



Diagnostics for Emerging Arbovirus Mitigation

Dr. Debi Boeras
Global Health Impact Group
Director, International Diagnostics Centre USA

Diagnostics for Arbovirus Mitigation



Mitigation = proactive measures aimed at reducing the risk, impact or effect of a disaster or a threatening disaster

Questions:

- How can diagnostics be used for arbovirus mitigation?
- Are effective diagnostic tools available?
- If so, how can they be widely deployed?

Diagnostics to Better Prepare, Prevent and Respond to Epidemics: lessons from the COVID-19 Pandemic



• Prepare:

- ✓ Landscape of what is available and in pipeline
- ✓ Target product profiles
 - Test evaluation through network of expert labs
 - Framework for specimen and data sharing
 - Promote local manufacturing for improving access
 - Education of care providers and communities to raise awareness

Prevent:

- ✓ Early and rapid case detection
- ✓ Deployment of measures to prevent transmission
 - Investment in real-time surveillance through connectivity solutions for better use of surveillance data

Respond:

- ✓ Rapid assessment of extent of outbreak
- ✓ Genomic sequencing
 - Community engagement re awareness
 - Stockpiling of diagnostics
 - Align with vaccine R&D or deployment

Laboratory Diagnosis: Dengue

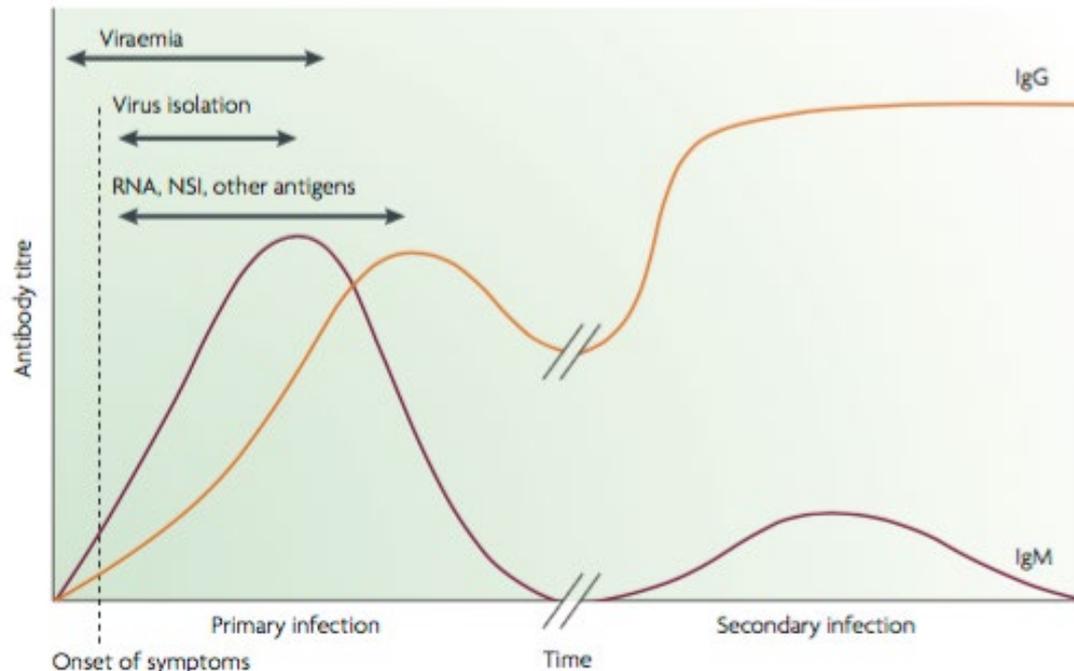


Figure 2 | Major diagnostic markers for dengue infection. The titre of the IgM and IgG response varies, depending on whether the infection is a primary or secondary infection.

Peeling RW, et al.. Evaluation of diagnostic tests: dengue. *Nat Rev Microbiol.* 2010 Dec;8(12 Suppl):S30-8. doi: 10.1038/nrmicro2459. PMID: 21548185.

