Arboviral Diseases Diagnostics Symposium

July 21, 2017

Puerto Rico Brain Trust for Tropical Diseases Research & Prevention

A program of Puerto Rico Science, Technology & Research Trust

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Puerto Rico Science, Technology & Research Trust

The State of Clinical Reference Laboratories in Puerto Rico and Plans for the Improvement of Arboviral Disease Diagnosis.

I. Background

This meeting brought together scientists, test developers, reference laboratories that administer and develop tests in Puerto Rico, representatives of the American Association of Public Health Laboratories (APHL) and the Caribbean Lab Association, experts in building interdependent lab networks, companies related to this industry and representative from Biomedical Advanced Research and Development Authority (BARDA) who all have an interest in improving arbovirus diagnostics in Puerto Rico.

What is an Arbovirus?

Arbovirus is a term used to refer to a group of viruses transmitted by arthropod vectors. Diseases caused by arthropod vectors are encephalitis, febrile illness and hemorrhagic fevers. Puerto Rico is home to endemic mosquito transmitted diseases including all four strains of dengue fever, Chikungunya and Zika. In Puerto Rico mosquitos transmit arboviruses through their salivary glands that cause fever and hemorrhagic fever. It is difficult for clinicians to precisely diagnose a patient that presents with fever without a laboratory test to confirm presence of dengue, Zika, Chikungunya or other type of febrile illness. Arboviruses can cause symptoms that coincide with more common febrile illnesses. For example Leptospirosis (also present in Puerto Rico) is caused by a bacteria, but patients experience symptoms for febrile illness similar to those caused by arboviruses, so it is easily undetected or misdiagnosed and will result in death if not correctly treated.

Role of technology in transformation of diagnostic methods

New advances in diagnostics for arboviruses and febrile illnesses are constantly progressing, but there is still a critical need for more precise (sensitive and specific), easy to use, rapid and affordable tests for point of patient care diagnosis. Tests will need to differentiate between co-circulating viruses like Dengue, Zika, Yellow Fever, Chikungunya and Influenza. Technology is helping to improve

characterization of genomic material. Rapid facilitation of effective and low cost tests are need to be administered on a widespread basis in areas experiencing endemic disease transmission, like Puerto Rico in order to effectively treat and control febrile illnesses. Diagnostic testing can be performed using molecular, cellular and immunological techniques. New methods for identifying and measuring biomarkers for diseases and their relationship to clinical conditions have stimulated test development.

Importance of correctly diagnosing arboviruses

Inaccurate diagnostic testing can harm patients. Misdiagnosis of febrile illness can lead to death and increased illness for the individual. It is important at the population level to understand presence of new arboviruses to Puerto Rico, increases in strains of dengue infections that may lead to epidemics and to monitor and control spread of arbovirus disease in the population through use of accurate diagnostic tools. For a young couple that may want to become pregnant, finding out if their febrile illness is caused by dengue or Zika virus is important. For medically fragile, elderly and youth a second, third or fourth dengue infection can result in life threatening complications due to hemorrhagic fever. Treatment of patients with Chikungunya would be different than monitoring febrile illness due to influenza or Zika viruses.

The role of diagnostic labs in the ever changing health industry

According to the American Public Health Lab Association, lab results are a critical component in approximately 70% of clinical decisions. Clinics and hospitals utilized diagnostic and reference testing to medically manage individuals. Public Health Labs use diagnostic and reference testing to do surveillance, monitoring and outbreak response in a population. Together these labs can form an interconnected network for rapid sharing of information to improve biosecurity, preparedness and decision making to counter public health threats like dengue, chikungunya, Zika, influenza, Leptospirosis and other febrile illnesses.

In addition, there are several routes for test developers to bring a test to market. One route is to develop a laboratory-developed test (LDT) and sell it as an in-house performance of the test as a service. These “in-house” developed diagnostics are regulated by CLIA (Clinical Laboratory Improvement Amendments of 1988). This path presents an opportunity for local laboratories and enables early adoption of new technology in endemic areas that are urgently in need of better tests.

II. Summary of Presentations

New York State Laboratory Overview of Services and Research Program by Dr. Kirsten St. George

New York State Laboratory

Dr. Kirsten St. George, Chief of the Laboratory of Viral Diseases at the New York State Laboratory, gave an overview of the state's services and research programs in the Virology Laboratories. She also described the New York State Clinical Laboratory Evaluation Program,that regulates the standards and operation of all clinical laboratories performing testing on New York State residents. This includes the review and approval of submitted information and validation data for non-FDA-approved diagnostic tests that are used in the laboratories. Dr. St. George described the NYS requirements for the information that must be submitted about those tests, in particular for molecular virology tests, and provided details of the required validation data. She then reviewed the timeline of Zika virus emergence and outbreaks, and discussed the preparations undertaken in the NYS laboratory relative to the global movement of the virus. She described the molecular assay that was designed and used in NYS for Zika diagnosis, including gene target locations, and gave a detailed review of the validation process, showing examples of the validation data. Dr. St. George closed with examples of some of the molecular Zika patient test data for NYS from 2016.

