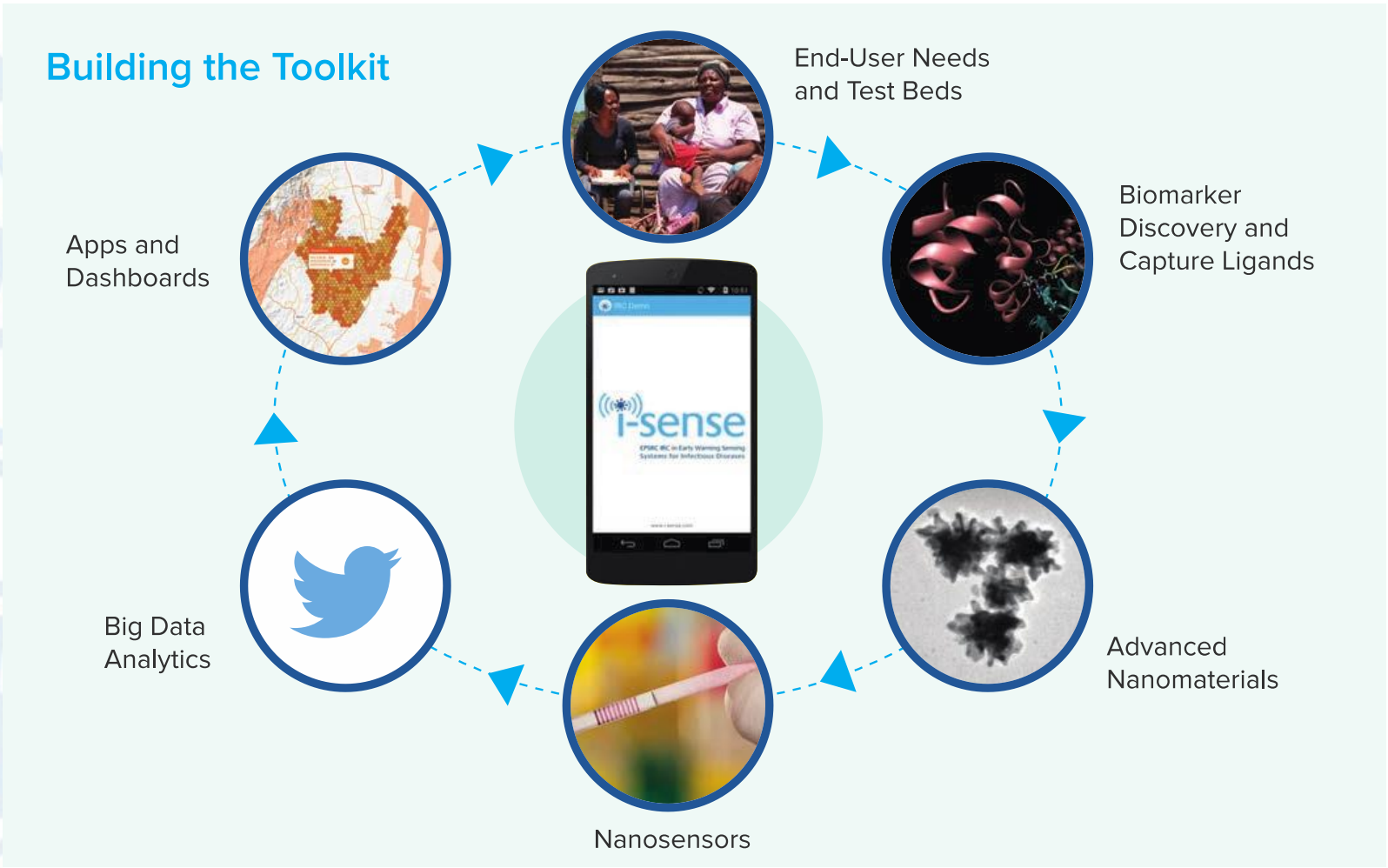
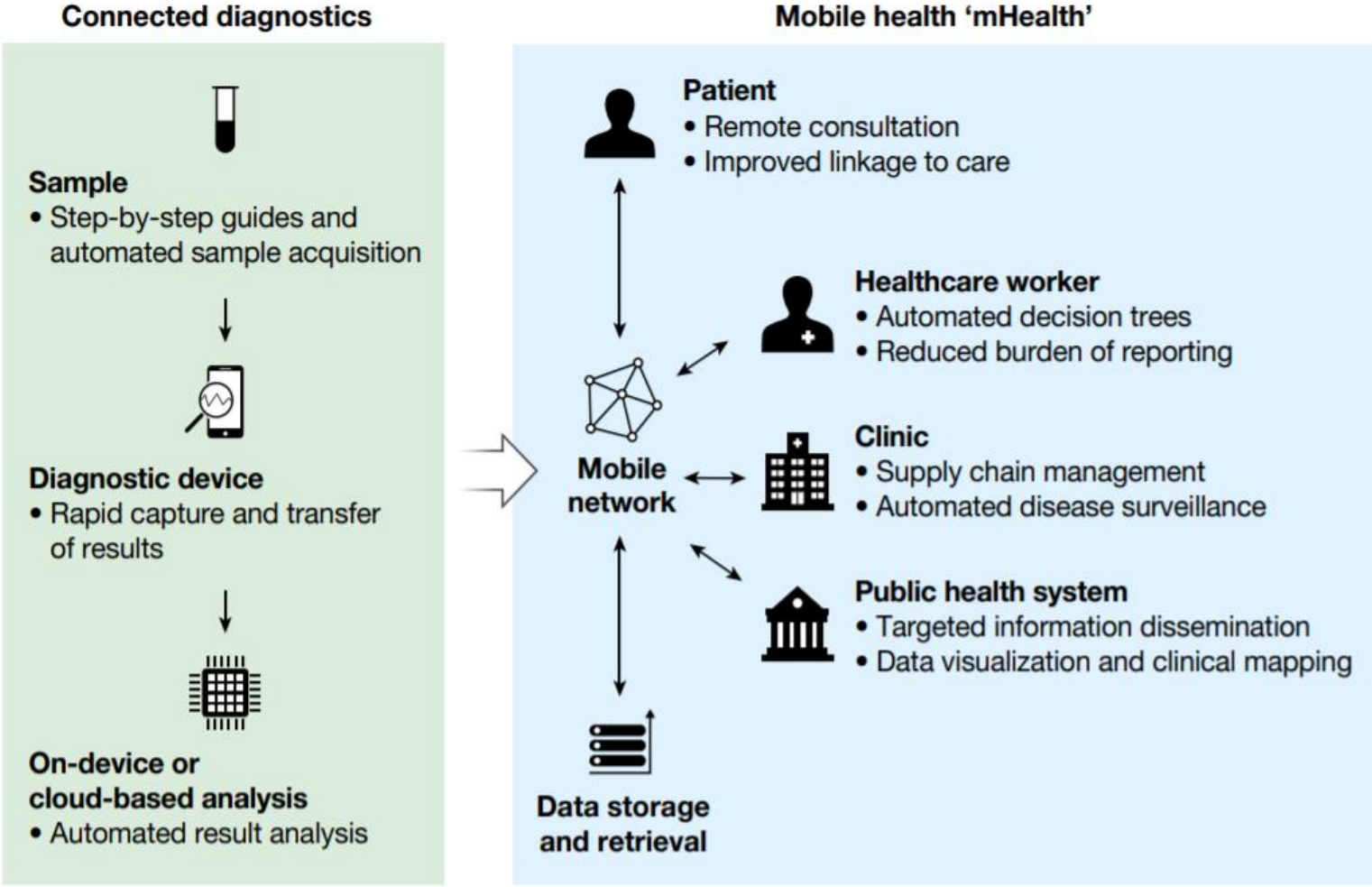
