

Workshop: AAAS-ACC

Cooperation on Science-Addressing shared challenges on communicable & non communicable diseases

Institute of Tropical Medicine “Pedro Kouri”, IPK



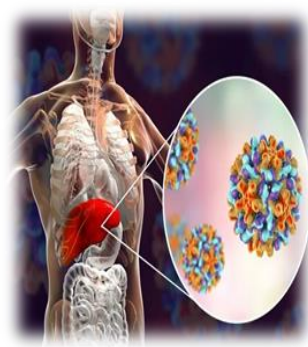
Dengue & other emergent arbovirosis

Prof. Maria G Guzman, MD, PhD, DrCs
Head, Center for Research, Diagnostic & Reference
President, Cuban Society of Microbiology & Parasitology
Director, WHO Collaborating Center for Dengue
lupe@ipk.sld.cu

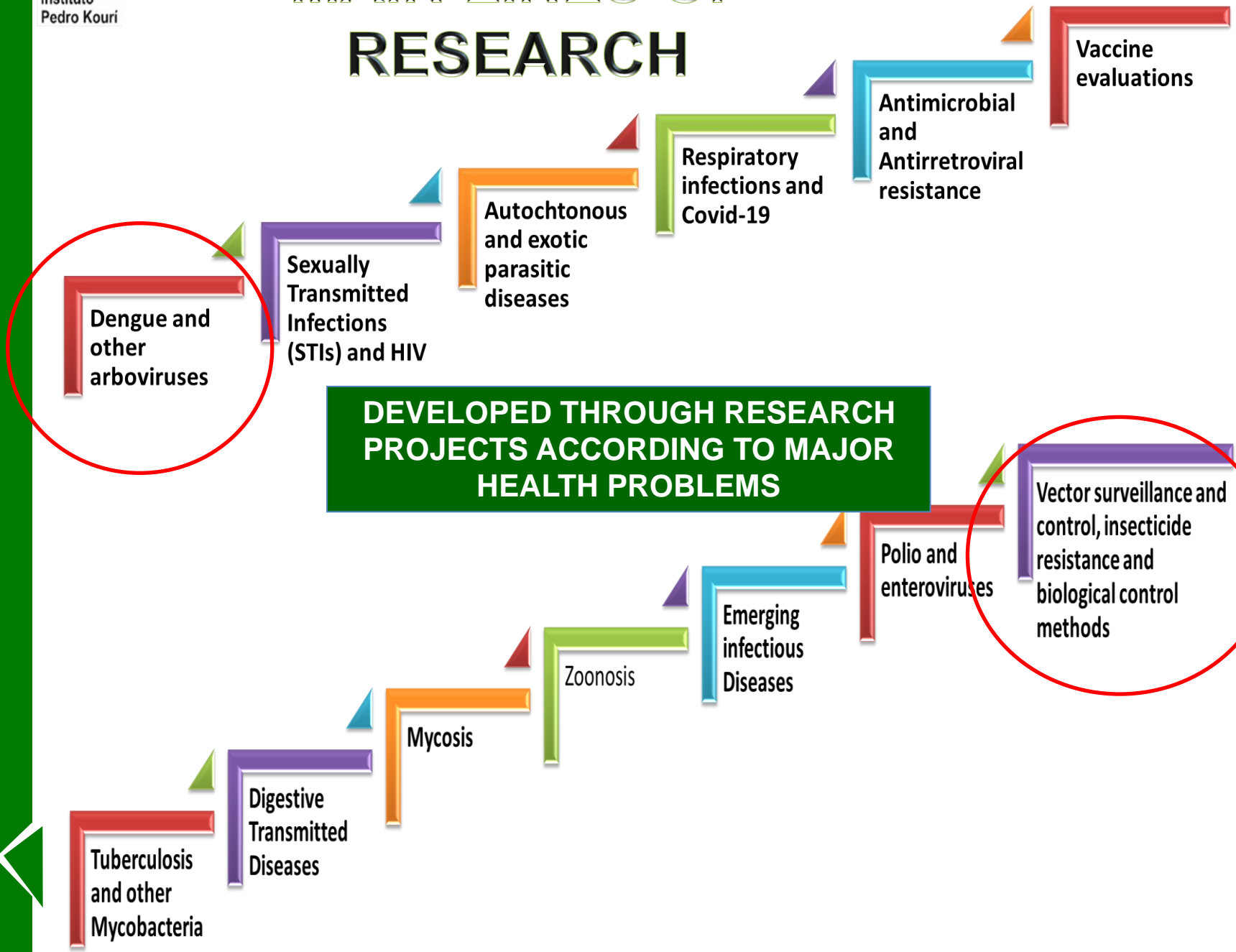
March 21, 2023



- ❖ National Reference Center for infectious diseases
- ❖ Provides highly specialized services in medical care, diagnosis, reference & surveillance on Infectious diseases
- ❖ Develops basic & implementation research
- ❖ Offers high level teaching activities
- ❖ Three Centers: a hospital, a center for medical surveillance & center for research and diagnosis (CIDR)



MAIN LINES OF RESEARCH



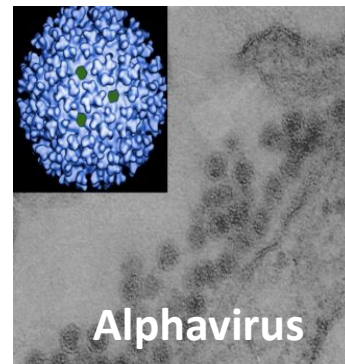
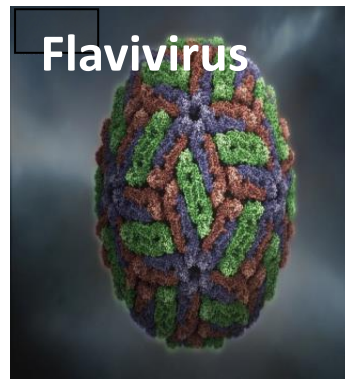
DENGUE, CHIKUNGUNYA, ZIKA:

ARBOVIRUSES OF MAJOR IMPORTANCE IN THE AMERICAN REGION

YELLOW FEVER URBANIZATION THREAT

Arboviruses:

- Transmitted by blood-feeding arthropods
- Maintained in nature in transmission cycles including replicating in blood-feeding arthropods that transmit virus in their saliva to vertebrates
- Replicates in vertebrates where become accessible to other arthropods completing the cycle



Currently aprox. 545 viruses (134 human illness)

IPK DENGUE/ ARBOVIRUS GROUP

- Multidisciplinary group of virologists, immunologists, epidemiologists, clinicians, entomologists, economists, mathematicians, sociologists, pharmacologists etc, working in dengue & other arbovirus
- In charge of the epidemiological, entomological & virological surveillance under the direction of the MOH