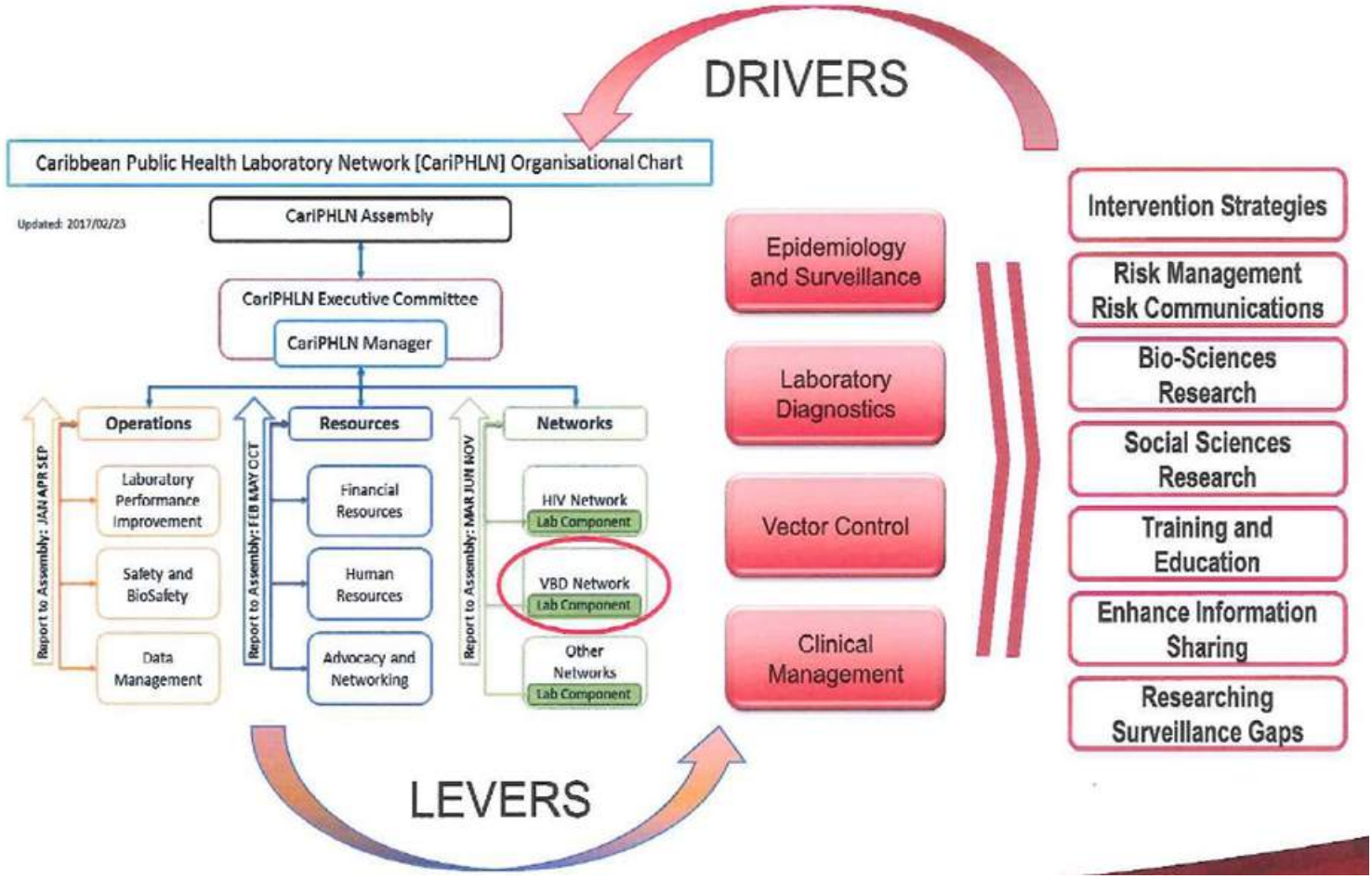
Caribbean Medical Labs Foundation presented by Dr. Valerie Wilson

Caribbean Laboratory Networks

Dr. Valerie Wilson from the Caribbean Medical Labs Foundation presented the Caribbean Laboratory Networks while highlighting their National Policy Framework. The Caribbean Public Health Laboratory Network's (CariPHLN) mission is to integrate public health laboratories in Caribbean Public Health Agency (CARPHA) Member States (Anguilla, Antigua, Barbuda, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Cayman Islands and Dominica) in order to strengthen and national and regional laboratory services, to enhance capacity for preparedness and response to existing problems and new public health emergencies. The vision is for every citizen and visitor to have quality laboratory services. The purpose is twofold: 1) to strengthen capacity of member states in surveillance, prevention and control of public health problems and 2) provide access to referral and specialized testing through the establishment of the Caribbean Public Health Laboratory Network to insure high quality standards throughout the region.

CariPHLN has six advisory groups (Laboratory strengthening, safety and biosafety, laboratory data management, advocacy and networking, human resources and finances. The local government has made a firm commitment for the regional lab initiative. Key components of the national laboratory policy are:
1) Laboratory governance network structure, 2) Quality management systems, 3) Laboratory support systems and 4) Information data management. The general CariVecNet Thematic Network is depicted in the following figure. It is clearly linked to the overall public health network with priority areas intended to benefit all public health labs that support disease prevention and control.

CariVecNet Thematic Network (Fig 1.1)



Rationale and Highlights of National Policy Framework

To support the Laboratory Network effort, a Non-government Organization, Caribbean Med Labs Foundation was established in 2008. The mission is to promote and support achievement of quality laboratory services in accordance with appropriate standards, through advocacy, resource mobilization, collaboration, research and education. An MOU was signed with CARPHA in 2016. The Policy lists Governments' responsibilities as: determining who will be allowed to operate a lab, conduct quality monitoring and accountability, and adequately funding public sector laboratory services for optimal coverage and access. Government support of Laboratory Networks is critical because communicable diseases and Caribbean economies are fragile and negatively impacted by breaking news of disease

outbreaks. Critical roles of the network are to identify disease outbreaks to facilitate rapid, effective public health action and to protect tourism and maintain the national GDP. Laboratory support is crucial to providing high quality patient care because approximately 80% of medical decisions are influenced by laboratory results.

Major challenges that have been identified as insufficient capacity, limited communications and transportation of materials, limited capabilities, lack of consistency in supply chain, limited equipment and sustainability. Requirements for establishing and maintaining this regional network are: 1) adequate and predictable financing, 2) well trained and motivated staff, 3) well stocked inventory, equipment and reagents, 4) robust electronic architecture of data, information processing and reporting network, 5) appropriate testing algorithms and general laboratory procedures, and 6) laboratory governance and network structures, 7) expert management, and 8) competent governance oversight.