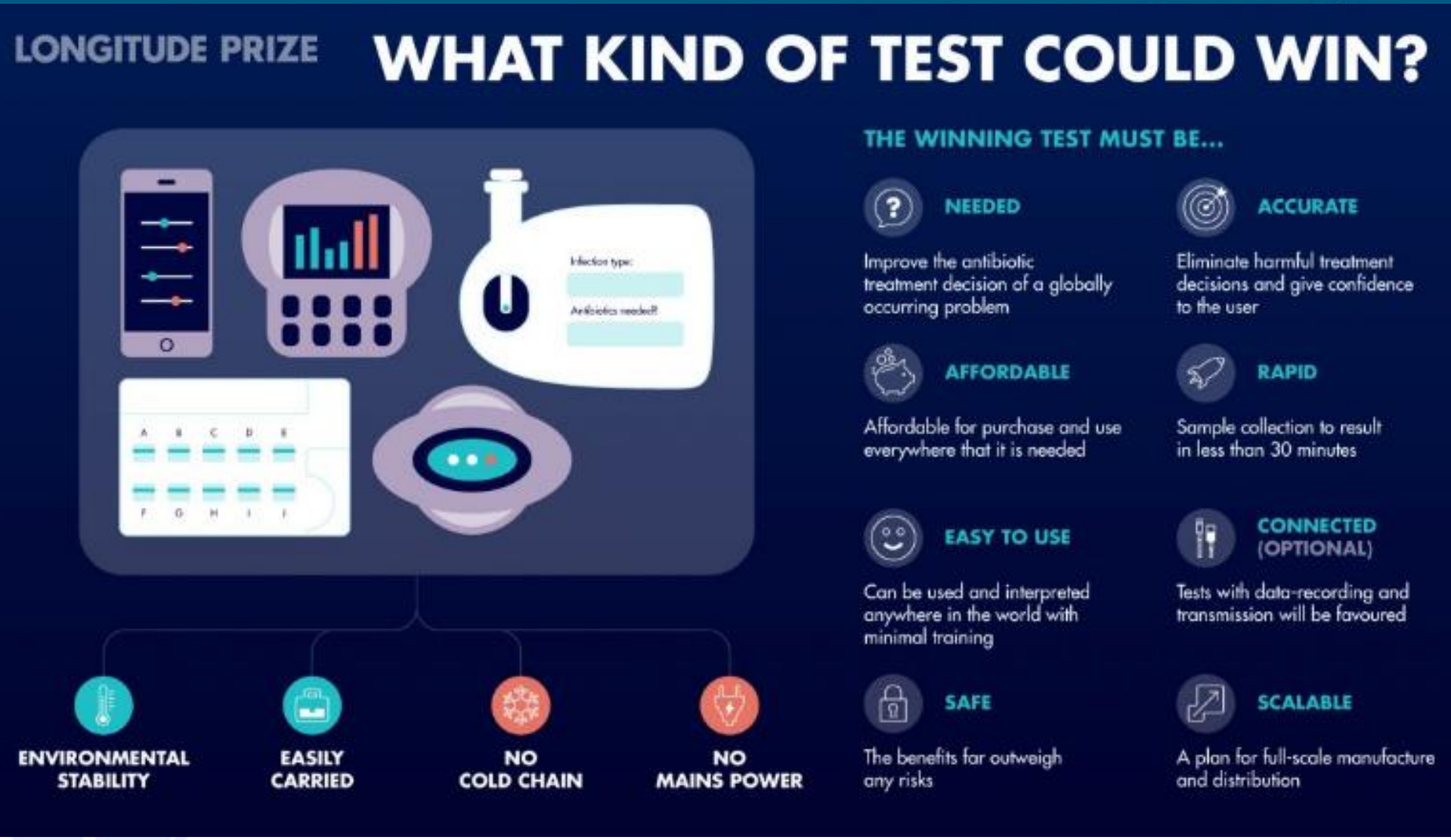