- Conduct research activities in diagnostic, vaccine, pathogenesis, immunology, omics (molecular epidemiology, human genetic), clinic, epidemiology, entomology & vector control, social, economic, climate research, etc through research projects with national & international institutions
- Close activity with PAHO/WHO/TDR as part of the Dengue WHO collaborating Center

ARBOVIRUS SURVEILLANCE & CONTROL

- Based on the Primary Health Care of Attention (APS). Clinical, epidemiological, entomological, environmental & lab surveillance
- Lab surveillance with two lab networks for molecular diagnosis & serology using a Cuban system for IgM detection (CIE-IPK). CIDR-IPK as the reference center
- Entomological surveillance (lab network). CIDR-IPK as the reference center
- CIDR-IPK: in charge of evaluations of diagnostic kits, insecticides & technologies
- Strong activity facing arbovirus emergencies
- IPK, reference center for the clinical management, epidemiological surveillance, vector control etc

MAIN CUBAN TOPICS OF INVESTIGATIONS IN DENGUE & OTHER ARBOVIRUSES

- Dengue & Zika clinical features
- Zika impact in pregnant woman
- Epidemiological factors for dengue transmission & DHF development
- Host risk factors for DHF & clinical overt
- Pathogenic mechanisms
- Host genetic, epigenetic & transcriptomic
- Immune response
- Virus evolution & molecular epidemiology
- Vaccine & antiviral investigations
- Entomological research & Mosquito control.
- Community participation & social studies
- Economic studies
- Prediction model development
- Climate, Environment & dengue
- Diagnosis & surveillance

**MINSAP
CIGB
CIE**

**Finlay Institute
INHEM**

Labiofam

PAHO/WHO

IMT, Belgium

Amberes Univ., Belgium

PI France,

PI Guadeloupe

Heidelberg Univ.