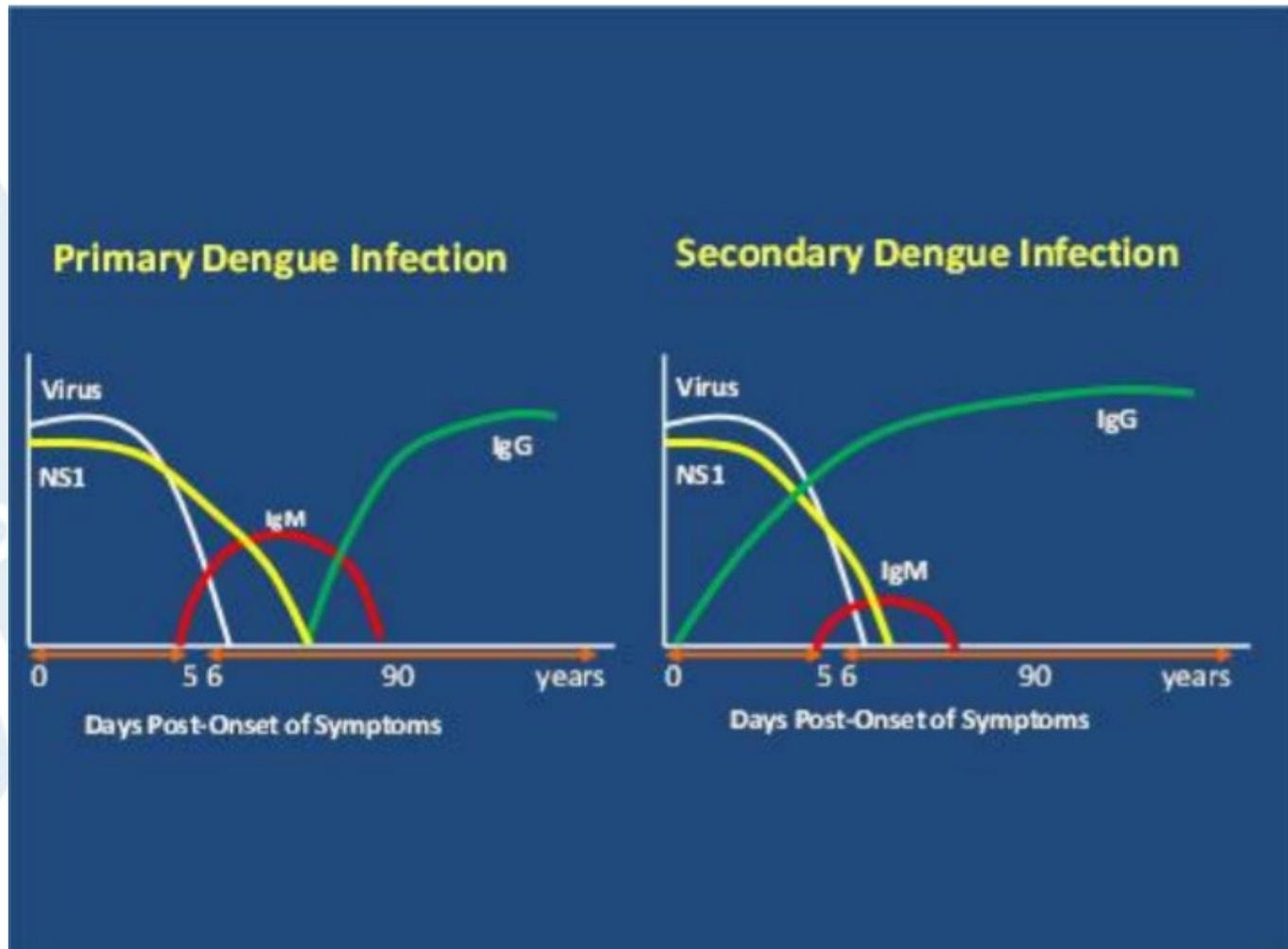
Patient Management:

- **Confirmed:** acute infection
 - Virus isolation
 - Nucleic acid detection
 - Antigen detection
 - Seroconversion for IgM
 - 4-fold rise in IgG titres
- **Highly suggestive:**
 - IgM positive because of its persistence over several months

Surveillance:

- Establish population baseline of IgM
- a potential outbreak is defined as more people testing positive for IgM or higher titres
- Confirmation of outbreak by RT-PCR

IgM and IgG Antibodies in Primary and Secondary Dengue Infection



Reproduced from U.S. Centers for Disease Control and Prevention;
<http://www.cdc.gov/dengue/clinicalLab/laboratory.html>.