EPSRC Engineering and Physical Sciences Research Council · UCL · Imperial College London · Newcastle University · London School of Hygiene &Tropical Medicine · University of Surrey · Public Health England

Health System Strengthening: Connectivity



Wood CS, Thomas MR, Budd J, Mashamba-Thompson TP, Herbst K, Pillay D, Peeling RW, Johnson AM, McKendry RA, Stevens MM. Taking connected mobile-health diagnostics of infectious diseases to the field. Nature. 2019 Feb;566(7745):467-474. doi: 10.1038/s41586-019-0956-2. Epub 2019 Feb 27. PMID:30814711



This infographic explains the most important criteria required for teams to meet in their test design to be considered for the prize, from being easily used and accessible by anyone, to pumping out its results in 30 minutes from the moment the sample is taken. The winning test will help reduce unnecessary use of antibiotics and/or help medical professionals know which antibiotic to use when.

Evolution of The Ideal Diagnostic Test

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2004

- **A** = Affordable
- **S** = Sensitive
- **S** = Specific
- **U** = User-friendly
- **R** = Rapid and robust
- **E** = Equipment-free
- **D** = Deliverable

2018

- **R** = Real time connectivity
- **E** = Ease of specimen collection
- **A** = Affordable
- **S** = Sensitive
- **S** = Specific
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- **D** = Deliverable

Mabey D, et al. Diagnostics for the developing world. Nature Rev Microbiol 2: 231-40, 2004.

Land KJ,et al. REASSURED diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. Nat Microbiol. 4(1):46-54.2019. e-pub Dec 2018.

Host Biomarkers evaluated in Patient Samples

Biomarkers (> 100)

- Blood cells and hematologic markers (e.g.: **WBC**, neutrophil counts, ESR, others)
- Inflammation markers (e.g.: **CRP, Procalcitonin**, HNL (pre-activation with fMLP), others)
- Cytokines (e.g.: IL-4, IL-6, IL-8, IL-5, IL-12, IL-13, IL-9, IP-10, PF-4, TRAIL, GM-CSF, others).
- Cell surface markers (eg.: CD64, Gal-9, CD35, CD32, others)
- Metabolic activity markers (e.g.: Glucose-CSF, lactate-CSF, Protein-CSF, others)
- Transcription signatures (10-52 gene cluster classifiers)
- Other biomarkers (HBO, inorganic compounds, microRNAs)

Comparisons

- Bacterial vs. any non-bacterial infection
- Bacterial vs. any viral infection
- Bacterial vs. any fungal infection
- Bacterial vs healthy controls
- Bacterial vs sterile inflammation

Diseases/Conditions

- Meningitis
- Gastroenteritis
- Sepsis
- Pneumonia and other Lower Respiratory Tract Infections (Acute Bronchitis)
- Upper respiratory tract infections (tonsillitis, pharyngitis, common cold)
- UTI (upper and lower)
- Postoperative infections,
- Infective endocarditis
- Others

Evaluation Outcomes

- Host biomarker levels
- Diagnostic performance (sensitivity, specificity)