OIEA

Others institutions

Research activities in diagnosis, vaccine, pathogenesis, clinic, epidemiology, entomology & vector control, social & economic research

- More than 400 papers published in High impact journals & several book chapters
- Volume book for the Spanish community (2016)

DEBATE

Open Access

Implementation Science

A modified theoretical framework to assess implementation fidelity of adaptive public health interventions

Dennis Pineda¹, Patrick Van der Stuyf², Maribel Carmen Zabala³, Maria Castro⁴ and Andre Pretorius⁵

Abstract: One of the major obstacles in implementation research from around the globe and adapting it to a specific context is its implementation as intended by the developers. It is crucial to have an intervention manual as intended effects. The purpose of this paper is to describe a modified theoretical framework to assess implementation fidelity of adaptive public health interventions.

Open Access

PLOS ONE

Evaluation of Commercially Available Diagnostic Tests for the Detection of Dengue Virus NS1 Antigen and Anti-Dengue Virus IgM Antibody

Elizabeth A. Humphreys¹, Sohee Yeh², Philipp Buchy³, Wich-Chai Nguyen⁴, Shanaka Devi Sekaran⁵, Delia A. Linton⁶, Susana Vasquez⁷, Elizabeth Carter⁸, Jose L. Palacios⁹, Harvey Arts¹⁰, Maria G. Guzman¹¹, Phyllis Othman¹², Julian Zou¹³, Maria G. Guzman¹⁴, and Phyllis Othman¹⁵

Abstract: Dengue viruses (DENV) are the most common mosquito-borne viral pathogens worldwide. Rapid and accurate diagnosis is essential for patient management and public health surveillance. This study evaluated the performance of commercially available diagnostic tests for the detection of dengue virus NS1 antigen and anti-dengue virus IgM antibody.

Introduction: Dengue is a major public health problem with over 1 billion people infected annually. Rapid and accurate diagnosis is essential for patient management and public health surveillance. This study evaluated the performance of commercially available diagnostic tests for the detection of dengue virus NS1 antigen and anti-dengue virus IgM antibody.

Methods: A total of 1000 samples were tested using five different diagnostic tests. The results were compared to the gold standard, reverse transcription-polymerase chain reaction (RT-PCR).

Results: The sensitivity and specificity of the tests varied significantly. The NS1 antigen test showed the highest sensitivity, while the anti-IgM test showed the highest specificity.

Conclusion: The results of this study indicate that the NS1 antigen test is the most accurate for the detection of dengue virus. The anti-IgM test is also a valuable tool for diagnosis.

Open Access

Journal of Virology

Dengue

Increasing Clinical Severity during a Dengue Virus Type 3 Cuban Epidemic: Deep Sequencing of Evolving Viral Populations

Romari Rodriguez-Rocha¹, Yoniel Jimenez², Maria G. Guzman³

Abstract: Dengue virus (DENV) is a major public health problem worldwide. This study investigated the evolution of DENV viral populations during a Cuban epidemic, focusing on the increasing clinical severity observed.

Introduction: Dengue virus (DENV) is a major public health problem worldwide. This study investigated the evolution of DENV viral populations during a Cuban epidemic, focusing on the increasing clinical severity observed.

Methods: Deep sequencing was used to analyze the genetic diversity of DENV viral populations during the Cuban epidemic.

Results: The study identified several mutations in the DENV genome that were associated with increased clinical severity.

Conclusion: The results of this study suggest that genetic changes in the DENV genome may contribute to the increasing clinical severity observed during the Cuban epidemic.

Significance: Understanding the evolution of DENV viral populations is crucial for developing effective control strategies and vaccines.

Keywords: Dengue virus, deep sequencing, viral evolution, clinical severity.

Open Access

Journal of Infectious Diseases

First dengue hemorrhagic fever epidemic in the Americas, 1981: insights into the causative agent

Romari Rodriguez-Rocha¹, Yoniel Jimenez², Maria G. Guzman³

Abstract: The first dengue hemorrhagic fever (DHF) epidemic in the Americas occurred in 1981 in Cuba. This study investigated the causative agent and its genetic characteristics.