In planning for a National Laboratory Policy for Puerto Rico, the following components should be considered: situational analysis, mission and vision statements and a list of essential elements for the national laboratory policy. These essential elements should include: 1) laboratory governance and network structure, 2) quality management systems, 3) laboratory support systems and 4) information and data management systems. The following table offers detailed description of requirements for each of the four essential aforementioned elements.

Components Required to Establish a National Laboratory Policy for Puerto Rico

Laboratory Governance and Network Structure	Quality Management Systems	Laboratory Support Systems	Information and Data Management Systems
1) National health policy & Strategy 2) Legislation & regulation a) National structure 3) Financing 4) Human resources 5) Partnerships & networking 6) Monitoring & evaluation 7) Sustainability	1) Policy Statement 2) Regulations to comply with National Standards 3) Regulatory System 4) Network Quality Monitoring and Evaluation System 5) Training and Education 6) Community & Customer Service 7) Research & Development	1) Policy Statement: cost effective, environmentally friendly and safe 2) Standardization of equipment, supplies and reagents 3) Procurement & Inventory Management 4) Equipment Management 5) Safety and Biosafety	1) Policy Statement: Connectivity, Consistency and Confidentiality 2) Laboratory Information a) Management Structures 3) Provision of surveillance, policy and administrative data 4) Public Communication

Training Needs

A special note on the importance of training for moving forward. The development and operation of a laboratory network to support disease surveillance and control requires provision of competent laboratory personnel and supporting policy structures for supporting and monitoring the network. A focused effort must be made to understand training gaps, and create specialized training to address existing gaps. The CariPHLN is available as a resource for training needs with the CMLF role in supporting policy development and advocacy.

Sentinel Enhanced Dengue Surveillance System: A Successful Model of Epidemiological and Clinical Research in Acute Febrile Illnesses, Puerto Rico 2012-2017 from Ponce Health Sciences University presented by Dr. Luisa Alvarado

Overview of SEDSS

There was a great need to create this Sentinel Enhanced Dengue Surveillance System in Puerto Rico because dengue is endemic and is difficult to differentiate from other acute febrile illnesses. Dengue can rapidly progress to severe dengue, with severe and life threatening complications. Correct diagnosis is critical to enable life-saving clinical monitoring and to establish appropriate prevention measure. Acute febrile illnesses in the differential diagnosis of dengue include the following: Chikungunya, influenza, leptospirosis, non-influenza respiratory viral disease, enterovirus, sepsis, Melioidosis, HIV seroconversion, Zika, and others (malaria, rickettsia, hepatitis A, rubella, measles, and typhoid. Much of what is known about dengue in Puerto Rico is based upon data collected by a passive surveillance system (PDSS) established in the 1960's. This system underestimated incidence and severity of dengue due to timing of initial report and lack of follow-up in clinical care. The World Health Organization recommends countries have both passive and enhanced surveillance to accurately monitor trends for febrile illnesses. In 2012, the facility-based sentinel enhanced dengue surveillance system (SEDSS) was established as a clinical research platform and to study the epidemiology, outcomes and prevention of dengue and febrile illnesses.

The main objectives of SEDSS are to: 1) determine etiology and epidemiology of acute febrile illness in a facilty-based outpatient and inpatient catchment system and 2) describe the disease spectrum of dengue compared to other acute febrile illnesses and identify early clinical and laboratory characteristics to help differentiate them. Specifically focusing on early indicators for developing severe dengue among children and adults. A longer term objective is to improve the understanding of the causes of acute febrile illness to guide clinical management, diagnostics, inform public health policy and direct prevention efforts. The SEDSS is located at St. Luke's Episcopal Hospital in Ponce, St. Luke's Episcopal Hospital in Guayama and at the Centro de Emergencia y Medicina Integrada El Tuque in Ponce. These

three sites provide a coverage area of approximately 853,389 residents from 20 municipalities. All patients presenting for care are queried for current or recent fever and all febrile patients are offered enrollment in SEDSS study. Clinical and demographic data are collected in emergency department and patients are placed into two categories out-patient and in-patient groups. A diagnostic algorithm is used to perform tests in four categories: blood, serum and urine specimens collected less than six days post illness, serum specimens collected greater than four days after illness onset, naso/oropharyngeal swabs by PCR and bacterial cultures.

Findings 2012-2015

43,567 patients with acute febrile illness presented to ED of study sites from 2012 to 2015 and 8,996 were enrolled. Half were female with median age of 12.8 years, 25% were hospitalized. Pathogens most frequently detected were CHIKV (18.2%), FLU A/B (11.9%), DENV (10.8%) and ORV (10.3%). Participants with DENV presented later and higher proportion were hospitalized (46.6%) than those with other diagnoses. 109 patients had a co-infection as detected by molecular detection of two or more pathogens.

