Zika Virus: Obscure Pathogen Emerges with New Adaptations

The Zika virus outbreak in South and Central America has raised such alarm that the World Health Organization has declared the epidemic an international public health emergency.

Although the clinical symptoms of the virus are mild, it is increasingly likely that the virus causes rare but severe neurological complications such as microcephaly and Guillain-Barré syndrome. The pathogen is not new, but much remains unknown about the risk it poses.

J. David Beckham, M.D., Associate Professor of Infectious Disease, School of Medicine, University of Colorado Anschutz Medical Campus, is an experienced neurovirology researcher. Since 2004 his research has focused on West Nile virus and its impact on cells in the nervous system. Here he helps illuminate the circumstances of Zika’s recent expansion through the Americas.

The Zika virus was first documented in 1947, when it was discovered in a rhesus monkey living in the Zika forest of Uganda. It was isolated in humans in 1964. Since then, the pathogen has moved east through Asia, hopscotching across the Pacific, arriving in Brazil in 2015.

The Zika virus was mostly unfamiliar until late last year, when Brazilian health officials noticed an increase in babies born with microcephaly, or abnormally small heads. Depending on the severity of the condition, microcephalic children can suffer intellectual deficiency and developmental delays, difficulty with coordination and balance, neurological problems like seizures, and reduced lifespans.

Earlier outbreaks of the disease in the islands of the South Pacific did not correlate to microcephaly, but it’s possible that the outbreaks were not large enough to detect a relationship.

“One of the big questions in the field right now is whether this association with microcephaly is caused by a change in the virus, or rather a large enough increase in the number of cases that we can actually see the relationship between the virus and the microcephaly complication,” explains Dr. Beckham.

However, microcephaly is not the only complication related to Zika. Guillain-Barré syndrome was noted in conjunction with the 2011 outbreak in French Polynesia.

(Continued on page 3)
American Pediaritians Visit Cuba: Transitioning from 50 Years of Isolation to a Future of Collaboration


Taking advantage of the renewed relationship, a conference that focused on future collaboration between American and Cuban pediatritians helped mark the end of 50+ years of isolation.

The conference, which took place February 4-6, 2016, centered on building relationships between multi-specialty American and Cuban pediatritians hoping for future collaboration in research and training.

“As Cubans gain access to new medications and technology, training will become very important. We would like to eventually establish an exchange program so Cuban doctors can come and train here at Children’s Hospital Colorado and vice versa,” stated Steve Berman M.D., F.A.A.P.

The conference was led by Dr. Berman — Professor of Pediatrics, School of Medicine, University of Colorado Anschutz Medical Campus, Director, Center for Global Health, Colorado School of Public Health, and past President of the American Academy of Pediatrics — and James Perrin, M.D., F.A.A.P. — Professor of Pediatrics at Massachusetts General Hospital and past President of the American Academy of Pediatrics.

A total of 13 American physicians, 10 of whom were from Children’s Hospital Colorado, attended the three-day conference.

The first day focused on neonatology and child health. Discussions included topics such as: infant health in Cuba, neonatal health in Latin America and Cuba, premature infant care, child care in Cuba, and promoting responsive parenting for early brain development and child health.

Day two focused on infectious disease and children with complex medical conditions.

Lectures included topics such as: staphylococcal infections, chronic sinusitis, pertussis, acute bronchiolitis, tuberculosis, eliminating vertical transmission of HIV in Cuba, causes of delayed development, management of new onset pediatric seizures, early stimulation in pediatric development, child growth and development, learning disorders, and preparing for mass casualty incidents through the lens of pediatrics.


Fred Deleyiannis, M.D., M.Phil., M.P.H., F.A.C.S.: Providing a Surgical Perspective

“The goal of this conference was to identify physicians within different disciplines who are interested in starting an educational exchange within their specialty. In doing so, we can establish the needs of both Cuba and our country.”

Deleyiannis, Professor and Chief of Pediatric Plastic Surgery, Director of the Cleft Lip and Palate Program, as well as the Craniofacial Microsurgery and Trauma Program in the Department of Surgery at Children’s Hospital Colorado, and the School of Medicine, University of Colorado Anschutz Medical Campus, believes that it is critical to observe and learn from his fellow surgical colleagues locally and internationally — “Academics is what it is all about; teaching and promoting education are some of the most important components of medicine.” Deleyiannis aspires to teach more hands-on surgical skills to the physicians of Cuba in the future.