Introduction: Dengue hemorrhagic fever (DHF) is a severe form of dengue infection. The first DHF epidemic in the Americas occurred in 1981 in Cuba.

Methods: Genetic analysis was performed on the causative agent of the 1981 DHF epidemic in Cuba.

Results: The study identified a novel genotype of dengue virus that was responsible for the 1981 DHF epidemic.

Conclusion: The results of this study provide insights into the genetic diversity and evolution of dengue virus in the Americas.

Significance: Understanding the genetic characteristics of the causative agent is essential for developing effective control strategies.

Keywords: Dengue hemorrhagic fever, genetic diversity, viral evolution.

Open Access

Journal of Infectious Diseases

Study Protocol

Clinical evaluation of dengue and identification of risk factors for severe disease: protocol for a multicentre study in 8 countries

James Jamrozik¹, Dong-Il Hong², Nguyen Thi Thanh Kieu³, Ivan Van Nguyen Van Kien⁴, Sophie Kozak⁵, Nguyen Ching-Hsin⁶, Yoon-Ki Kim⁷, Jee-Hee Lee⁸, Imreola Petrus Sandoval⁹, Gabriela Maria Martin Afonso¹⁰, Ida de Mendonca¹¹, Mubinka Sankar¹², Ali Alzamil¹³, Andrea Caputo¹⁴, Ibrahim Ali¹⁵, A. Manoj¹⁶, Emma Mayhew¹⁷, Inésica Rosal¹⁸, Maria Helena¹⁹, Scott B. Halstead²⁰, Mary Guevara²¹, Cameron Simonsen²², Nguyen Thi Thuy Phuong²³, Douglas Brock²⁴, Maria Wells²⁵, Maria Wells²⁶, Scott B. Halstead²⁷

Abstract: Dengue is a major public health problem worldwide. This study aims to evaluate the clinical presentation and identify risk factors for severe disease in eight different countries.

Introduction: Dengue is a major public health problem worldwide. This study aims to evaluate the clinical presentation and identify risk factors for severe disease in eight different countries.

Methods: A multicentre study will be conducted in eight countries to evaluate the clinical presentation and identify risk factors for severe disease.

Results: The study will generate valuable data on the clinical presentation and risk factors for severe disease in different countries.

Conclusion: The results of this study will contribute to the understanding of dengue and the development of effective control strategies.

Significance: This study is a landmark in the field of dengue research and will provide valuable insights into the disease.

Keywords: Dengue, clinical evaluation, risk factors, multicentre study.

Open Access

Journal of Infectious Diseases

Approaches to Refining Estimates of Global Burden and Economics of Dengue

Donald S. Shepard¹, Eduardo A. Undurraga², Miguel Betancourt Covarrubias³, Maria G. Guzman⁴, Scott B. Halstead⁵, Eve Harris⁶, Rose Hand Mulla⁷, Kristy C. Murray⁸, Roberto Tapia-Caceres⁹, Duane J. Nisalak¹⁰

Abstract: Dengue is a major public health problem worldwide. This study explores different approaches to refining estimates of global burden and the economics of dengue.

Introduction: Dengue is a major public health problem worldwide. This study explores different approaches to refining estimates of global burden and the economics of dengue.

Methods: Various approaches were used to estimate the global burden and economics of dengue.