*For most biomarkers (with the exception of the most studied ones in **bold**) there are few quality studies on antibiotic use, clinical outcomes, cost-effectiveness, safety and acceptability

Main References:

Kapesi et al. PLoS One (2016), Systematic review (host biomarkers)
Sager et al. BMC Medicine (2017), Review (Procalcitonin)
Cooke J, Butler C, Hopstaken R, et al. BMJ Open Resp Res (2015), Narrative review (CRP, level of care)

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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

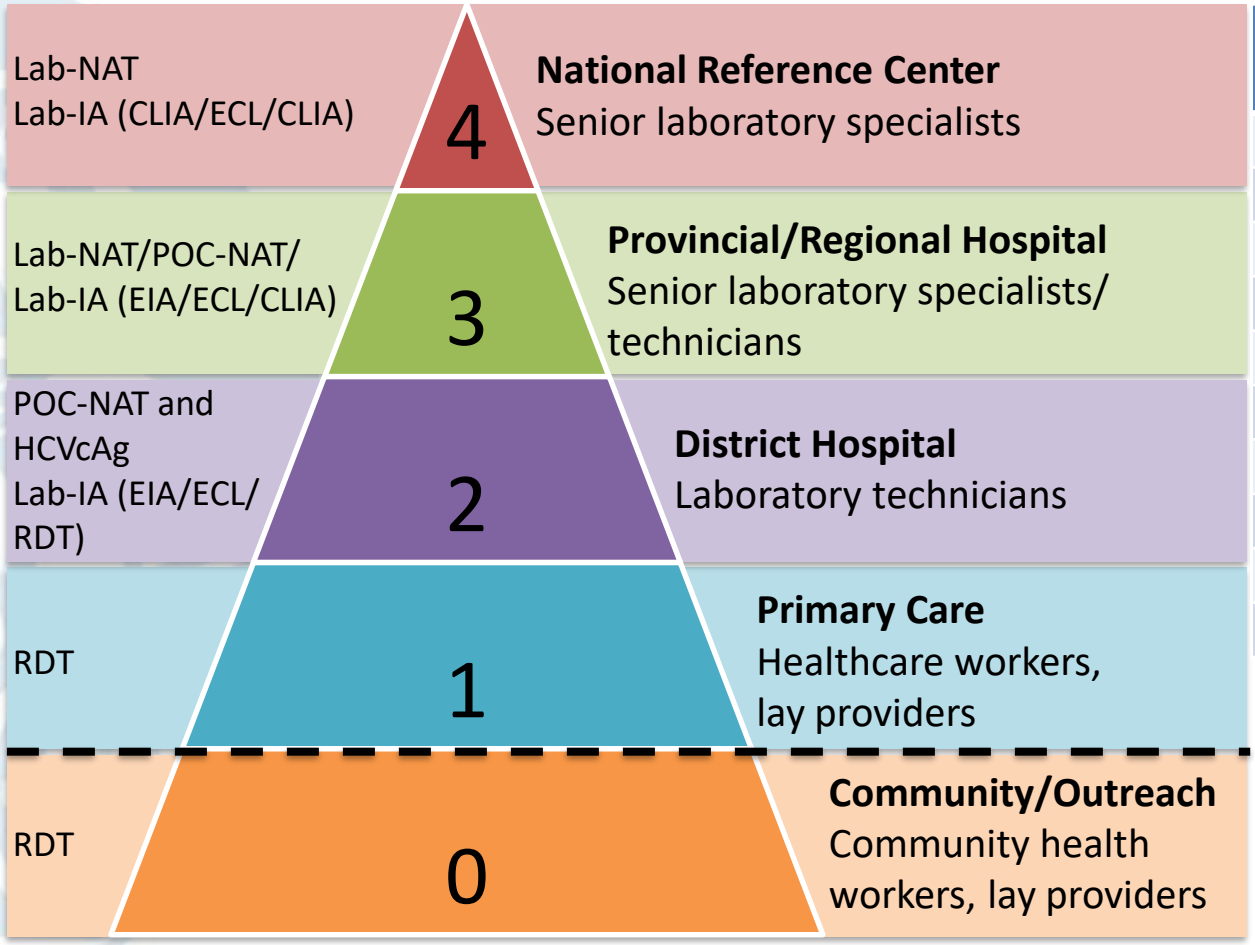
D = Deliverable

- ✓ Accuracy
- ✓ Accessibility
- ✓ Affordability

The paradigm of non-inferiority for regulatory approval of new health products is no longer valid for diagnostics when we need to consider the trade-off between accuracy and access.

But how do we put a value on access?