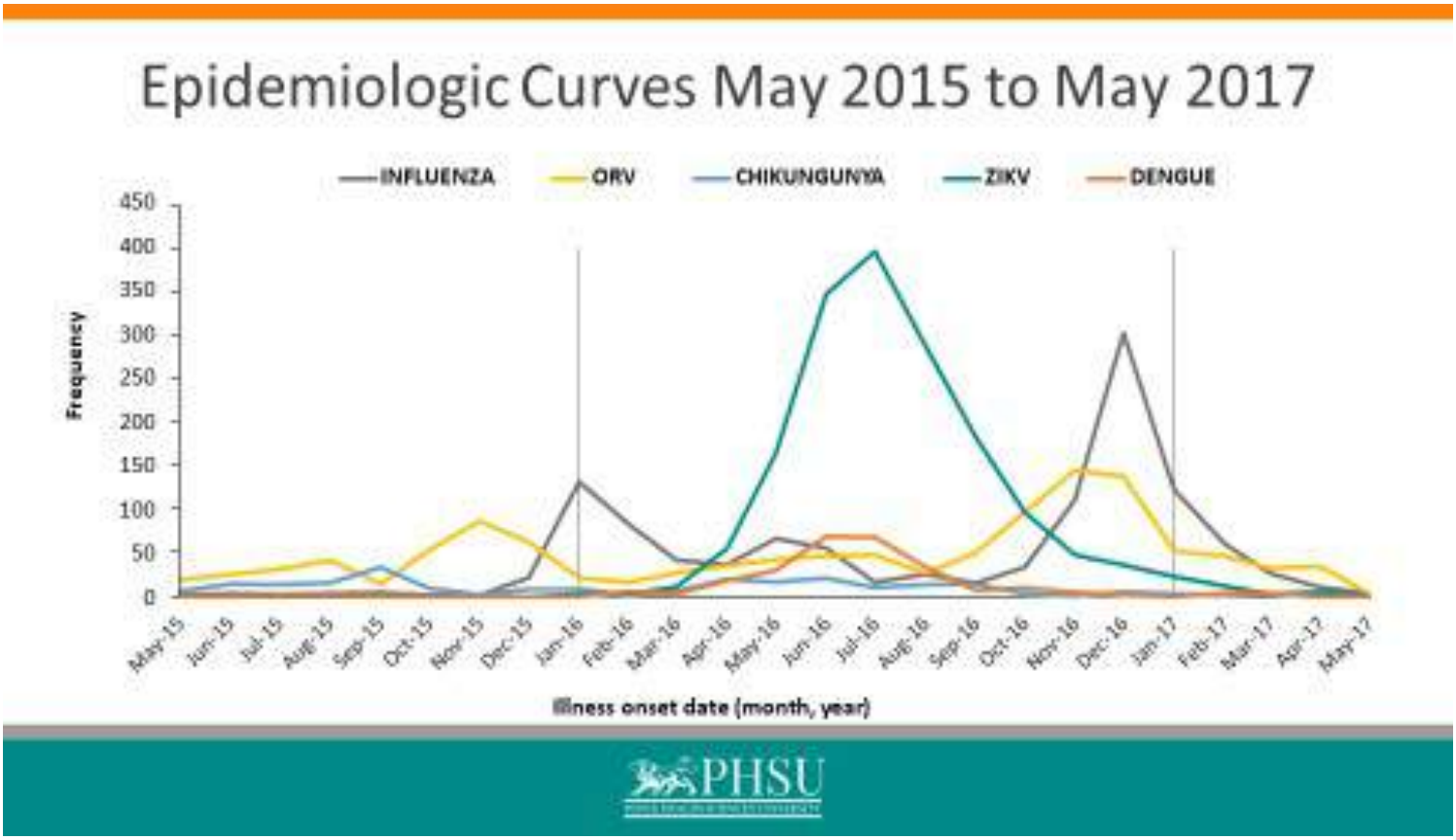
SEDDS Update - 2015-2020

Objectives were to maintain enhanced surveillance for febrile illnesses in Puerto Rico, and also respond to new epidemiologic trends and address research questions of emergent pathogens. The strategy was to expand enrollment to capture a milder spectrum of AFI disease. Expanded inclusion criteria were to include adults 21 years or older who arrive to hospital with one of following combinations or signs related to illnesses under study: rash and red eyes (non-purulent conjunctivitis) and rash and joint pain. An additional 313 participants were enrolled with expanded inclusion criteria.

Findings 2015-2017

Pathogens identified in new study phase were as follows: ORV 12%, CHIV 2%, FLAV 0.4%, FLU 13%, DENV 0.3%, Dual infection 1% and no pathogen detection in 55% of study sample (n=9,063). The following figure shoes trends in epidemiological curves by pathogen from May 2015 to May 2017.

Figure 1.2 Epidemiologic Curves for Major Pathogens over Time (May 2015-May 2017)



SEDSS as a Clinical Research Platform

SEDSS data have been used to identify the following:

- Clinical markers to differentiate dengue from other Acute Febrile Illnesses.
- Early indicators of patients at risk for developing severe dengue
- Spectrum of disease and risk factors for hospitalization of chikungunya
- Pediatric Outcomes of ZIKV Infection Projects
- DENV IgG and Zika Severity

SEDSS data and collaborations have helped to produce significant findings on persistence of Zika virus in body fluids and perinatal transmission of Zika virus. In addition, SEDSS data was used to investigate clinical markers to differentiate dengue from other acute febrile illnesses in children and adults. This

data has been used to conduct the Pediatric Outcomes of Prenatal Zika Exposure (POPZE) cohort study that examined prospective and retrospective cases to study the spectrum of physical and neurological abnormalities and neuro-developmental outcomes of prenatally ZIKA exposed infants from birth to 12 months. Another spin off study is the Outcomes of Postnatal Acquired Zika Virus Disease (PAZI) which aims to describe the clinical neurodevelopmental outcomes of children one year and older following acute onset of postnatally-acquired ZIKV disease.

Future Directions

Methods and findings from the SEDSS Study will be used to pursue and strengthen research collaborations within Puerto Rico and the U.S. for the study of acute febrile illness. Findings will contribute to the expansion of the platform in clinical epidemiologic research in areas of diagnostics, therapeutics and vector control. SEDSS Study has contributed to research capacity through the mentoring of medical and public health students, medical residents and faculty.