Challenges towards serologic diagnostics of emerging arboviruses

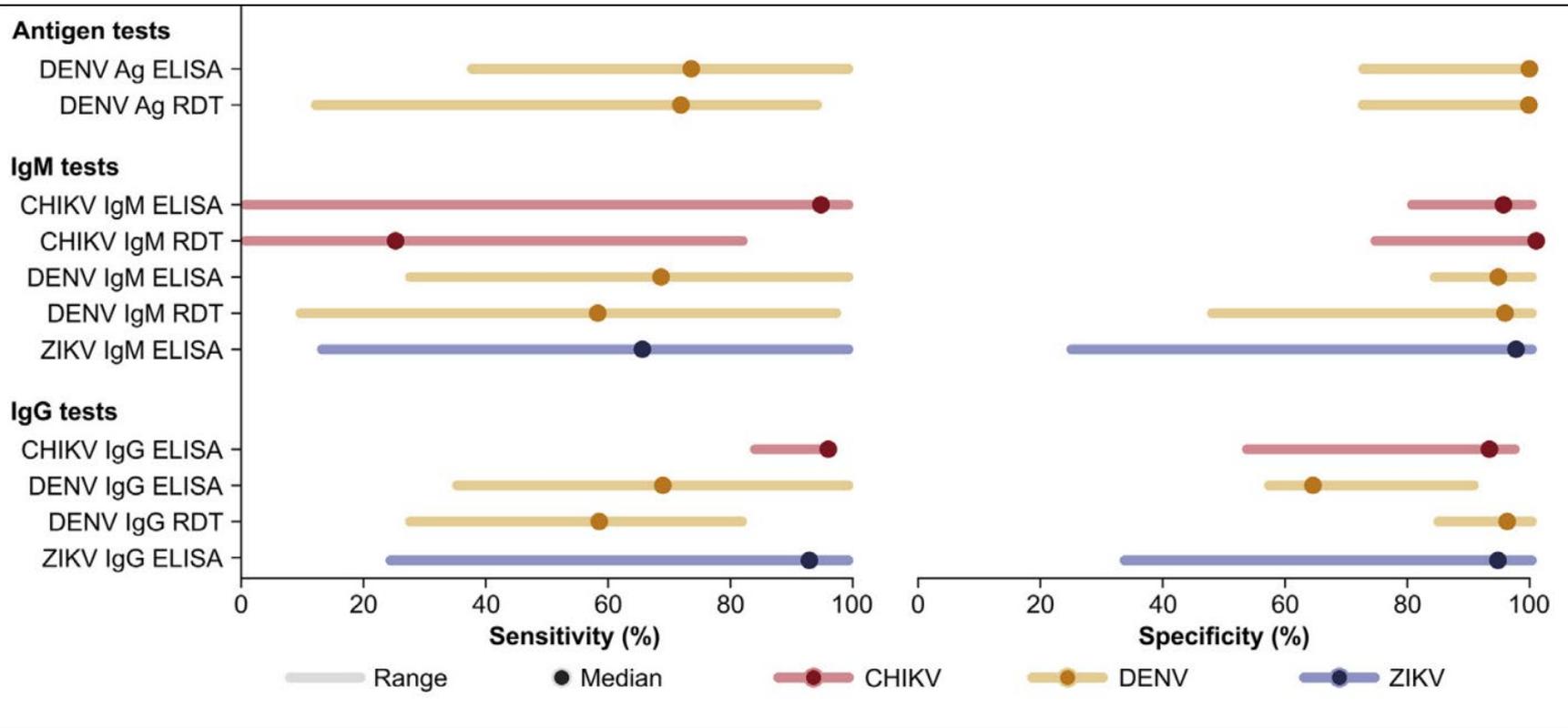


Fischer et al retrieved data on the performance of commercially available antibody- and antigen detecting tests from 89 peer-reviewed articles through a systematic literature research in PubMed