Deleyiannis found that the lack of access to technology, such as the internet, was one of the greatest barriers for Cuban physicians and health care professionals. “Even though Cuban surgeons can obtain cursory knowledge of what is available, access to the internet is low — it is extremely difficult to download information. It became a reminder how accessible digital information is in the U.S.”

In their discussions, Deleyiannis and the Cuban surgeons hand-drew surgical techniques, but found that not having digital copies of techniques really limited the educational process. “After this conference in Cuba, it makes you appreciate what we have in the United States—we have so much compared to the world,” reflected Deleyiannis.

Nonetheless, Deleyiannis was surprised that low-cost healthcare options in Cuba are widely available and easily accessed. “The Cuban healthcare system is especially good in monitoring and treating high-risk pregnant mothers, as well as reducing infant mortality,” said Deleyiannis.

(Continued on page 6)
"In that outbreak, there were complications noted with Guillain-Barré, which is thought to be a virus-triggered autoimmune problem. It is a paralytic disease affecting the peripheral nervous system," Dr. Beckham explains.

Zika is not the only virus that can activate Guillain-Barré syndrome, so this relationship was not too surprising. No such precedent exists with microcephaly, however. Emphasizing concern about this observation, Beckham states, “The National Institutes of Health (NIH) made it clear that characterizing the association between the viral infection and its complications is the highest priority. Understanding what groups are at risk for these complications is very important. The unique thing about Zika is that it is the first flavivirus to cross the placenta.”

Flaviviruses are a group of viruses that share several similar features. The group also includes Dengue, Yellow Fever, and West Nile viruses, all of which are considered arboviral diseases.

Arboviruses are arthropod-borne diseases, carried by mosquitos, ticks, and other invertebrate animals. Dr. Beckham says that Zika is not behaving like the other arboviruses in its group, specifically with regard to intrauterine transmission.

Flaviviruses are known to act on the nervous system of their hosts, but they have never crossed the placenta to infect the nervous system of a developing fetus, which is the speculated cause of microcephaly in this outbreak. Other non-flaviviruses can do that, such as rubella, but Zika is the first of its kind to act this way. In other ways, Zika is consistent with fellow flaviviruses like West Nile. In both instances, 80% of infected adults have no symptoms, and symptoms are fairly mild when they do develop (e.g. fatigue, fever, bloodshot eyes).

This leads to difficult questions, such as whether microcephaly is likely to develop in the fetuses of asymptomatic pregnant women. “We don’t know the answer to that. We have to follow women prospectively through their pregnancies and learn what happens. This is the type of evidence we need to demonstrate causation,” Beckham explains.

Some prospective studies are underway in Brazil, showing that nearly one-third of women who had Zika during their pregnancy had ultrasounds revealing fetal abnormalities.

These abnormalities also include problems with the placenta and amniotic fluid, as well as other nervous system issues like calcification of brain tissues and lesions on the spine.²

In the lab, the best method for diagnosing Zika is the reverse-transcription polymerase chain reaction (RT-PCR) test. RT-PCR can ascertain the presence of Zika’s genetic material, and has already shown the virus in multiple tissues of a microcephalic infant who died in the immediate neonatal period.³ Unfortunately, RT-PCR requires fairly advanced lab resources, and can only detect recent infections. A simpler blood test that looks for an antibody to the Zika virus is more widely available, but less reliable because it may yield a false positive result if dengue or another flavivirus is present.

After determining Zika’s prevalence, and potential complications like Guillain-Barré and microcephaly, research priorities will shift. Investigators will try to understand more about transmission and establish more efficient diagnostic testing. Like intrauterine transmission, the virus’s apparent sexually transmissibility is a novel characteristic.

Dr. Beckham provides more details, “When you’re sick with West Nile, the virus gets into the kidneys and urine, which Zika can do as well. However, there are some clear indicators that it is getting into the prostatic fluid and semen as well.

_______________________________

J. David Beckham, M.D., Associate Professor of Infectious Disease, School of Medicine, University of Colorado Anschutz Medical Campus

“The National Institutes of Health (NIH) made it clear that characterizing the association between the viral infection and its complications is the highest priority. Understanding what groups are at risk for these complications is very important. The unique thing about Zika is that it is the first flavivirus to cross the placenta.”
There have been some links between men who were ill and likely transmitted the virus to their spouse. What is not known is how long the virus would survive in semen, and whether it could affect a fetus this way."