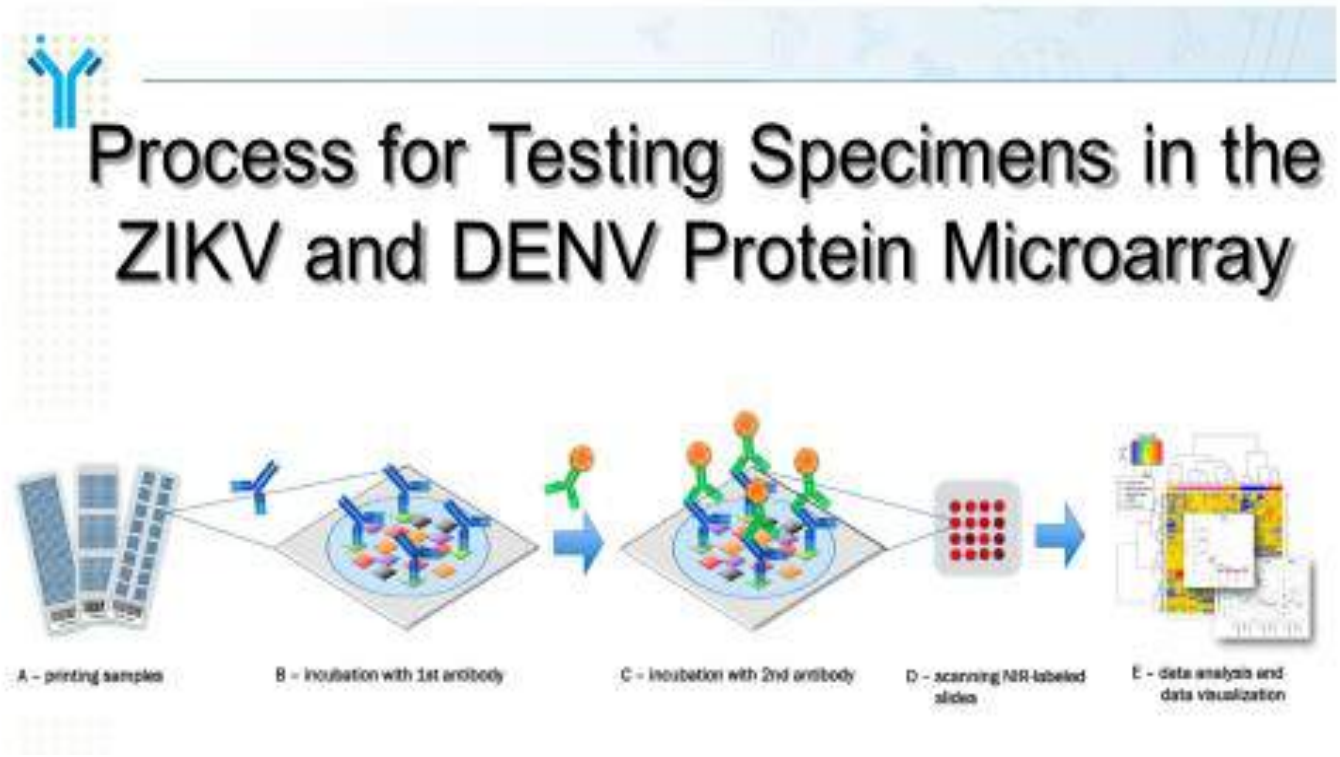
Rapid Proteomics Technology for the Development of Precise Immunoassays for Arboviruses by Dr. Ignacio Pino from CDI Labs in Mayaguez, Puerto Rico

Cross Reaction in Current Methods

It is widely known that ZIKV and DENV cross react in IgM Tests. There is also cross-reactivity in the Zika MAC-ELISA test. The Plaque Reduction Neutralization Test is also not useful for discerning Zika and dengue viruses in IgM positive cases in Puerto Rico. In a brief test comparing PRNT utility for both viruses, the PRNT test provided a definitive result on only 36% of cases with 65% remaining unspecified.

Principle of Protein Array-Based Biomarker Discovery

This technology empowers basic and translational research for antibody specificity and bio pharmaceutical development. In order to promote biomarker discovery, a cost-effective rapid workflow for serum profiling. A protein fluid applied to a protein micro-array chip allowing for antibodies in fluid to react with proteins found on surface of micro array chip. The array is washed and the antibody targeted interactions are revealed by applying a fluorescently tagged isotope specific secondary antibodies. Signal captured using the microarray scanner are then converted to numerical values that are analyzed using bio informatics software.