Identify challenges towards serologic diagnosis of emerging arboviruses:

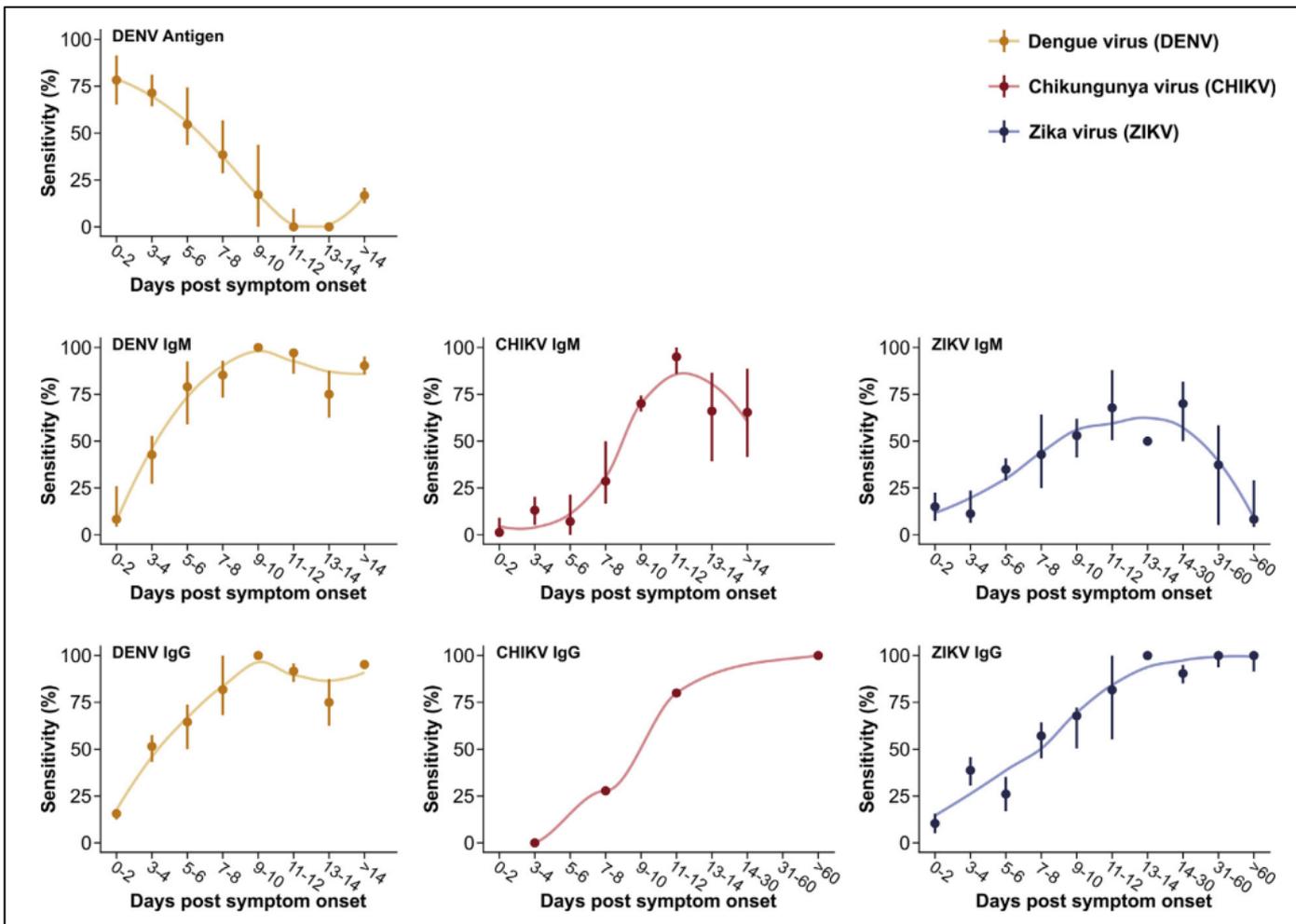
- 1. Intrinsic properties affecting the performance of different test formats**
- 2. Timing of serological testing is crucial:**
right test for the right patient at the right time
- 3. Individual infection histories affect diagnostic test performance**
Secondary infections and the original antigenic sin
- 4. Global mixing of antigenically related viruses**
- 5. Polyclonal B cell activation and environmental factors**