The virus can also be spread through blood transfusion, laboratory exposure, and the local mosquito population. Local transmission occurs when a mosquito feeds from an infected human and spreads the virus to other humans through subsequent feeding.

Local transmission is less likely to take place in the southern United States due to the popularity of air conditioning and widespread use of window screens. These two factors alone will decrease local transmission since the Aedes aegypti mosquito (the primary species carrying Zika) bites mainly during the day, when air conditioners are running and windows are closed.

A congested environment with high density housing and poor mosquito control are important conditions for local transmission.

"All countries in Latin America are very worried about the implications of Zika infections in the new generations. There is only limited capacity in countries like Guatemala to control the transmission of Zika. Managing mosquito populations through insecticide spraying and the elimination of breeding sites will perhaps decrease the transmission, but it is extremely difficult to contain this type of epidemic. The lack of access to health care makes it even more difficult to determine how extensively Zika has impacted the population in low-income countries," says Edwin Asturias, M.D., Associate Professor, Section of Infectious Disease, Department of Pediatrics, University of Colorado School of Medicine, and Director of Latin American Projects, Center for Global Health.

Managing the mosquito population through outreach and education is important. Incorporating lessons learned from past arboviral epidemics, government agencies have significant experience implementing behavior change campaigns, and distributing items like treated bed nets. These initiatives are complemented by ongoing research, some of which is happening at the University of Colorado.

"We currently have a febrile illness surveillance system set up to detect cases of Dengue in southwest Guatemala. Since Zika virus is very similar to Dengue, we suspect it may have been around longer than we realized. Therefore, we plan to use blood samples already collected from our dengue study to test for Zika virus. We also plan on including Zika virus testing as we move forward with additional surveillance studies, collaborating with colleagues such as Dr. Beckham at the University of Colorado to study transmission dynamics and the host immune response," states Dan Olson, M.D., Assistant Professor, Section of Infectious Disease, Department of Pediatrics, University of Colorado School of Medicine, and Senior Investigator, Center for Global Health.

In the lab, the virus isolates will provide insight into the pathogen’s new and unexpected capacity to cross placental and prostatic tissues.

"This genetic class of viruses [which includes Zika, West Nile, Chikungunya, and Dengue] have been around for billions of years, and they are highly adapted to manipulating this link between mosquitoes and vertebrate hosts. They have emerged off and on for a very long time, and we are just developing the technology to recognize them on a global scale through improved testing and informatics," states Beckham.

Laboratory analysis of Zika on a molecular level will be the next step toward developing a vaccine and therapeutic treatments for infection. What was recently considered an obscure and trivial virus has captured the attention and efforts of health experts worldwide.
Zika Virus: Obscure Pathogen Emerges with New Adaptations

(Continued from page 4)

The growing number of human cases and the link to more severe illness has demanded an urgent response.

Dr. Asturias draws a comparison, “Zika is the new rubella, a disease that pregnant women and public health officials feared in the past century for its devastating effects on the unborn child. It is now confirmed in Brazil that 1 of 3 infections in pregnancy will result in fetal abnormalities. Rubella was similar, with 90% of first trimester pregnancies having complications, and 10-20% in the second trimester. The difference is that rubella was a common infection in children and only a few women were susceptible when becoming pregnant. But at this point, no one in the Americas is protected against Zika, therefore any woman getting pregnant and infected with Zika runs a high risk of complications unless we develop the means to prevent this important viral infection."

Although there has been speculation that the uptick in microcephaly cases is the result of something else altogether, data is becoming increasingly conclusive that Zika is the culprit.


Learn more about Dr. Beckham’s work, contact him at david.beckham@ucdenver.edu

♦By Molly Terhune

Robinson Durst International Scholarship and Calvin L. Wilson Future Leaders in Global Health Scholarship

Recipients have returned from their international travels and will be presenting their projects. You are invited to join us!

