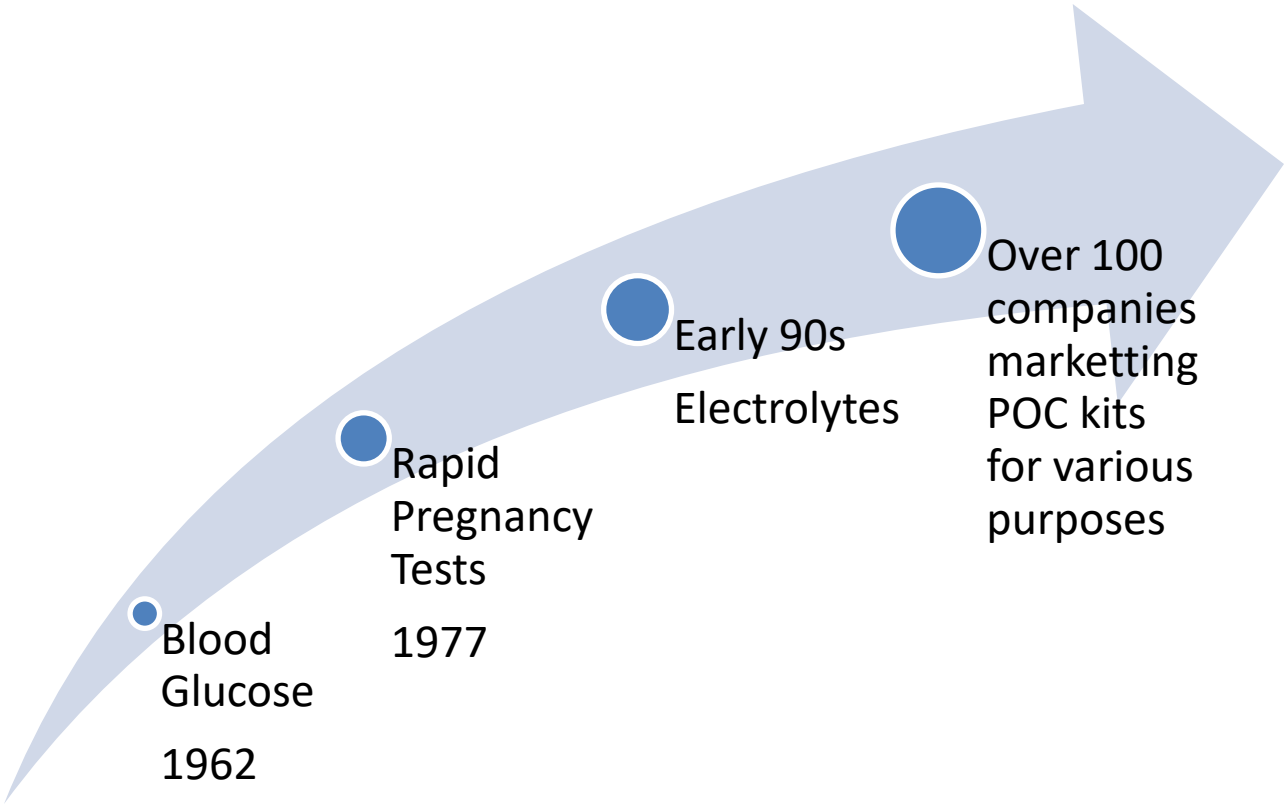
Point of Care (POC) diagnostics for microbial infections and POC susceptibility measurements: The need in Indian context

Dr. Ramesh Paranjape

Definition of POC

- “a medical test that is conducted at or near the site of patient care”.
- “any test that is performed at the time at which the test result enables a clinical decision to be made and an action taken that leads to an improved health outcome”.
- “a diagnostic test that is performed near the patient or treatment facility, has a fast turnaround time, and may lead to a change in patient management”


Blood Glucose
1962
Rapid Pregnancy Tests
1977
Early 90s
Electrolytes
Over 100 companies marketting POC kits for various purposes

Panel 2: WHO ASSURED criteria of ideal characteristics for a point-of-care test in resource-limited settings

- Affordable by those at risk of infection
- Sensitive (few false negatives)
- Specific (few false positives)
- User friendly (simple to perform and needs minimum training)
- Rapid (to enable treatment at first visit) and robust (does not need refrigerated storage)
- No equipment
- Delivered to those who need it