Performance of Antigen and Antibody Detecting Tests for Arboviruses



Fischer C, et al. Challenges towards serologic diagnostics of emerging arboviruses. Clin Microbiol Infect. 2021 Sep;27(9):1221-1229. doi: 10.1016/j.cmi.2021.05.047. Epub 2021 Jun 7. PMID: 34111589.

Sensitivity of Arbovirus Antigen and Antibody Detecting Tests over Time



Diagnosis of Acute Dengue Infection using a single serum sample



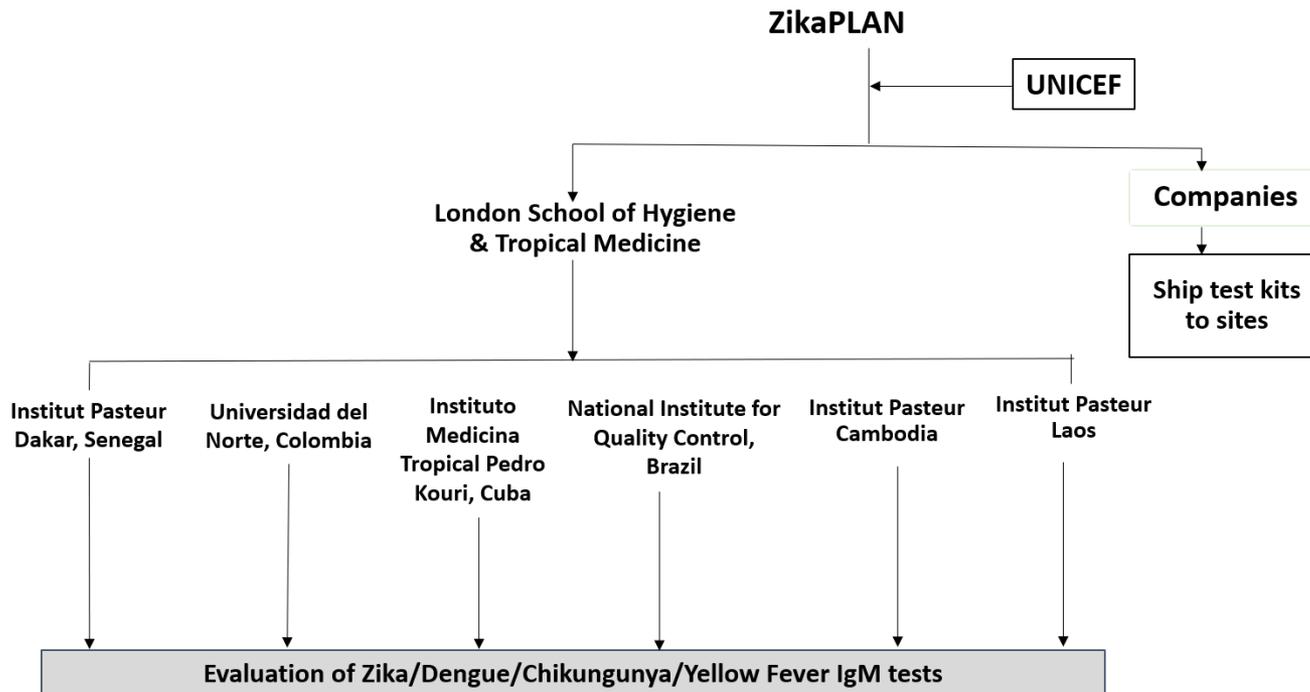
- Retrieved 1,234 paired serum samples from laboratory confirmed dengue patients, archived at the CDC Dengue Branch at San Juan, Puerto Rico between 2005-2011
- Tested the acute sample from each pair with IgM ELISA, DENV-1-4 real-time RT-PCR and NS1 antigen ELISA
- Finding: testing combinations of either IgM ELISA + RT-PCR or IgM ELISA + NS1 Antigen ELISA accurately identified >90% of primary and secondary dengue cases from a single serum specimen collected during the first 10 days of illness