NO Test is Perfect: Trade-Off between Access and Sensitivity



Access	Sensitivity			
	100	90	80	70
100	100	90	80	70
90	90	81	72	63
80	80	72	64	56
70	70	63	56	49
60	60	54	48	42
50	50	45	40	35
40	40	36	32	28
30	30	27	24	21
20	20	18	16	14
10	10	9	8	7

CLIA, chemiluminescence immunoassay;
ECL, electrochemiluminescence immunoassay; EIA, enzyme immunoassay; Lab-NAT, laboratory-based; NAT, nucleic acid tests; POC-NAT, at point-of-care; RDT, rapid diagnostic test.

WHO Guidelines on Hepatitis B and C Testing. Available at: http://apps.who.int/iris/bitstream/10665/254621/1/9789241549981-eng.pdf?ua=1 (accessed July 2018).

FDA Approval OraSure HIV Test in 2012: Accessibility vs Accuracy

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Accuracy	Professional Use		Over-the-Counter	
	Minimum Recommended Performance: lower bound of 2-sided 95% CI	Actual Performance	Minimum Recommended Performance for the lower bound of 2-sided 95% CI	Actual Performance
Sensitivity	**98%**	99.3% (98.4-99.7%)	**95%**	92.98% (86.6-96.9%)
Specificity	**98%**	99.8% (99.6-99.9%)	**95%**	99.98% (99.9-100%)

A risk-benefit model showed that in the first year of use:

~ 4,500 new HIV infections identified among those not aware of their HIV status
~ 2,700,000 who would test negative

~4,000 transmissions would be averted, outweighing the individual risk of ~1,100 false negative results
The product would need to have clear messages on the implications of test results

The Rapid Test Paradox: rapid vs sensitivity

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Goal of Study: to determine the situation in which a rapid chlamydia test might be more cost-effective and lead to more infections being treated than laboratory-based tests

Study design: A decision analysis framework was used to compare a rapid CT test with a lab based PCR assay, for screening women at an STD clinic; variables include:

- prevalence; test sensitivity and specificity
- probability of developing pelvic inflammatory disease (PID)
- likelihood that patients will wait for the rapid test results or return to the clinic for treatment

Results:

-A rapid test with a sensitivity of 65% led to more cases of CT infections being treated than PCR (sensitivity of 90%) if the return rate was <65%

- By the time infected patients return, 3% of them had already developed PID

Gift at al. STD 26:232-40, 1999

Diagnostic Yield of p24 Antigen POCT

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Long delays in returning test results for early infant diagnosis of HIV often causes loss-to-follow-up prior to ART initiation in resource-limited settings

A p24 Antigen POC test was evaluated in Mozambique in 879 HIV-exposed infants <18 months of age at 3 primary healthcare clinics

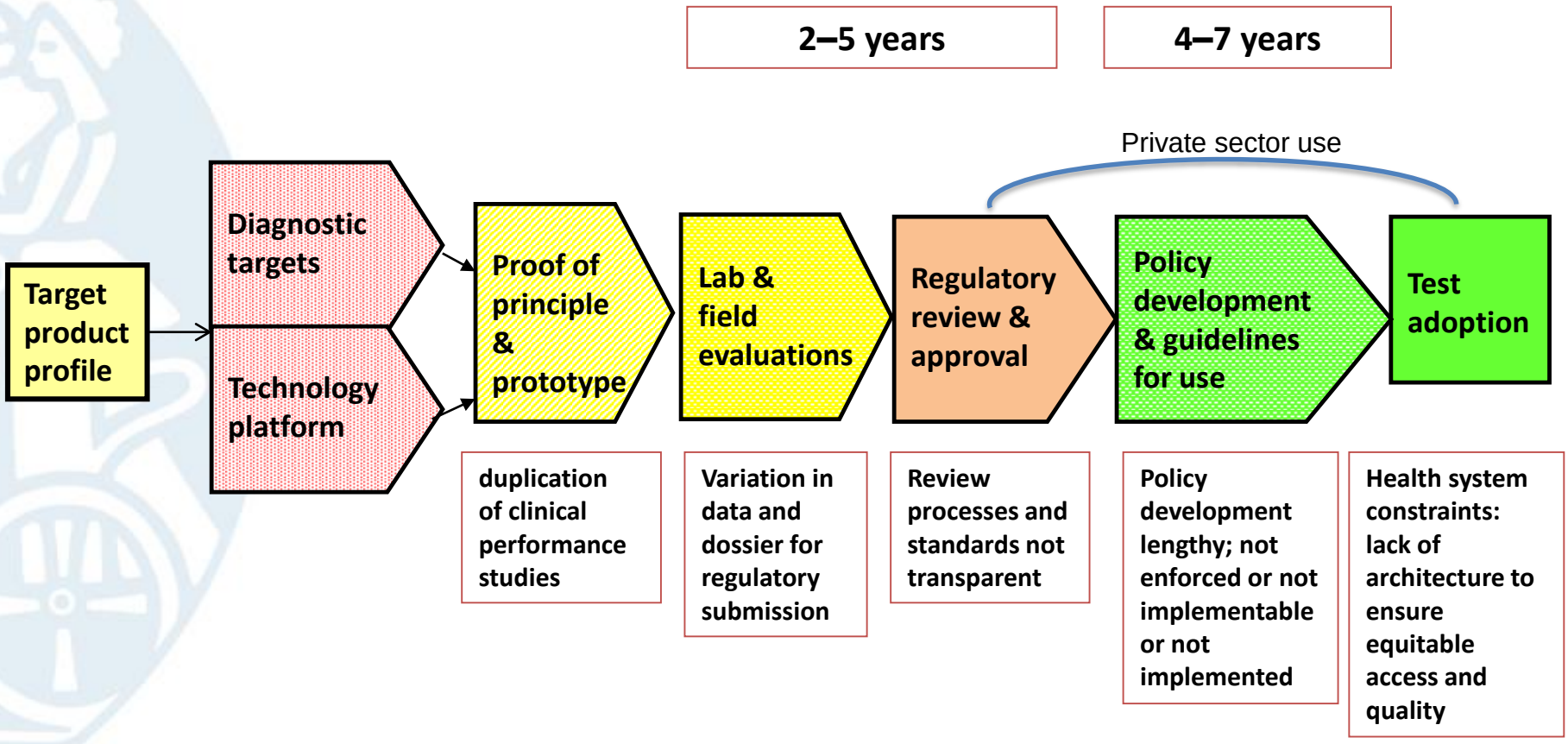
Heel pricked blood samples was tested on-site by nurses using a prototype POC test for HIV Gag p24 antigen detection and compared to laboratory-based nucleic acid testing on dried blood spots.