Advantages

Reduced tum around time

Improved patient morbidity & mortality
Reduction in hospital admission

Improved interaction between patient and carer

Reduction in clinical visits

Improved cost of care

Reduction in administrative work associated With test requesting & reporting

Applications

Measure	Ideal reporting requirements
Diagnostic accuracy	
Binomial test result	Sensitivity and specificity, likelihood ratio positive and negative, positive and negative predictive values, and receiver operating curve
Continuous test measure	Bland-Altman plot and limits of agreement
Clinical effect	
Patient-centred outcomes	Number of people initiating treatment, time to treatment initiation, number of visits needed, percentage retained in care, improved adherence, and reduced morbidity and mortality
Costs	
Near universal costs	Total material costs per test, price and lifespan of device and equipment, and test time
Location-specific costs	Required training for personnel, salary of health worker doing test, transportation of specimens, and costs for quality control
Common hidden costs	Local taxes, cost of shipping and storing materials, maintenance costs, and discount rate

Table: Assessment of diagnostic point-of-care tests for use in resource-limited settings

POC Tests

Hospital/facility based

- The goal of point-of-care testing is to obtain immediate test results to help guide an emergent intervention.
- Emergency Depts/ICUs
  - Blood group cross-matching
  - Measurement of electrolytes
  - Treatment of Sepsis
  - Ante-natal clinics

Field Based

- **The goal of point-of-care testing is to expedite diagnostic testing without the need for services of a remote clinical laboratory to accelerate treatment initiation, triage patients appropriately, and improve health outcomes.**
- **Surveillance**
- **Monitoring of health**
  - **Blood glucose**
  - **Pregnancy**
- **Diagnosis of Infectious diseases**
  - **HIV, TB, Malaria**

Hospital/Facility based

- **MATRIX-ASSISTED LASER DESORPTION/IONIZATION TIME-OF-FLIGHT MASS SPECTROMETRY (MALDI-TOF MS) FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING**
- **FLEXICULT SSI-URINARY KIT FOR URINARY TRACT INFECTION DIAGNOSIS AND SUSCEPTIBILITY TESTING**
- **BIOFIRE FILM ARRAY RESPIRATORY PANEL (RP) FOR THE DETECTION OF BACTERIAL AND VIRAL PATHOGENS.**
- **BREATH TESTS FOR THE DIAGNOSIS OF INFECTIOUS DISEASES**

Field based

- BIOSENSOR PLATFORM FOR RAPID ANTIMICROBIAL SUSCEPTIBILITY TESTING
- LOOP-MEDIATED ISOTHERMAL AMPLIFICATION (LAMP)
- PCR

Table. Newly discovered microbes of public health importance

Year	Microbes	Disease
1975	Parvovirus B-19	Fifth disease
1976	*Cryptosporidium parvum*	Cryptosporidiosis
1977	Ebola virus	Ebola haemorrhagic fever
1977	*Legionella pneumophila*	*Legionnaire's disease*
1977	Hantaan virus	Korean haemorrhagic fever
1977	*Campylobacter jejuni*	Gastroenteritis (food poisoning)
1980	Human T-lymphotropic virus I (HTLV-I)	T-cell leukemia/lymohoma
1981	Toxin producing strains of *Staphylococcus aureus(golden staph)*	Various infections
1982	*Escherichia coli* O157:H7	Food poisoning
1982	HTLV-II	Lymphoma
1982	*Borrelia burgdorferi*	Lyme disease
1983	Human immunodeficiency virus	AIDS
1983	*Helicobacter pylori*	Duodenal and gastric ulcer and stomach cancer
1985	*Enterocytozoon bieneusi*	Microsporidiosis diarrhoea
1986	*Cyclospora cayatanensis*	Diarrhoea
1988	Hepatitis E virus	Hepatitis
1989	*Ehrilichia chafeensis*	Human monocytic *Ehrilichiosis*
1989	Hepatitis C virus	Liver cancer (hepatocellular carcinoma)
1991	Guanarito virus	Venezuelan haemorrhagic fever
1991	*Encephalitozoon hellem*	...
1991	New species of *Babesia*	Babesiosis haemolytic disease
1992	*Vibrio cholerae* O139	Cholera
1992	*Bartonella henselae*	Bacteremia, endocarditis, bacillary angiomatosis and peliosis hepatis
1993	Sin nombre virus	Hantavirus cardiopulmonary syndrome (HCPS), aka Four corners virus or Navajo flu
1993	Encephalitozoon cunculi	...
1994	Sabia virus	...
1995	Human herpes virus 8(HHV-8)	Kaposi's sarcoma
1999	Nipah virus[a]	...
2002	SARS coronavirus[a]	Severe acute respiratory syndrome
2003	Influenza A (H5N1)[a]	Avian Influenza
2009	Influenza A(H1N1)	Swine Flu
2012	Novel coronavirus	Severe respiratory infection

Adapted from WHO, 2005[4]
[a]First identified in Asia.