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

Incentivising Test Development for Diseases of Epidemic Potential



- UNICEF and USAID collaborated on an Advanced Purchase Commitment (APC) mechanism to incentivise companies to continue the development of more accurate and accessible Zika diagnostics for case detection and surveillance
- Tests that fulfilled the APC performance specifications were independently evaluated using archived samples from a biobanking and evaluation network
- UNICEF has committed to procuring millions of these validated tests for countries to use in their arbovirus surveillance programmes



1. Develop evaluation panels and consensus protocol
2. Sites contribute well-characterised specimens collected from primary and secondary arbovirus infections and negative controls
3. Companies sent required number of tests to each site for evaluations in country
4. 'Sudden Death'
5. Sites reimbursed by companies
6. Data aggregated for analysis

Results: SD Biosensor ARBO Panel

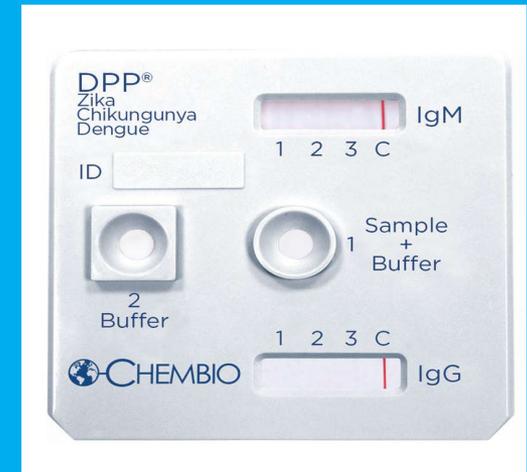
	ZIKV IgM	DENV IgM	DENV NS1	YFV IgM	CHIKV IgM
Sensitivity	96.8% (88.8-99.0)	71.8% (64.2-78.5)	90%*	84.6% (80.2-91.1)	86.3% (80.2-91.1)
Specificity					
- vs ZIKV	NA	62.9%	100%	80.0%	98.4%
- vs DENV	86.7%	NA	NA	92.3%	100%
- vs YFV	68.8%	68.8%	61.5%	NA	100%
- vs CHIKV	98.7%	98.7%	100%	100%	NA
Specificity vs Arboviruses	90.9%	81.5%	89.1%	92.0%	99.3%
-vs IgG	80%	100%	-	-	77%
-vs healthy controls	100%	100%	100%	100%	100%
Overall specificity	90.8% (85.5-94.6)	83.5% (73.8-86.5)	90.2%	92.4% (87.4-95.9)	97.5% (94.9-99.8)



Boeras D, et al. Evaluation of Zika rapid tests as aids for clinical diagnosis and epidemic preparedness. EClinicalMedicine. 2022 Jun 4;49:101478.

Results: Chembio DPP[®] ZCD System

	ZIKV IgM	DENV IgM	CHIKV IgM
Sensitivity	79.0% (72.1-84.8)	90.0% (84.5-94.1)	90.6% (85.8-94.1)
Specificity			
- vs ZIKV	NA	90.0% (73.5-97.9)	98.8% (93.3-100)
- vs DENV	94.3% (84.3-98.8)	NA	96.3% (81-100)
- vs CHIKV	98.4% (91.3-100)	78.6% (49.2-95.3)	NA
- vs YFV	95.4% (77.1-100)	72.7% (49.8-89.3)	90.9% (70.8-98.9)
Specificity vs Arboviruses	96.3% (90.7-98.4)	81.8% (70.4-90.2)	96.9% (92.3-99.1)
-vs ZIKV IgG	100% (69.1-100)	NA	NA
-vs healthy controls	100% (94.8-100)	100% (92.1-100)	98.0% (89.3-100)
Overall specificity	97.1% (93.8-98.9)	89.2% (81.9-94.3)	97.2% (93.6-100)



Boeras D, et al. Evaluation of Zika rapid tests as aids for clinical diagnosis and epidemic preparedness. EClinicalMedicine. 2022 Jun 4;49:101478.