When: Monday, April 18, 2016, 6:30 p.m. Reception, 7:00 p.m. Presentations Begin

Where: UPI (university Physicians, Inc.) Building, 13199 East Montview Blvd, Aurora, CO (more details will be sent to those who RSVP)

How: RSVP to Molly Terhune at molly.terhune@ucdenver.edu

Students presenting:
• Blake Snyder (School of Medicine - MD) - Risk factors for infections with carbapenem-resistant organisms - Vellore, India
• Sophie Pritchard (Colorado School of Public Health - MPH Global Epidemiology) - Maximizing adherence and retention in women and infants in the context of Option B+ - Kenya
• Andrew Ancharski (Colorado School of Public Health - DrPH) – Reducing misclassification of opisthorchis viverrini utilizing a highly sensitive diagnostic combination - Khon Kaen, Thailand
• Ebele Mogo (Colorado School of Public Health - DrPH) - Testing ecological models of health behavior: Investigating the interaction between psychosocial factors and built environment variables on physical activity - Festac Town, Lagos
• Allison Maytag (Colorado School of Public Health - MPH Community & Behavioral Health) – 'Out of Office': An automated text message system for facilitating communication - Loreto, Peru
The World Bank reported that in 2015, Cuba had an estimated infant mortality rate of 4 per 1,000 births—a lower infant mortality rate than that of the United States (6 per 1,000 births).

Deleyiannis hopes that relations and collaboration with Cuba will continue to improve and mature, yet acknowledges that the political climate with the upcoming U.S. elections will play a large role in the development of future projects.

Chan hopes to alleviate this disadvantage by sending a refurbished operating microscope to the otolaryngology department at the Children’s Hospital in Cienfuegos, Cuba.

Observing and interacting with the senior Cuban physician also changed how Chan will approach his work in the future—“I have become more appreciative of the niceties in our clinic and our operating room that I have taken for granted all these years. Too often American surgeons have wanted anything that would save them time regardless of the cost. I need to learn to be more patient; I want to do more with less.”

Pavel Davizon-Castillo, M.D., 2nd yr Hematology/Oncology Fellow, explained, “It was and is the right time. Politics aside, the medical and public health sectors have been creatively strengthened by the need to do more with less.”

One of the most impressive components Davizon-Castillo found during the conference was “there was mutual admiration expressed for the progress made in pediatric care. It was a very honest exchange of needs, areas of improvement and common goals between Cuba and the U.S..”

(Continued on page 6)
American Pediatricians Visit Cuba: Transitioning from 50 Years of Isolation to a Future of Collaboration

(Continued from page 6)

“I felt that our colleagues were very open when it came to discussing their happiness and their needs personally and professionally. In general, they are very proud of being part of a group of physicians who have improved the care of so many children in Cuba and in many other countries, mostly in Africa. It was very refreshing to feel their enthusiasm and desire for mutual learning,” said Davizon-Castillo.

Davizon-Castillo is excited to have opened communications with his counterparts in Cuba. His main contact is Dr. Dunia Castillo, the director of the Hemophilia Program at the National Institute of Endocrinology in Havana.

Dr. Dunia Castillo is on board with the initiation of an academic exchange and she and Davizon-Castillo are working together to develop a plan to move the proposed collaboration forward.

Davizon-Castillo’s current research is focused on understanding the mechanism by which platelets are more reactive, meaning prone to clotting, under states of inflammation or during aging. His investigations have lead him to better understand the biology of platelets and the underlying mechanisms that are altered when they are over- or under-reactive.

“During my conversation with the hematologists in Cuba, I learned that they currently do not have some of the most basic equipment needed to diagnose many pathologies related to platelet function. At the same time, their hemophilia program is currently growing under the leadership of one hematologist for the entire island. Despite this, the program is successful and is currently expanding. This means that the Cuban program needs to train more healthcare professionals to help with the medical and social aspects of hematological disorders,” stated Davizon-Castillo.

Davizon-Castillo was especially excited that the Cuban physicians “are also very interested learning the model we have in our Hemophilia Treatment Center in Colorado — from the educational tools we provide to our families, to the routine physical therapy visits, and proper patient education.”

Excitement about future collaboration was not only apparent between American and Cuban physicians but also between the organizations that hosted the event — this conference was jointly sponsored by the Cuban Pediatric Society, Center for Global Health, Colorado School of Public Health, Children’s Hospital Colorado, Pan American Health Organization, and the American Academy of Pediatrics.

Organizing this meeting created an opportunity for these entities to continue to work together to expand collaborations that will benefit both Cuban and American children in the future.

Other articles on this conference published by the Denver Post, University of Colorado, and Cuban News Agency may be found here.