HIV/AIDS

CD4 cell count,[31,32] HIV antigen, and HIV antibody[33]

Other infectious diseases

African trypanosomiasis,[34] chlamydia,[35] cryptococcus,[36] cryptosporidium,[37] falciparum malaria,[38] giardia,[39] group A streptococcus,[39] hepatitis C,[40] influenza A and B, parainfluenza, respiratory syncytial virus, schistosomiasis,[41] syphilis,[42-44] tetanus,[45] trypanosomiasis,[46] tuberculosis,[47,48] and visceral leishmaniasis[49,50]

TABLE I. Unmet needs for point-of-care (POC) tests in the developing world

	Current diagnosis	Unmet need for POC test
Syndromes/conditions		
Acute lower respiratory infections	Syndromic management using Integrated Management of Childhood Illness algorithms	Test/biomarker to distinguish between bacterial and viral pneumonia
Febrile illness in children	Presumptively treat for malaria in areas of high endemicity	Multiplex POC test for common causes of fever
Sexually transmitted infections, including HIV	Syndromic management for patients presenting with symptoms; POC tests to screen for HIV and syphilis	POC test for genital chlamydial and gonococcal infections; POC test for paediatric diagnosis of HIV; POC test for CD4 and viral load
Antenatal care	POC test for HIV; haemoglobin POC test for anaemia	Multiplex POC test for screening HIV, malaria, syphilis, and anaemia
Diseases		
Malaria	Rapid antigen detection tests	
Tuberculosis	None	Test for active tuberculosis and antimicrobial susceptibility
Human African trypanosomiasis	None that works well	POC test for staging disease; POC test of cure
Visceral leishmaniasis	POC serological test works well in India but not in Africa	POC test of cure

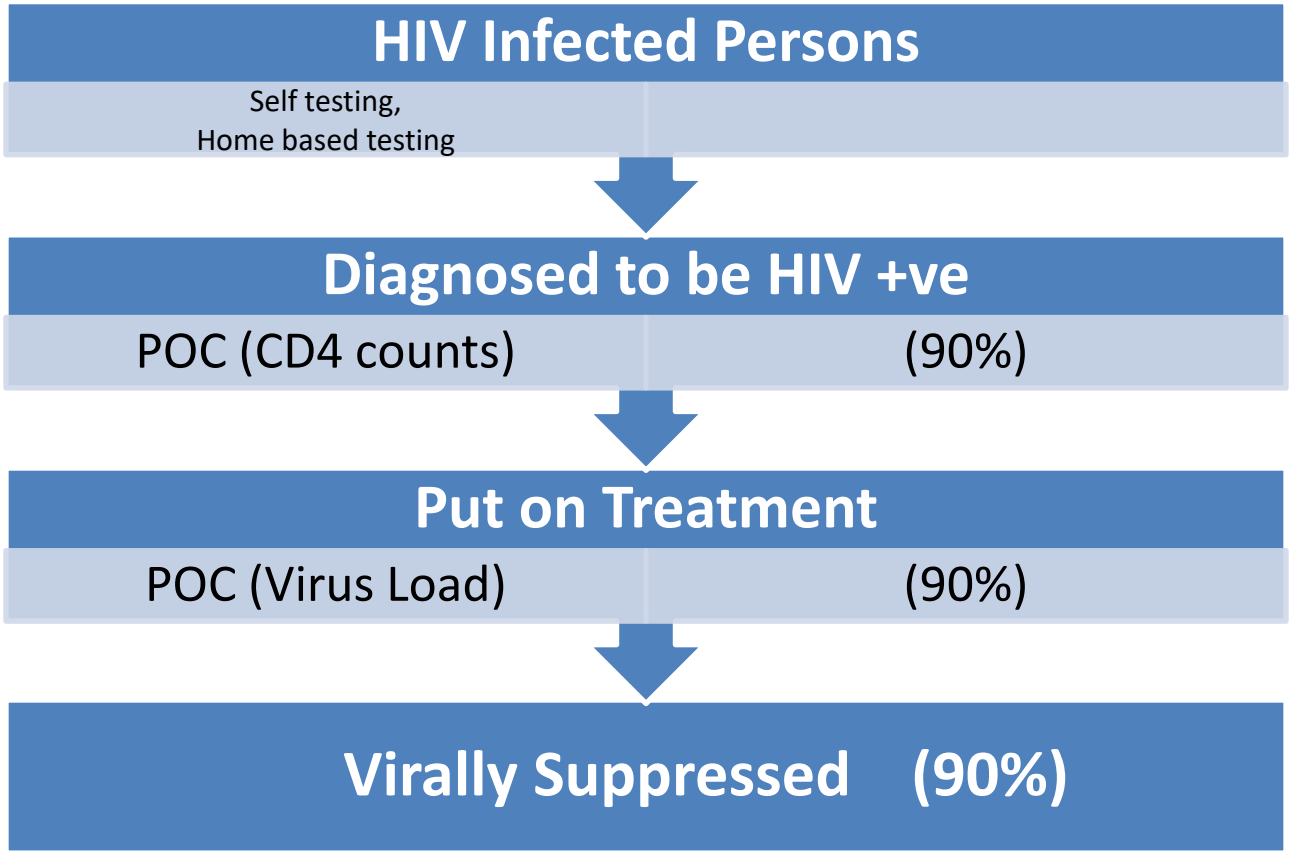
HIV, human immunodeficiency virus.