ZIKA FORUM



Zika Feasibility Study: Lessons from Senegal

By Mohamed Abass Yugo

Aknowledgements: Dr. Amadou Sall , Rose Mbaye
Hamidou Thiam, Dr. Fatoumata Sarr, Rokhaya Diop,
Mam Coumba Diouf, Dr. Cheikh Loucoubar

Institute Pasteur Dakar

29 March 2022



Zika Feasibility Study: site selection



IPD selected 9 testing facilities from 2 regions (Fatick, Kedougou) based on previous evidence of Zika transmission at district level. Kedougou have the highest known transmission in Senegal and sites in Fatick have one of the lowest.



The sites are all located in the vicinity of national parks with an ecosystem that favors the arbovirus development cycle.



IPD is a WHO Collaborating Centre for Arbo and haemorrhagic fever viruses and has developed the 4S (Sentinel Syndromic Surveillance Senegal) since 2012



Kedougou: 2 Health centers and 4 Health Posts
Fatick: 1 Health Center and 2 Health posts



36 Health professionals trained (23 at Kedougou and 13 at Fatick)

20 Bajenu Gox (CHWs) trained (12 at Kedougou and 08 at Fatick)



Health professionals include doctors, nurses and midwives

Zika Feasibility Study: Community Engagement Activities



**Implementing missions (2)
Supervision Missions (7): 4K/3F**

247 talks/Community engagement activities were held: 3399 people benefited (21 men and 3378 women)

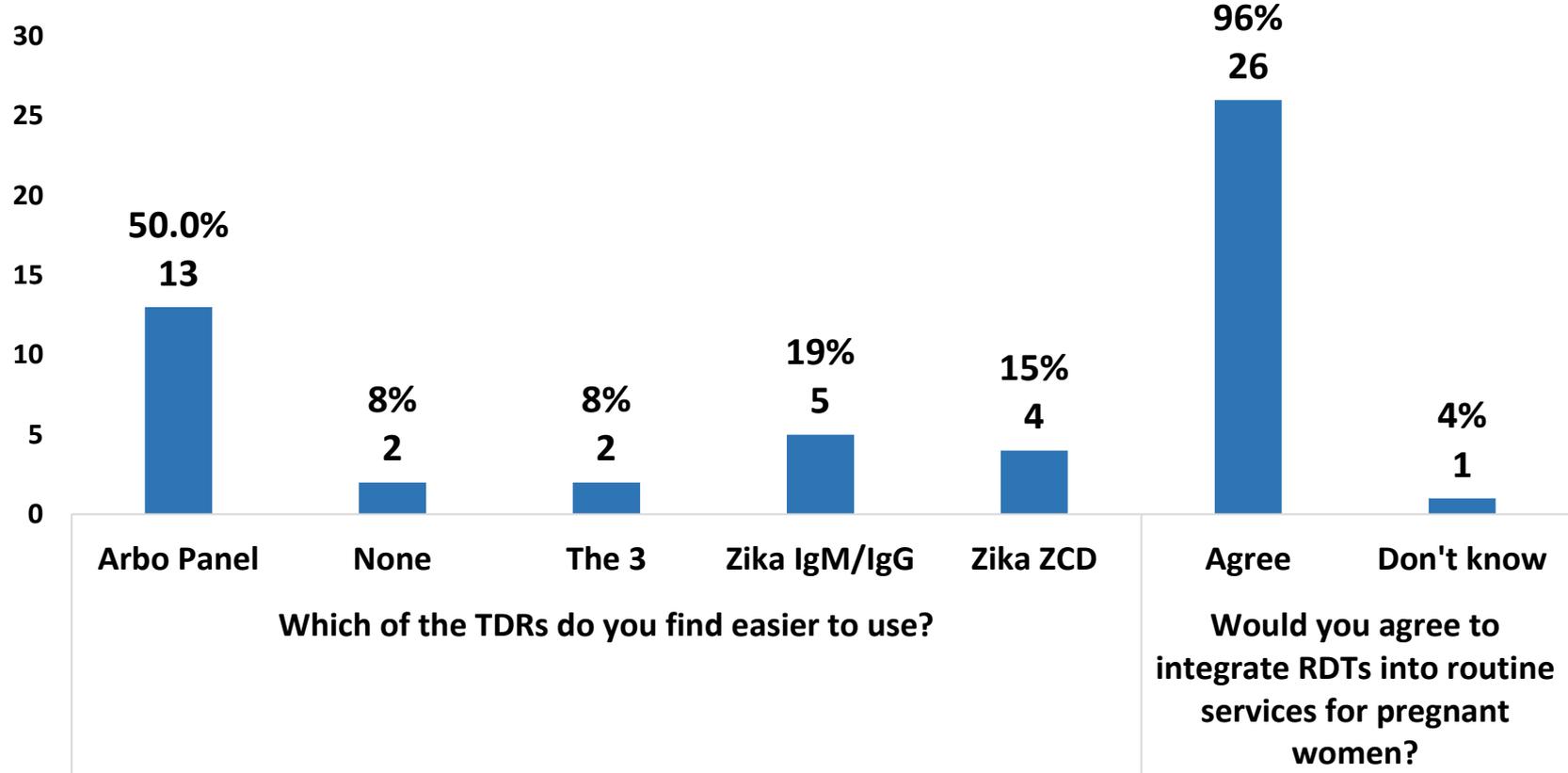
Of the 3378 women: 278 were pregnant and 19 pregnant women received a RDT test