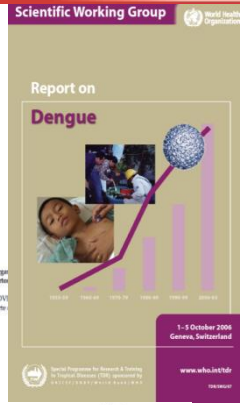
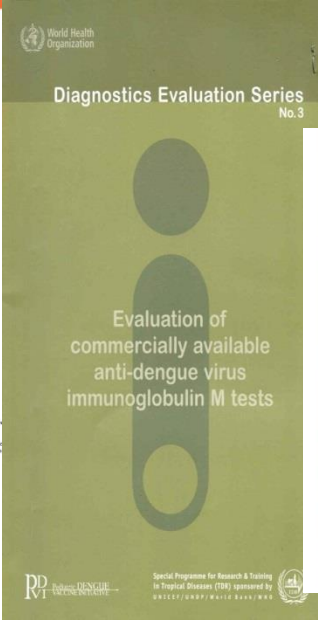
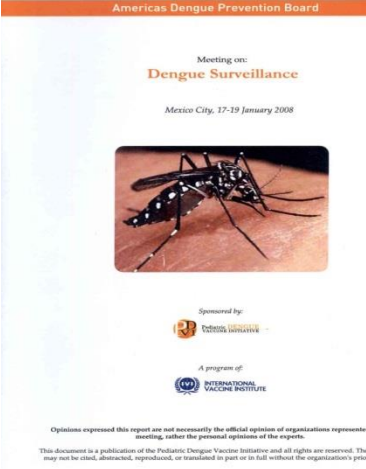
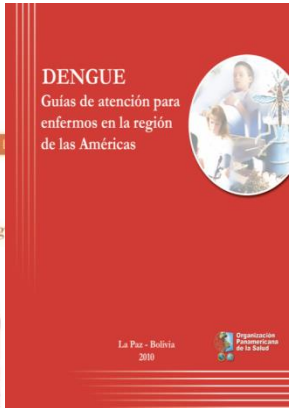
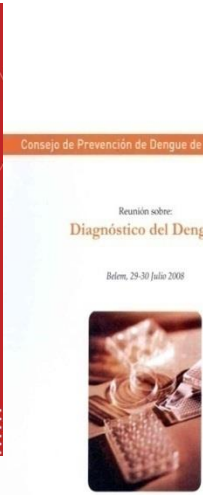
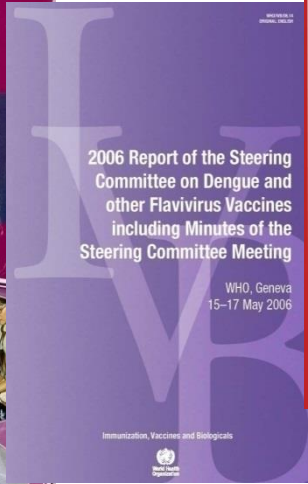
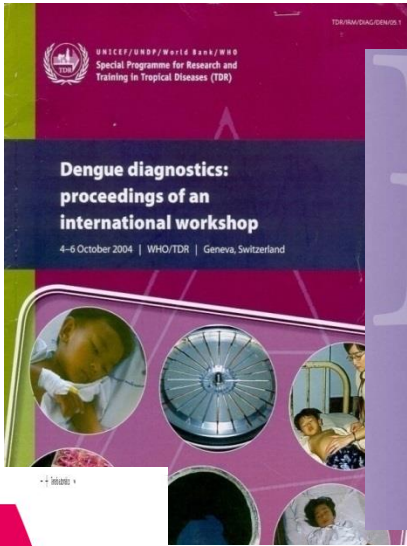
Results: The study found that different approaches yielded varying estimates of global burden and economics.

Conclusion: The results of this study highlight the importance of using multiple approaches to estimate the global burden and economics of dengue.

Significance: This study provides valuable insights into the global burden and economics of dengue.

Keywords: Dengue, global burden, economics, estimation.

PARTICIPATION AT INTERNATIONAL DENGUE EXPERT GROUPS



COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

ARBOVIRUSES

Virology/Immunology: Risk factors for DHF

Confirmation of secondary infection as the main risk factor for DHF, identification of the importance of interval time between infections in the disease severity, the importance of the viral sequence of infections & the inherent age specific susceptibility to DHF during second DENV infections.

Escape Mutant Hypothesis: first demonstration in three different dengue epidemics in a same population that disease severity accompanying secondary DENV infections increased month to month. Unique observation.

Identification of HLA-A, -B, -C, and -DRB1 allele frequencies in Cuban individuals with antecedents of dengue 2 disease in collaboration with Harvard School of Public Health, Boston. First study with the highest significant association HLA genes-dengue

Enhanced severity of secondary dengue-2 infections: death rates in 1981 and 1997 Cuban outbreaks

María G. Guzmán¹, Gustavo Kouri¹, Luis Valdés², José Bravo¹, Susana Vázquez¹ and Scott B. Halstead³

Original Report

Effect of age on outcome of secondary dengue 2 infections

María G. Guzmán¹, Gustavo Kouri¹, José Bravo¹, Luis Valdés², Susana Vázquez¹ and Scott B. Halstead³

PRIMER

Dengue infection

María G. Guzmán¹, Doreen J. Gubler², Aloysio Tapiero³, Eric Martines⁴ and Scott B. Halstead⁵

ABSTRACT

Hypothesis

Do escape mutants explain rapid increases in dengue case-fatality rates within epidemics?