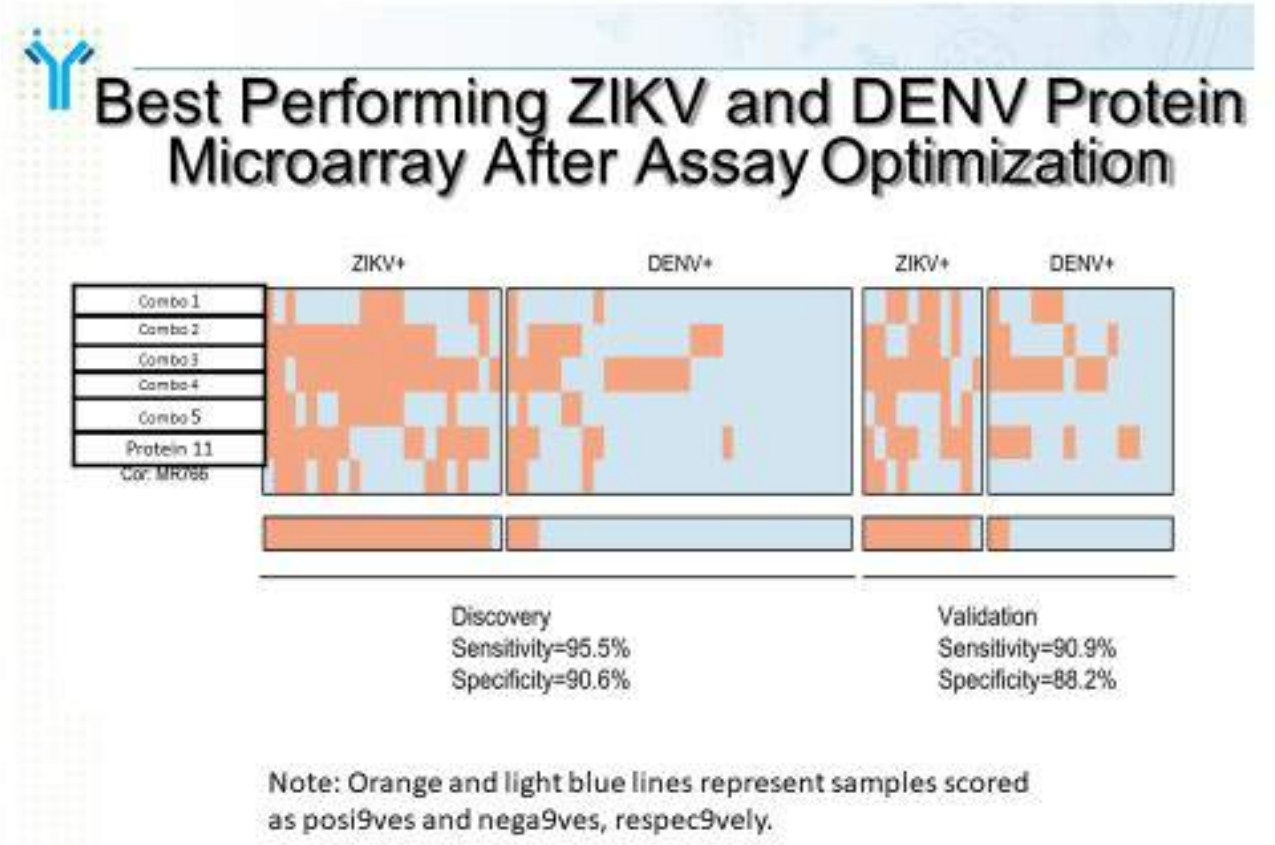


ZIKV and DENV Protein Microarray Development

CDi performs initial research to fabricate ZIKV/DENV Protein Arrays. Description of the cohort from Puerto Rico begins with serum samples available from CDC in Puerto Rico were used for elaboration of the discovery stage and validations panels. Zika specimens were collected during the 2016 epidemic in Puerto Rico. DENV specimens were collected from 2010-2012, prior to the arrival of ZIKV in Puerto Rico. Of the 49 dengue IgM positive samples as confirmed by the CDC MAC-ELISA, 33 were from patients with confirmed DENV RT-PCR positive results by the CDC DENV-RT-PCR. The 33 Zika IgM positive samples were dengue IgM negative and collected from patients with Zika RT-PCR positive results by the CDC TRIOPLEX test. The best performing ZIKV and DENV protein microarray after assay optimization is depicted in the below figure.

Next Steps

The validation of the performance of the most promising biomarker panel with a large cohort study is one of the most important next steps. Secondly, the optimization of sensitivity to detect flavivirus infected patients vs. non-flavivirus infected patients in order to convert existing text to an efficient



Note: Orange and light blue lines represent samples scored as posi9ves and nega9ves, respec9vely.

diagnostic tool. Finally, then to shorten and optimize the entire procedure. Immediate uses of the ZIKV- DENV Protein Microarray are for vaccine development and vaccine efficacy monitoring. The profiling of immune response and sub-typing, the evaluation of the formulation and time course studies for vaccine development. Pre-screen clinical trial participants, assessing the effectiveness and identification of markers associated with protection for Vaccine efficacy monitoring. The ultimate goal being the high- throughput immunoassay for precise multiplex diagnosis of ZIKV-DENV-CHIKV.

III. Clinical Reference Laboratories' Presentations and Discussion

Invited Laboratories (alphabetical order)

1. Centro Citopatológico del Caribe*
2. Core Plus, Servicios Clínicos y Patológicos
3. High Profile Laboratory¥
4. Immuno Reference Lab
5. Laboratorios Borínquen
6. Laboratorio Clínico Toledo

7. LOGIC Diagnostics (PHSU)
8. Quest Diagnostics
9. Southern Pathology Services

* *Centro Cito Patológico del Caribe discontinued testing for Arboviral diseases.*

[¥] *High Profile Laboratory was not able to send a representative to the Symposium but expressed interest in being part of the Arboviral Diagnostics Reference Laboratories Workgroup.*

Laboratory Facilities in Puerto Rico and Elsewhere

PR - North and Metropolitan Area

- Immuno Reference Lab
- Laboratorio Clínico Toledo
- Core Plus, Servicios clínicos y Patológicos
- Quest Diagnostics
- Borinquen Laboratories

PR - South

- LOGIC Diagnostics (PHSU)
- Southern Pathology Services
- Core Plus, Servicios clínicos y Patológicos
- Laboratorio Clínico Toledo

PR - West

- LOGIC Diagnostics
- Laboratorio Clínico Toledo

Continental US and International

- Quest Diagnostics
- LOGIC Diagnostics

Laboratory Certifications and Personnel Experience

All the reference laboratories in the work group are certified by local and external agencies such as CLIA and the WHO. The staff in every lab include competent administrative personnel, Clinical or Medical Directors and/or Pathologists, and highly skilled testing personnel including American Society for Clinical Pathology (ASCP)-certified Medical Technologists. All laboratories have couriers to serve client- laboratories island-wide.

Laboratories Testing Capacity

All laboratories have increased testing capacity with automated and robotic equipment that provide high throughput. Most laboratories use FDA-cleared and approved tests and equipment.

Experience in the Development of Diagnostic Tests for Infectious Diseases

Except for Quest diagnostics and LOGIC Diagnostics, most laboratories do not have experience in the development of In-house or FDA-approved diagnostic tests for infectious diseases.

Capacity for Developing Diagnostic Tools for Arboviral Detection

Some of the laboratories have implemented or are in the process of implementing FDA-cleared serological and molecular testing for DENV, CHIKV and ZIKAV. Many of the labs own equipment with open-access platforms suitable for the development of novel diagnostic tools. Although not all the laboratories may be up to the challenge of an FDA 510 K pre-market submission, all laboratories in the work group are interested in the development of in-house CLIA-certified diagnostic tests.