Zika Feasibility Study: Health Workers answers



Health workers' opinion of the project, N=27



Key Findings: importance of community engagement



All end users found the RDTs to be **highly useful and valuable** for increased screening of pregnant women for Zika and for use at sentinel surveillance sites to provide quick results.



Thanks to the community engagement activities, more women are aware and come to consult. Community engagement improves trust between women and health professionals.



The use of RDTs has made it possible to diagnose on a timely manner. It has facilitated epidemiological surveillance for the diseases.

96.3% Health workers agree to the integration of RDTs into routine services for pregnant women.

Challenges related to the non-winter season (season when there are few cases of fever) and also to market gardening, agriculture and the sale of mangoes



Better operability: Use of arbo panel at the ANC/Health posts sites

Multiplex Tests (Arbo panel and ZCD system) better suited for surveillance

Single test (DPP Zika) better suited for point-of-care diagnosis at the district level health center

Easy to use multiplex (Arbo Panel) is more suited for surveillance at health structures closest to the community

Summary

Status:

- **Dengue diagnostics are now on the WHO Essential Diagnostics List**
- Rapid diagnostic tests (RDTs) exist for point-of-care diagnosis, but their quality is not assured
- There is ongoing work to develop multiplex tests for patient management and surveillance
Some multiplex tests are available but they are not affordable for programs

R&D needs:

- **more rapid but less expensive multiplex molecular tests to distinguish febrile illness caused by dengue, chikungunya and Zika viruses**
- **more specific antigen or molecular detection tests to confirm Zika infection for patient management at the point of care are needed**
- **more specific and high throughput antibody detection tests that can be used on a population basis for surveillance of arbovirus infection and for epidemiologic studies are needed**
- **Connectivity solutions linking data from diagnostic laboratories and point-of-care test readers and devices provide early warning for infectious disease outbreaks, and timely information for disease control and prevention, increasing the efficiency of health care systems and improving patient outcomes**



Thank you

LSHTM/IDC: Debi Boeras, Noah Fongwen
Zika evaluation sites colleagues

Feasibility study in Senegal: Amadou Sall, Rose Mbaye Hamidou Thiam,
Dr. Fatoumata Sarr, Rokhaya Diop, Mam Coumba Diouf, Dr. Cheikh
Loucoubar, Moahammed Abass Yugo

University of Colorado centre for Global Health: May Chu

Funding: UNICEF: Nagwa Hasanin