Need for POC in Indian Settings

- Tuberculosis: Diagnosis and Susceptibility
- HIV: Susceptibility and Virus load
- Flaviviruses: Diagnosis
- Malaria: Diagnosis and Susceptibility
- Respiratory Infections
- Sexually transmitted infections
- Sepsis

Laboratory independent diagnostic tests for just four infections (bacterial pneumonia, syphilis, malaria, and tuberculosis) could prevent more than 1·2 million deaths each year in developing countries

Way forward to Achieve 90-90-90 objectives of UNAIDS by 2020



Evaluation of HIV serology POCs: NARI experience

- The rapid tests being extensively used for HIV diagnosis for the last 15 years are example of POCT for HIV diagnosis
- New POCs: test on oral fluid
  - Three different rapid kits evaluated (Calypte Aware HIV1 /2 , OraQuick Rapid HIV1/2, Oracheck HIV)
  - Qualitative *in vitro* immunoassay for the detection of antibodies to
  - All three kits showed good sensitivity, specificity and PPV
  - Results were clear and easy to interpret
  - 95 % respondents were willing to give oral sample as it is less invasive than venepuncture sample
  - The healthcare staff felt that the sample collection has less bio-safety hazard

Evaluation of CD4 POCs: NARI experience

- POCs evaluated: BD FACSPresto and PIMA Alere CD4 analyzer
- Multisite study
- More than 700 samples

- Range of CD4 counts (50 to >1000 cells/mm3)
- Minimum error rate: <5%
- Field based analysis of PIMA:

  Inter-machine comparison : %CV<10%.

  91% requiring ART were correctly identified

Bigtec Labs *has developed a handheld diagnostic platform for rapid pathogen detection of any disease and allows DNA amplification. Currently, the company is validating the product specifically for hepatitis B, C and HIN1 where with a single drop of blood the diagnosis can be made within minutes*

“Our battery operated, real-time micro-PCR is poised to revolutionize medical analysis and treatment in-field, and in the laboratory, by reducing the analysis time and driving down the cost of medical diagnostics by orders of magnitude,” claims Chandrasekhar Nair, director of Bigtec Labs.

Effect of point-of-care CD4 cell count results on linkage to care and antiretroviral initiation during a home-based HIV testing campaign: a non-blinded, cluster-randomised trial

Mitesh A Desai et al Lancet HIV 2017
http://dx.doi.org/10.1016/ S2352-3018(17)30091-7

- **A two-arm, cluster-randomised, controlled efficacy trial in two districts of western Kenya. with ongoing HBCT.**
- **Housing compounds were randomly assigned (1:1) to point-of-care CD4 cell counts (366 compounds with 417 participants) or standard-of-care (318 compounds with 353 participants) CD4 cell counts**
- **participants in the point-of-care group, 215 (58%) had linked to care within 6 months versus 108 (34%) of 321 in the standard-of-care group**