Laboratory Needs to Build Capacity for the Development of Arboviral Diagnostic Tests

The needs of the specific laboratories to building capacity for Arboviral testing vary from clerical and administrative to funding, however there were some common needs expressed by most laboratories, these include:

- Mentorship and training on test development
- Cost-effective validation and standardization methods
- Return of investment and appropriate insurance reimbursement
- Protection of scientific contribution
- Infrastructure
- Specimen provision involving access to patient samples and proficiency panels
- Centers for Disease Control (CDC) – Quality Assurance (QA) and Quality Control (QC) Guidelines

Needs for Puerto Rico, as an Endemic Area for Arboviral Diseases, to Develop a Responsive and Integrated Diagnostic Infrastructure as Identified by Participating Laboratories

The most pressing needs expressed by the reference laboratories in order for Puerto Rico to develop an effective and integrated response for Arboviral diagnosis can be summarized in the following three main areas:

1. Stronger association with research organizations: academic and industrial,
2. Increased involvement with CMS and private insurance companies in the discussion, and
3. Improved networking with:
   - Puerto Rico Department of Health
   - CDC/Health and Human Services (HHS)
   - Other reference laboratories to understand other's capabilities and capacity
   - Puerto Rico Science, Technology and Research Trust (PRSTRT)

Summary of Discussion

Moderators:

- Kelly Wroblewsky, MPH, MT – Association for Public Health Laboratories (APHL).
- Valerie Wilson, MS, MBA from Caribbean Med Labs Foundation (CMLF).

The discussion began by expanding on the needs presented by the representatives of the reference laboratories, as well as the needs for an integrated Arboviral diagnostic infrastructure for Puerto Rico. Dr. Francisco J. Dávila Toro from Quest Diagnostics, brought up the necessity to do research on the statistics of people in Puerto Rico with potential symptoms for Arboviral diseases that visit hospitals seeking diagnosis/treatment.

Dr. Kirsten St. George, from the New York State Department of Health commented on the need for an Instant Management (IM) Response System to deal with future outbreaks in Puerto Rico. She indicated that such a response system should be flexible enough to manage diverse types of disease agents. An example of why such a flexible system is important is the most recent Influenza pandemic that was followed by a flavivirus outbreak. Dr. Jose F. Cordero, Executive Director of the Brain Trust, added to Saint George's idea suggesting an IM Response System for Puerto Rico could be based on the common denominators known to exist between the disease agents that are commonly transmitted in the Caribbean.

St. George expanded on the concept suggesting putting in place a team of clinical laboratories that meet on a regular basis developing preparedness strategies that could be implemented faster in case of an outbreak. Dr. Jorge Muñoz, Laboratory Director of the CDC-Dengue Branch in San Juan, added the importance of developing and integrated testing algorithms to ensure a thorough diagnosis, and to prevent leaving potential patients undetected (false negatives). The moderators presented a question to the participants on the feasibility of putting in place an IM Response System like the one under

discussion. A follow-up to that question was, "What might potentially present barriers to the proposed plan?" The participant like the concept of putting together a Clinical Lab Working Group for Increased Preparedness and the main factor identified as a barrier to this activity was a lack of economic resources. Lcd. Ilia Toledo, Director of Laboratorio Clínico Toledo, raised the issue that in previous epidemics, as it was in the Zika response, the Puerto Rico Department of Health (PRDH) guidelines required diagnostic testing to be performed by the CDC and the PRDH, only. In addition, when patients are given the option of having to pay at a private clinical laboratory versus free testing at the CDC or PRDH, they generally prefer the cost-free option. Dr. Munoz replied to this comment, emphasizing the importance to work in close collaboration with the PRDH and the CDC to ensure a complete and consistent testing algorithm be followed by all laboratories involved in the response.

Various representatives of the reference laboratories commented on the possibility of receiving a commitment on behalf of the test-developing companies to support participating reference laboratories that decide to implement their tests.

The moderators then presented the participants with a follow-up question for discussion, "What do you perceive the largest regulatory barriers for testing development to be?" Dr. Kareni Pérez, from Core Plus Laboratory, mentioned that one of the main barriers could be access to patient specimens. Dr. Muñoz commented on the limitations of the CDC to distribute patient samples and proficiency panels. Dr.

Francisco Dávila considered the possibility of obtaining specimens from the Continental US through Quest Diagnostics. Dr. Saint George explained the use of artificial RNA as a means of reducing the need for patient specimens for the initial implementation phases for diagnostic test development.

Another barrier, identified by Dr. John Lee from the Biomedical Advanced Research and Development Authority (BARDA), was the challenge of convincing the U.S. Congress to approve funds to support diagnostic development for emerging infectious diseases when there are limited data on the etiology and epidemiology of the emerging infectious agents.

Laboratory Foundation (CMLF), proposed to all participants that we form a working group to establish a plan for the next steps in the development of an Immediate Management Response System for Puerto Rico (PRIMRS). Ms. Lucy Crespo, CEO of the Puerto Rico Science, Technology and Research Trust (PRSTRT) offered the Trust and its resources as a platform to hose and enable the formation and activities of the proposed PRIMRS Working Group.

IV. Needs and Next Steps

These next steps are intended to address the needs identified during this technical meeting by participating clinical reference labs and meeting participants. The following table summarizes needs and how they correspond to each other and to the proposed next steps.

Reference Lab Needs	Puerto Rico Needs	Next Steps
1) Mentorship and Training	1) Stronger Association with Academic and Industrial Research Associates	• Gather and analyze descriptive epidemiological data on prevalence and incidence of Arboviral disease and emerging infectious disease. • Collaboration with stakeholders to build Immediate Management Response System for PR. • Establish working group of Clinical Reference Laboratories to put in place Immediate Management Response System for region facilitated by Science Trust. • Explore access to patient samples and use of artificial RNA for diagnostic test development • Include insurance industry in proposed working group
2) Cost-effective validation and standardization		
3) Protection of Scientific Contribution	2) Improved networking with Puerto Rico Department of Health, CDC/HHS, other reference laboratories and the Puerto Rico Science, Technology, and Research Trust.	
4) CDC Quality Assurance and Quality Control Guidelines		
5) Appropriate insurance reimbursement	3) Increased involvement of CMS and Insurance	

During the group discussion of the Arbovirus Disease Diagnostic Symposium a consensus was reached that the most important next steps towards the achievement of a responsive and integrated Arboviral diagnostic infrastructure for Puerto Rico are as follows:

- Gather and analyze basic descriptive epidemiological data on the prevalence and incidence of Arboviral disease along with increased data on etiology and epidemiology of emerging infectious

agents in order to accurately communicate the magnitude of the problem for Puerto Rico and Caribbean Region to the U.S. Federal Government agencies and private foundations.