P24 antigen vs PCR on dried blood spots (DBS)	**Sensitivity**	**Specificity**
	71.9% (95% CI: 58.5–83.0%)	**99.6%** (95% CI: 98.9–99.9%)
Overall agreement: Cohen Kappa =0.80; 95% CI: 0.71–0.89		

Despite its lower sensitivity, the POC test had the potential to provide test results to up to 81% more infants compared to the laboratory-based test on DBS.

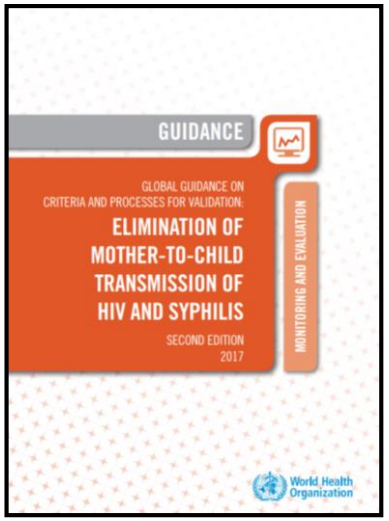
Meggi B et al. (2017) Point-Of-Care p24 Infant Testing for HIV May Increase Patient Identification despite Low Sensitivity. PLoS ONE 12 (1): e0169497.

Pathway to Access for Diagnostics: lengthy and fragmented, with gaps, duplication and uncertainties



The Diagnostic Quality Continuum

1. Test quality by WHO PQ, stringent regulatory authority or equivalent
   - Manufacture
   - Approval for use
   - Availability in market
2. Post-market Surveillance, Batch/lot testing by national reference lab
   - Procurement
   - Storage
3. Lab Quality Management System for national/sub-national lab network
   - 3.1. Quality of testing: Performance (Proficiency)
   - 3.2. Quality of diagnosis: Algorithms used
   - 3.3. Data management: Result reporting & record