TB Diagnosis

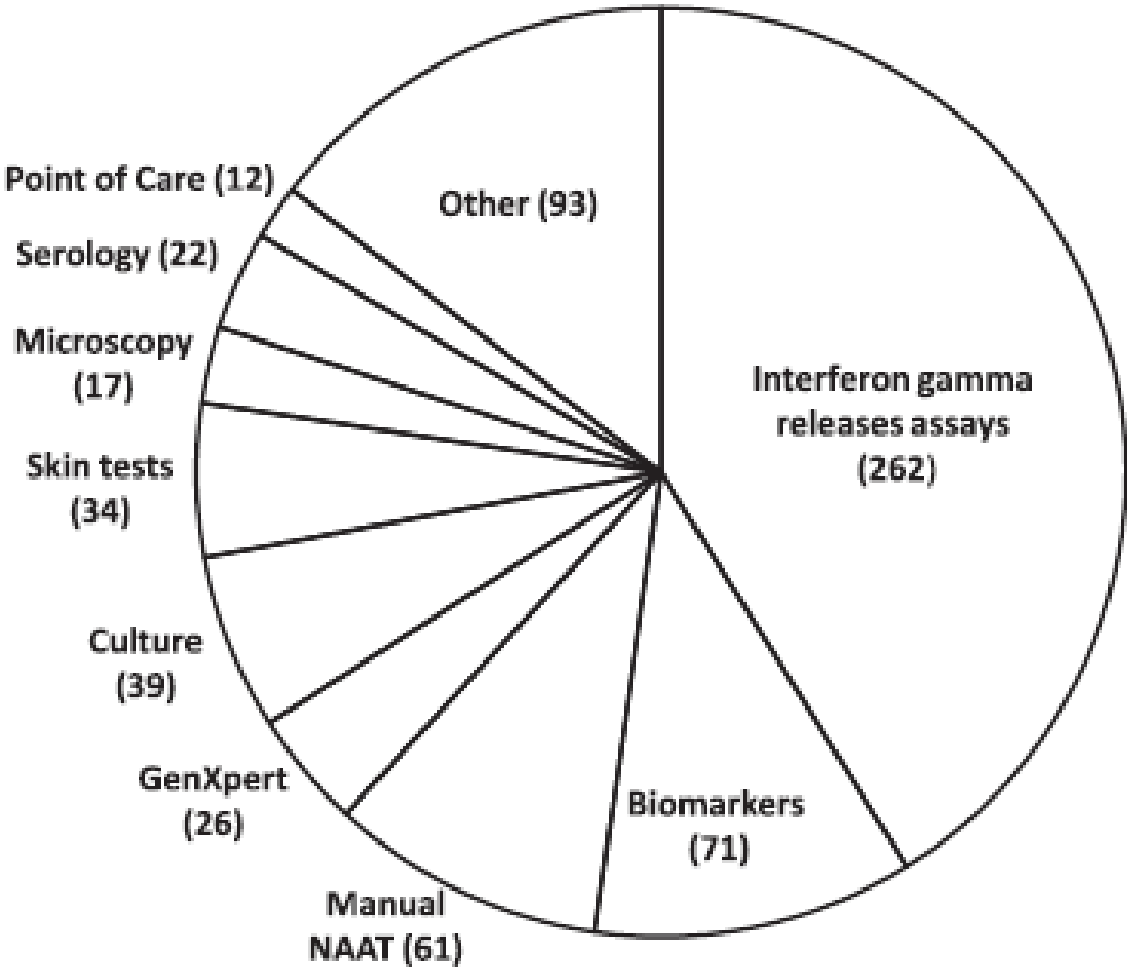


Table 2 | **Minimum specifications for a point-of-care test for diagnosis of tuberculosis (TB)***

Parameter	Minimum specification
Test outcome	• Initiation of treatment
Sensitivity in adults, regardless of HIV status	• Smear-positive culture-confirmed cases: 95% • Smear-negative culture-confirmed cases: 60–80%‡
Sensitivity in children, including in cases of extra-pulmonary TB, regardless of HIV status	• Culture-confirmed cases: 80% • Probable TB cases: 60%
Specificity in adults	• 95% (compared with culture)
Specificity in children	• 95% (compared with culture) • 90% for culture-negative probable cases
Throughput	• 20 tests per day by a single operator
Waste disposal	• Environmentally acceptable disposal such as simple burning or burying
Storage and stability	• No cold chain required, stable at 30 °C for 24 months and at higher temperatures for shorter periods
Instrumentation	• Maintenance free • Robust in tropical conditions • Acceptable replacement cost • Must fit in a backpack, be shock resistant and work from a battery
Operation characteristics	• To be used with minimal instruction
Cost	• Below US$10 per test when in production

*As recommended by an expert meeting facilitated by the Médecins Sans Frontières (MSF) Access Campaign, Treatment Action Group (TAG) and Partners in Health (PIH), held in March 2009. Detection of extra-pulmonary TB is preferable but is not a minimal requirement. See Further information for the full recommendations regarding minimum test specifications. ‡There was no consensus regarding the minimum sensitivity required in smear-negative cases.