María G. Guzmán, Gustavo Kouri, Scott B. Halstead

During the Cuban dengue epidemics of 1981 and 1997, significant mortality increases were observed in the proportion of fatal cases that presented an dengue hemorrhagic fever or dengue shock syndrome (DHF/DSS), and a case-fatality ratio for both dengue fever and DHF/DSS. We believe that these increases can be explained by the hypothesis that some of the population of arboviruses against dengue 2 virus exhibit other natural antigenic variations and with "escape mutants" characteristics based on dengue 2 viruses. These heterotypic antibodies do not prevent secondary dengue 2 infections, but work to down-regulate the disease to mild forms or asymptomatic infections. A population of dengue 2 viruses that replicate in dengue 2-susceptible hosts receive heterotypic neutralization. When inoculated into a new dengue 2-susceptible host, these viruses are free to interact with the new abundant infection-avoiding antibodies to produce severe disease.

Key Text
 DOI:10.1093/infdis/jab015

BRISQ REVIEW

Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: an historical perspective and role of antibody-dependent enhancement of infection

María G. Guzmán, Mayling Alvarez, Scott B. Halstead

RESEARCH

Neutralizing Antibodies after Infection with Dengue 1 Virus

María G. Guzmán¹, Mayling Alvarez², Rosmarí Rodríguez-Roche¹, Luis Valdés³, Tere Benítez⁴, Tere Benítez⁴, Susana Vázquez¹, Luis Vireo⁵, Angel Alvarez⁶, Ernest A. Gould⁷, Gustavo Kouri¹ and Scott B. Halstead⁸

Human Immunology (2007) 68, 531–540



HLA-A, -B, -C, and -DRB1 allele frequencies in Cuban individuals with antecedents of dengue 2 disease: Advantages of the Cuban population for HLA studies of dengue virus infection

Beatriz Sierra^{1*}, Roberto Alegre^{2*}, Ana B. Pérez³, Gissel García⁴, Katharina Sturm-Ramirez⁵, Oluigbenga Obasanjo⁶, Egllys Aguirre⁷, Mayling Alvarez⁸, Rosmarí Rodríguez-Roche⁹, Luis Valdés¹⁰, Phyllis Kanki¹¹, María G. Guzmán^{12*}

COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

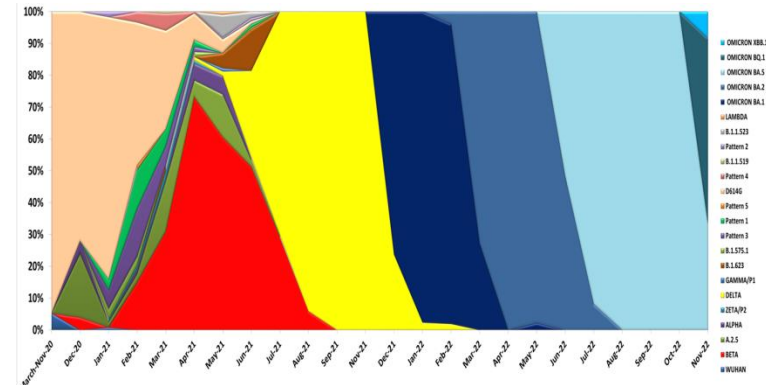
Laboratory & dengue genomic surveillance

- Reagent donation & training for dengue & other arboviruses through RELDA/PAHO
- Reagent donation for SARS CoV-2 nucleotidic sequence (genomic surveillance)

CDC of Puerto Rico

Berkeley University

SARS variants in Cuba, 2020-2023



COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

Entomology

- Insecticide resistance, Florida & Notredame Universities
- Training in molecular entomology, J. Hopkins University
- Collaboration with UTMB in a TDR/WHO project

COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

Epidemiology

- Identification of early warning indicators to identify dengue epidemics
- Methodology for identification of dengue hot spots, Mexico, Colombia, Cuba
- Evaluation of control methods and residual insecticides in Mexico
- Studies of population mobility in the spread of epidemics
- Organization of the network DENTARGET
In collaboration with Emory University

COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

Community participation for dengue control

Development of several symposia:

- Adaptation of COMBI Guidelines in Cuba. National workshop with further replication at regional and PHC levels.
- Knowledge translation research on empowerment strategies. In collaboration with Colorado School of Public Health
- Panel “Communication, participation, equity and SDH: synergies and contributions to integrated vector management, 2022. In collaboration with Universidad George Washington

Am J Trop Med Hyg. 2017;97:101-107.
doi:10.4269/ajtmh.16-0488
Copyright © 2017, by the American Society of Tropical Medicine and Hygiene

Perspective Piece

Why Did Zika Not Explode in Cuba? The Role of Active Community Participation to Sustain Control of Vector-Borne Diseases

Marta Castro,¹ Dennis Pletz,¹ Maria G. Guzman,¹ and Claire Berninger²

¹Pedro Kouri Tropical Medicine Institute, Havana, Cuba; ²Colorado School of Public Health, University of North Carolina, Chapel Hill, North Carolina

Abstract: As the global public health community develops strategies for sustainable Zika prevention and control, assessment of the Cuban response to Zika provides critical lessons learned. Cuba's early and successful response to Zika, grounded in the country's long-standing dengue prevention and control program, serves as a model of rapid mobilization of research efforts. Sustaining this response requires applying the evidence generated within the Cuban dengue program that active community participation improves outcomes and is sustainable and cost-effective. There is also a need for implementation science efforts to assess the transferability of lessons learned from Zika prevention and control to other pathogens and from one context to another in addition to how to take these efforts to scale.

COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

Biosafety trainings in collaboration with UTMB, 2017

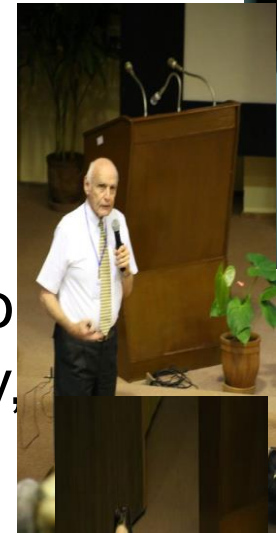
- Course/ Training for Biosafety Level 3 in International Biosafety Training Center (5 participants)
- Course/Training in Animal Biosafety Level 3
- BSL-3 Biocontainment Operations Training (1 participant)
- Course on Clinical Containment (1 participant)
- BSL-2 Training Course at IPK (Theoretical class, 53 participants & Practical course, 14 participants).



COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

Training & Building capacity

- Dengue International course: participation of prestigious professors from NIH, CDC Puerto Rico & Atlanta & J. Hopkins, Berkeley, Emory, Texas Medical Branch, North Caroline, Notredame, New York Sate, Wisconsin, Harvard, California Davis, Ohio State, Pennsylvania State Universities, in the topics of vaccine, pathogenesis, diagnostic, entomology & vector control, epidemiology, social communication etc
- Symposium: New Advances in our knowledge of the *Aedes aegypti* biology and its control
Organized by AAAS, JHMRI, ACC & IPK, 2017



COLLABORATIVE WORK WITH USA INSTITUTIONS AND SCIENTISTS

Scientific collaboration IPK, Havana, Cuba- State University of Ohio (OSU), USA

- Symposium “Infectious Diseases: New approaches in Immunology and Therapies” First Edition. November 12 to 14, 2018, Pedro Kourí Institute of Tropical Medicine (IPK), Havana, Cuba.
- Advances in Immunology and Therapy of infectious diseases: From Bench to Bed, 2nd Edition. 2019, Hotel Meliá Habana, Cuba
- Previously, two courses on Immunology of Infectious diseases with Harvard University