Courtesy of Dr. XS Chen, National STD Centre, China

Accelerate Regulatory Approval and Policy Development

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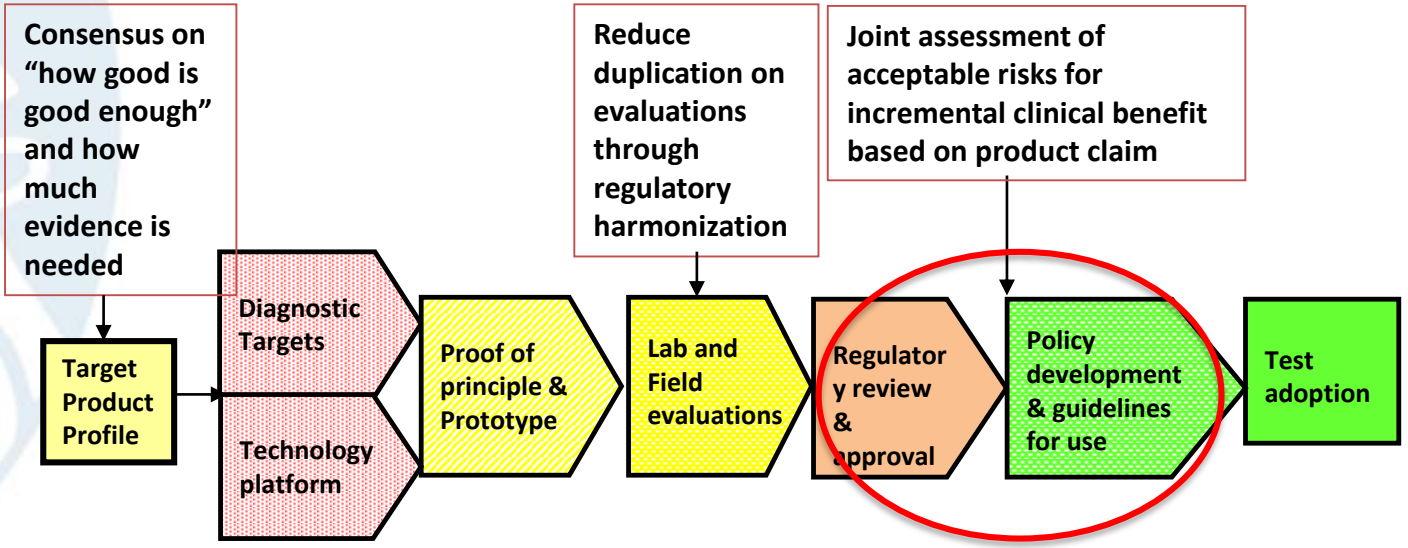
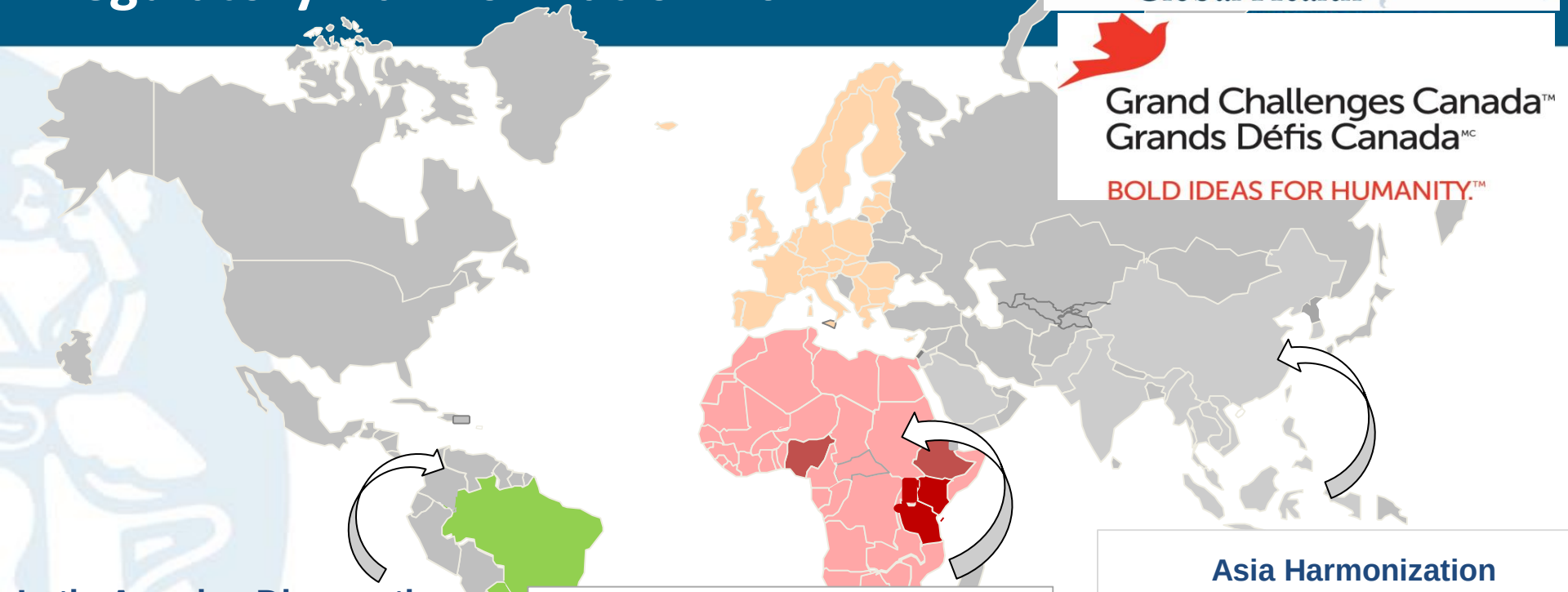
- **Joint assessment and harmonization or reliance will reduce duplication of diagnostic evaluations and regulatory approval and policy development from 7-10 years to 1-2 years**
- **Working with WHO, Africa CDC, ALADDIV, the Global Diagnostic Alliance, regional harmonization working groups and the Longitude Prize**



Progress towards IVD Regulatory Harmonization 2012-4

Grand Challenges in Global Health

Grand Challenges Canada™
Grands Défis Canada℠
BOLD IDEAS FOR HUMANITY.™



Latin America Diagnostic Alliance (12 countries)

Pan-African Harmonization Working Party (15 countries)

Asia Harmonization Working Party (24 countries)

McNerney R, **Peeling RW**. Regulatory In Vitro Diagnostics Landscape in Africa: Update on Regional Activities. Clin Infect Dis. 2015 Oct 15;61Suppl 3:S135-40.