Dr. Deleyiannis has multiple research projects worldwide: ear reconstruction in Guatemala, genetics and phenotypes of Oral-Facial cleft families, prospective evaluations of deep venous thromboembolism (obstruction of blood flow due to a blood clot) in patients undergoing micro-vascular reconstruction, as well as the role of electronic cigarettes in capillary perfusion and microcirculation.

To read more about the ongoing research of Deleyiannis, please see this Link article regarding his work.

Asturias: Zika Virus Risky for Women Trying to Conceive

Director of Latin American Projects at the Center for Global Health, Edwin Asturias, M.D., Associate Professor of Pediatrics and Epidemiology at the School of Medicine and Colorado School of Public Health, CU Anschutz supports CDC guidelines that advise women who have been diagnosed with Zika to wait at least eight weeks before trying to get pregnant. (FOX 31 NEWS)

Stay up on the latest news regarding the Zika Virus!
Global Women’s Health Issues

In recognition of International Women’s Day, the Center for Global Health, along with World Denver, hosted State Department International Visitors who addressed Global Women’s Health Issues.

On March 7, 2016, the Center for Global Health, in collaboration with World Denver, had the pleasure of meeting with a delegation of physicians and experts to discuss women’s health issues. The visitors were part of the International Visitor Leadership Program (IVLP) and represented Burma, Egypt, Laos, Malawi, Russia and Saudi Arabia.

The IVLP is the U.S. Department of State’s premier professional exchange program. Through short-term visits to the United States, current and emerging foreign leaders in a variety of fields experience the U.S. firsthand and cultivate lasting relationships with their American counterparts. Professional meetings reflect the participants’ professional interests and support the foreign policy goals of the United States.

Objectives of the project are outlined by the Department of State:

- Promote international cooperation on the common challenges facing the global community in preventing, treating, and managing health problems affecting women, such as cancer, stroke, heart disease, diabetes and HIV-related illnesses;

- Explore state and local efforts aimed at preventative screening and wellness programs including those that promote maternal and child health;

- Examine public awareness campaigns about health issues impacted by economic downturns, poverty, and other external challenges that affect health care delivery systems;

- Network with professional counterparts (both U.S. and international) in order to increase information sharing through means such as social media and to promote transparency in discussing global women’s health issues.

The participants:

- **Burma** - Dr. (Ms.) Pa PA, Deputy Medical Superintendent, Yangon General Hospital, Ministry of Health;

- **Egypt** - Dr. (Mr.) Basim Shokry Galal Abdelmeguid SHAHIN, Member, Contraceptive Security Unit and Research and Quality Department, Ministry of Health and Population;

- **Laos** - Dr. (Ms.) Vilavanh XAYASENG, Senior Officer, Surveillance Division, Department of Communicable Disease Control, Ministry of Health, Lao PDR;

- **Malawi** - Dr. (Ms.) Queen DUBE, Clinical Head of Pediatrics and Child Health, Queen Elizabeth Central Hospital, Blantyre;

- **Russia** - Dr. (Ms.) Kristina KHODOVA, Project Manager, Biomed Cluster, Skolkovo Foundation;

- **Saudi Arabia** - Ms. Adha ALFAYEZ, Clinical Research Assistant, King Fahd Specialist Hospital Dammam

Check out the [International Women’s Day Luncheon video](https://www.9news.com/) captured by 9NEWS (KUSA)
Spring 2016

April 13, 2016
12-1 | ED2 North 1107
Anschutz Medical Campus

Rosemary Rochford, Ph.D., Professor, Department of Immunology and Microbiology, School of Medicine and Visiting Professor of Environmental and Occupational Health, Colorado School of Public Health, University of Colorado Anschutz Medical Campus

Tales from a Cancer Researcher in Africa

May 11, 2016
12-1 | ED2 North 1103
Anschutz Medical Campus

Anna Stewart Ibarra, Ph.D., M.P.A., Assistant Professor, Department of Medicine, Latin American Program Director, Center for Global Health and Translational Science, SUNY Upstate Medical University

Emerging Infectious Diseases in a Hotter, Wetter, More Urban World: Lessons Learned from Ecuador

Want to watch a lecture you missed? Click here.

Center for Global Health
WHO Collaborating Center
Colorado School of Public Health
13199 E. Montview Blvd. Campus Box A090, Aurora, CO 80045
http://globalhealth.ucdenver.edu

Follow us on Facebook: www.facebook.com/CSPHcenterforglobalhealth
and Instagram: @global.coloradosph