- Facilitate clinical reference laboratories collaboration with the New York State Department of Health, Puerto Rico Department of Health, and the Centers for Disease Control and Prevention and the Puerto Rico Science, Technology and Research Trust to build an Immediate Management Response System for Puerto Rico and to insure a complete and consistent use of the testing algorithm by all labs participating in outbreak responses.

- Create a working group comprised of clinical laboratories that will meet 1-2 times per month at the Puerto Rico Science, Technology and Research Trust with the goal of putting into place the Immediate Management Response Systems for Puerto Rico and the Caribbean for increased preparedness. This working group will be facilitated by the Brain Trust for Tropical Disease Research and Prevention.

- Explore the access to patient samples and the alternative use of artificial RNA as an option in the initial implementation phases of diagnostic test development.

- Include representative from the insurance industry in the proposed working group so that test development and test administration can be offered at a sensible price point to patients, but will also help cover the laboratories' expenses associated with test development and administration.

Summary by Rafael Tosado, PhD CDC-Dengue Branch, San Juan, PR and Leslie Maas Cortes, MHS Puerto Rico Science, Technology and Research Trust.

Technical workshop: Arbovirus Diagnostic Development in Puerto Rico

Friday, July 21, 2017 Puerto Rico Science, Technology and Research Trust: Innovation Center Conference Room (2nd Floor)

9:00-9:10 am	Welcome	Lucy Crespo, CEO PRSTRT José F. Cordero, Executive Director Brain Trust
9:10-9:20 am	Introduction to Puerto Rico Clinical Consortium for Investigation	Kosmas Kretsos, PhD, MBA Executive Director Puerto Rico Consortium for Clinical Investigation
9:20-9:40 am	Arbovirus Diagnostics in Puerto Rico before and after Zika: New Challenges and Opportunities	Jorge Muñoz Jordán, MD, MPH Chief, Surveillance and Research Laboratory Dengue Branch Puerto Rico CDC
9:40-10:05 am	Laboratory Developed Tests in a State Public Health Department	Kirsten St. George, PhD Chief, Viral Diseases, Wadsworth, NYSDOH Clinical Professor, Biomedical Sciences University at Albany, SUNY, Albany, NY
10:05-10:30 am	Public Health Laboratories and Diagnostic Test Development for Infectious Diseases	Kelly Wroblewski, MPH, MT (ASCP) Director Infectious Diseases Association of Public Health Laboratories (APHL), U.S.
10:30-10:50 am First Floor	Morning Break	Sponsored by ROCHE Diagnostics Roche
10:50-11:15	Creating Diagnostic Lab Networks in Caribbean	Valerie Wilson, MS, MBA Director Caribbean Med Labs Foundation
11:15 am -12:05 pm	Local Reference Lab Presentations - I 11:15-11:25am – Logic Diagnostics, PRI 11:25-11:35am - Immuno Reference Lab 11:35-11:45am - Laboratorio Clinico Borinquen 11:45-11:55am - Southern Pathology Services 11:55-12:05am - Laboratorio Clinico Toledo	Dr. Vanessa Rivera Amill, Director Rosa I. Martinez Vela, Director Lcda. Lydia M. Cora, Director Rosa Vélez, Scientific Director Lic. Ilia M. Toledo, Director
12:05-1:15 pm First Floor	Lunch and Networking	Sponsored by ROCHE Diagnostics Roche
1:15-1:55 pm	Local Reference Lab Presentations - II 1:15-1:25pm - Core Plus 1:25-1:35pm - Quest Diagnostics 1:35-1:45pm - Centro Citopatológico Caribe 1:45-1:55pm - Lab Patología Dr. Noy, Inc.	Dr. Kareni J. Perez Torres, Coordinator Francisco J. Dávila Toro, MD, Director Katherine Dávila, Director Judith Betancourt, Administrator
1:55 – 2:10 pm First Floor	Networking Break	Sponsored by ROCHE Diagnostics Roche
2:10-2:30 pm	A Synthesis of State of Sentinel Labs in Puerto Rico and Future Directions	Rafael Tosado Acevedo Dengue Branch Puerto Rico CDC
2:30-2:55 pm	The Sentinel Enhanced Dengue Surveillance System: A Successful Model of Epidemiologic and Clinical Research in Acute Febrile Illness in Puerto Rico	Dr. Luisa Alvarado, MD, FAAP Professor Pediatrics Infectious Diseases Division, PRI Ponce Health Sciences University
2:55-3:15 pm First Floor	Afternoon Break	Sponsored by ROCHE Diagnostics Roche
3:15-3:40 pm	Rapid Proteomics Technology for the Development of Precise Immunoassays for Arboviruses	Dr. Ignacio Pino, PhD, CEO CDi Laboratory
3:40-4:45 pm	Panel Discussion: Enhancing our capacity to develop "in house" diagnostic tests Facilitators: Kelly Wroblewski, MPH, MT from APHL and Valerie Wilson MS, MBA from CMLF	
4:45-5:00 pm	Closure and Next Steps	José F. Cordero, MD, MPH

Pre-Meeting Readings

1. Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: Interim Guidance for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus for Persons with Possible Zika Virus Exposure - United States, September 2016. MMWR Morb Mortal Wkly Rep **2016**; 65:1077-81.
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