FOUR RESEARCH PROJECTS APPROVED BY CRDF GLOBAL AWARDS, NIH. CRDF GLOBAL – US-CUBA

Collaborative Arbovirus Research Initiative 2017 & pending of execution

- ❑ *Wolbachia* studies as a new tool to control residual *Ae. aegypti* & *Ae. Albopictus* populations in Cuba in collaboration with Kentucky University
- ❑ Exploring Cuban *Ae. aegypti* vector competence in collaboration with J. Hopkins University
- ❑ “Role of lipids associated with African-Ancestry protection, in Dengue & Zika infectious process”. In collaboration with the University of California, San Diego
- ❑ Study the influence of the time of the properties of antibodies after a primary dengue infection in Cuban individuals. In collaboration with the University of North Carolina

IPK CURRENT MAJOR INVESTIGATIONS

- Clinic cohorts of children & adults with dengue after COVID-19 pandemic (new epidemiological situation). Minsap
- Zika impact in pregnant woman, zikalliance-EU project
- OMICs Sciences & Artificial Intelligence applied to human virus Research in collaboration with Amberes & Brussels universities
- Vaccine development in collaboration with CIGB-Cuba
- Evaluation of SIT for *Ae. aegypti* control in a Havana municipality, Minsap-OIEA
- National Map of *Aedes* insecticide resistance, Minsap
- Development of an integrated dengue surveillance model including alert/action system, viral-entomological surveillance, hot spots, human motility etc. in collaboration with PAHO
- Health related social vulnerability and arbovirosis outcomes (morbidity, severity and mortality) in the context of syndemic interactions.

OVERALL INTERESTS OF COLLABORATION

- ❑ Development of joint research projects on dengue & other arboviruses focused on epidemiology, entomology/vector control, virology & immunology, social investigations....
- ❑ Scientific Exchange, teaching activities & capacity building
- ❑ Transference of technologies (NGS, Bioinformatics, Molecular Diagnostics, biomarkers validation & others)

INSTITUTO DE MEDICINA TROPICAL "PEDRO KOURÍ"
"PEDRO KOURÍ" TROPICAL MEDICINE INSTITUTE
XIII CURSO INTERNACIONAL DE DENGUE
XIII INTERNATIONAL DENGUE COURSE



**XVIII International Course on Dengue &
 other arboviruses**
August 14- 25, 2023
"85 Anniversary of IPK foundation"



- Haroldo Bezerra, OPS/OMS
George Dimopoulos, Johns Hopkins, EUA
Anna Durbin, Johns Hopkins Bloomberg School of Public Health, EUA
 Pierre Echaubard, SOAS, Universidad de Londres, Reino Unido
 Florence Fouque, TDR/OMS
 Leticia Franco, OPS/OMS
 Lionel Gresh, OPS/OMS
 Nildimar Honorio, FIOCRUZ, Brasil
 Olaf Horstick, Universidad de Heidelberg, Alemania
 Thomas Jaenisch, Universidad de Heidelberg, Alemania
Linda Lloyd, GT-arbovirus internacional, USA
 Kleber Luz, Universidad Federal Rio Grande Du Norte, Brasil
 Pablo Manrique-Saide, UADY Yucatán, México
 Jairo Mendez, OPS/OMS
 José Moya, OPS/OMS, Cuba
Jorge Muñoz, CDC, Puerto Rico
 Norma Pavia, UADI, Yucatán, México
Gabriela Paz Bailey, CDC, Puerto Rico
 Koen Peeters, Instituto de Medicina Tropical, Amberes, Bélgica
 Alina Pérez, OPS/OMS, Cuba
 Ernesto Pleites, Hospital Bloom, El Salvador
 Diana Rojas Alvarez, WHO Emergency program
 Hichem Salim, Universidad de Vrije, Bruselas, Bélgica
 Philippe Selhorst, Instituto de Medicina Tropical, Bélgica
 Xaveer Van Ostade, Universidad de Amberes, Bélgica
 Wim Vanden Berghe, Universidad de Amberes, Bélgica
 Veerle Vanlerberghe, Instituto Medicina Tropical, Amberes, Bélgica
Gonzalo Vazquez Prokopec, Universidad de Emory, EUA
 Anubis Vega Rua, Instituto Pasteur Guadalupe
 Raman Velayudhan, NTDP/OMS
 Wilmer E. Villamil Gómez, Secretaria de Salud, Barranquilla, Colombia
Stephen Whitehead, NIAID, NIH, EUA
 Qingxia Zhong, NTDP/WHO