Table 3 | **Priorities to be addressed for development of a point of care (POC) test for tuberculosis (TB)**

Priority	Aim
Further investment	• To discover and validate biomarkers to detect active TB • To encourage technological innovation and development of improved test platforms to include the detection of multiple targets
Enhanced collaboration	• To combine the discovery of biomarkers and the development of methods for their detection
Regulatory control	• To prevent poor-quality tests being sold and used, particularly in the private health sector in developing countries
Biomarker validation	• To assess the diagnostic value of combined targets for multiplex assays
Technology assessment	• To assess the robustness of novel POC technology through field testing
Test performance	• To independently assess and compare new tests as they enter the market; studies should be of high quality and adhere to standards for the reporting of diagnostic-accuracy studies (STARD) recommendations
Impact studies	• To assess the clinical and socio-economic impact of new tests in order to guide their implementation

Indian POCs for Malaria Diagnosis

Name	Manufacturer	Species Dx	Antigen	Stability
Paracheck-Pf	Orchid Biomedical Systems	Pf	*PfHRP-2*	4 - 40
Rapid Malaria Pf/Pv	Accu-tel	Pf & Pv	PfHRP-2 and *P.vivax pLDH*	2 - 30
ParaHIT-F	(Span Diagnostics Ltd	Pf	*PfHRP-2*	4 - 40
Parabank	Zephyr Biomedicals	Pan-specific	Pan-pLDH	4 - 30
Malascan	Zephyr Biomedicals	Pf & Pan-specific	PfHRP2 and aldolase	4 - 30
Parascreen	Zephyr Biomedicals	Pf or non-Pf mixed	PfHRP2 and pLDH	4-30
First Response Malaria (pLDH/HRP2combo test)	Premier Medical Corporation	Pf or non-Pf mixed	PfHRP-2 and pan-pLDH	1 - 40

Table 1: Characteristics of dengue rapid diagnostic tests mentioned in this paper.

Manufacturer	Product name	Analytes	Storage temperature (°C)	Quoted accuracy (Sn/Sp[a])	Sample[b]	1°/2°
Merlin	Dengue Fever IgG and IgM Combo Device	IgM/IgG	2–30°C	IgM 96/98 IgG 97/98	S/P/WB	Yes
Standard Diagnostics	BIOLINE Dengue Duo NS1 antigen and IgG and IgM Combo Device	NS1 Ag IgM/IgG	1–30°C	NS1-Ag 92.8/98.4 IgM/IgG 99.4/93.0	S/P/WB	Yes
Biosynex	Immunoquick Dengue Fever IgG and IgM	IgM/IgG	2–30°C	IgM 97.6/98.3 IgG 95.2/96.6	S/P/WB	Yes
Biorad	STRIP	NS1 Ag	2–8°C	NS1-Ag 92.3/98.8	S/P	No
Alere	Panbio Dengue Early Rapid Kit	NS1 Ag	2–8°C	Not stated	S	No
Alere	Panbio Dengue Duo Cassette	IgM/IgG	2–8°C	S[b] convalescent—1°[c] −85.1/91.6; 2° −98.8/91.6 P acute—1° −58.3/45.0; 2° −100/45.0 WB acute—1° −71.4/91.2; 2° −77.4/91.2 WB convalescent—1° −78.6/85.3; 2° −100/85.3	S/P/WB	Yes
MP Diagnostics	ASSURE	IgA	2–28°C	Not stated	S/P/WB	No

Sn/sp[a]: sensitivity/specificity.
[b]S–serum; P: plasma; WB: whole blood.
[c]Primary and secondary infections; manufacturer claims RDT can differentiate

Challenges

1. **Lower sensitivity compared to laboratory based assays**
2. **Issues related to Quality Assurance: Internal controls, external controls, documentation, EQAS**
3. **Usually higher cost (Eg GenExpert)**
4. **Lack of regulatory standards for approval of diagnostics;**
5. **Validation and field testing**
6. **Variable quality of laboratory services; Training & interpretation (esp for self tests)**

THANK YOU!