Joint Regulatory Reviews

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

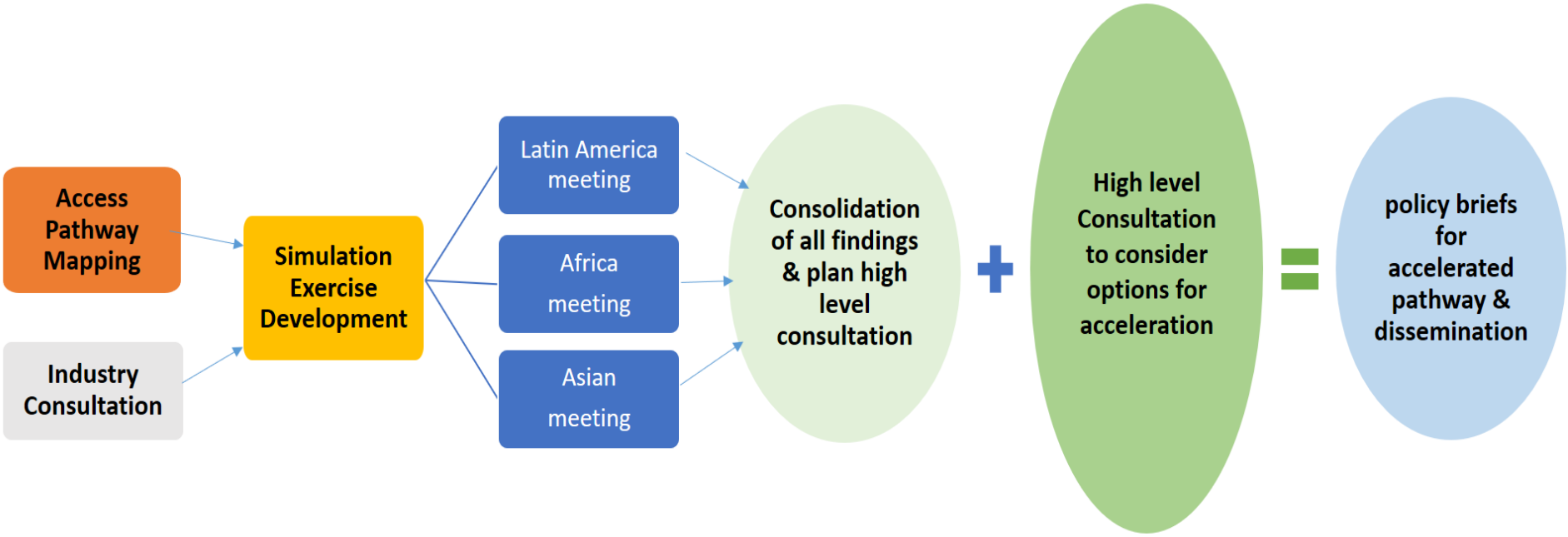
The value of multi-country joint regulatory reviews: The experience of a WHO joint technical consultation on the CYD-TDV (Dengvaxia®) dossier

Kirsten Vannice [a], Liliana Chocarro [b], Michael Pfleiderer [c,1], Ahmed Bellah [d], Michael Ward [d], In-Kyu Yoon [b], Joachim Hombach [a,*]

[a] World Health Organization, Department of Immunization, Vaccines and Biologicals, Geneva, Switzerland
[b] Dengue Vaccine Initiative – International Vaccine Institute, Seoul, South Korea
[c] Chair of Consultation, Paul Ehrlich Institut, Langen, Germany
[d] World Health Organization, Department of Essential Medicines, Geneva, Switzerland

Vannice K et al. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.07.044

The Chatham House Challenge:
Accelerating Access to Quality-assured Diagnostics



Activity 1 and 2: Q4 2019, Q1 2020

Activity 3: Q1 2020

Activity 4: Q2 2020

Activity 5: Q2 2020

Activity 6: Q3 2020

Summary

- Accessible diagnostics that can be performed at the point-of-care are critical for countries to reach SDGs, combat AMR and be prepared for epidemics
- Technological innovation in recent years has yielded simple rapid tests that are accessible but not as accurate as laboratory-based tests
- The paradigm of non-inferiority can no longer be used for the regulatory approval of accessible diagnostics
- There is an urgent need for joint assessment of risks and benefits by regulators and policy makers that accelerate the access pathway

Acknowledgement

LSHTM/IDC:

Noah Fongwen, Debra Boeras, Robert Luo, Joe Tucker, Priyanka Shrestha, Helen Kelly, Catherine Wedderburn, Ben Cheng, Olivia Varsaneux, Lindi van Niekerk, Rachel Chater, Philomena Raftery, Jason Ong, Jack Butterworth, Hannah Miyanji, Adriana Goncalves and members of ALADDIV

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