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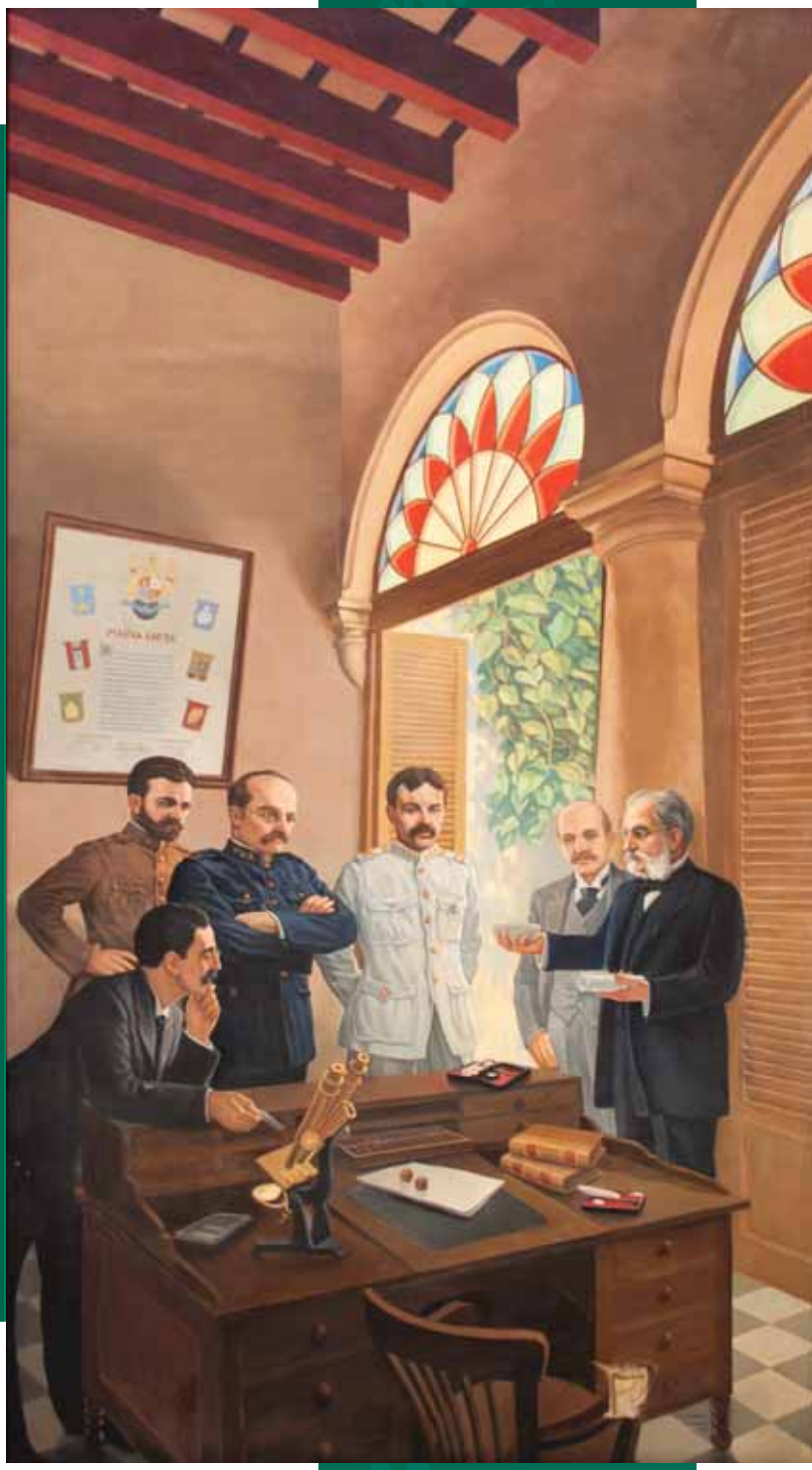
The Path to US–Cuba Health & Science Cooperation



History's Rocky Road to Collaboration

Joint Work vs. Cancer, TB & Polio

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Climate Change, Disasters & Arbovirus Threats

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How can science help address the many divisions in our communities, in global society, and in science itself? Science plays a unique and important role in how people see and understand the world, and how lines and distinctions are drawn. At this Annual Meeting, we look for ways science is bringing together people, ideas, and solutions from across real and artificial borders, disciplines, sectors, ideologies, and traditions. How can science working across boundaries improve its ability to find solutions to the pressing problems of our age? How can scientists, wherever they work, more effectively engage with the broader society? How can we find better ways to engage the public, especially in expanding access to science and scientific careers? At the international level, science diplomacy builds bridges between countries. How can we encourage more of this, and utilize science as a common ground more locally as well? Can science contribute information that might reduce or mitigate the starkly divergent interests of different populations and demographics, such as urban and rural communities? What boundaries most impede your research or your career? While acknowledging that some boundaries are useful and necessary, the meeting theme considers how research can be applied to problematic separations in the world, and how unhelpful boundaries within science are being addressed.

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Cover: *Finlay's Triumph, painting by E. Valderrama, shows Carlos J. Finlay Barrés presenting his research to the US Army yellow Fever Commission; pictured left to right, Finlay's son (Carlos Finlay Shine), Jesse Lazear, James Carroll, Walter Reed, Finlay.*

Back cover: *Romay Vaccinating his Children, painting by Ramón Loy of Tomás Romay Chacón vaccinating his children to encourage public acceptance of the smallpox vaccine.*

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MEDICC Review

Editorial Board

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US–Cuba Health and Science Cooperation: They Persisted

> The first truly universal society was the society of researchers. May the coming generation establish a political and economic society which will insure us against catastrophes.
> —Albert Einstein in Havana, December 19, 1930

Few may be aware of Einstein's 30 hours in Cuba, just as the world was plummeting into the Great Depression. He was received by the most illustrious academics of his day, leaving the entry above in the Golden Book of the Geographic Society of Cuba. He spoke before what was then the Academy of Medical, Physical and Natural Sciences of Havana—precursor of the Cuban Academy of Sciences. The chair he occupied still sits in the Academy's great hall.

But as his words indicate, he hoped that society would follow the steps of researchers, coming together in truly universal fashion to protect humanity from catastrophes—perhaps of its own making. Science in the public interest was no stranger to Albert Einstein, who also insisted upon visiting the city's poorest neighborhoods during his brief stay in Havana. In 1930, it was the capital of a country that had gone from being the "ripe fruit" destined to fall into the lap of the United States to being briefly occupied by the US military, all the while an economic appendage of its neighbor to the north. Over the decades, and despite tumultuous relations between the United States and Cuba—exacerbated after the Cuban revolution by US regime-change programs and a draconian embargo—experts in the sciences, public health and medicine from the two countries have managed to form alliances for the benefit of both their peoples.

Above all, this issue is a tribute to these scientists' dedication and their recognition that shared problems require a shared search for solutions, broad and respectful debate of hypotheses, and a willingness to put society before self. In the pages that follow, we publish lessons from their experiences, in the hope that these will inspire others to join forces to address the challenges faced by both countries, and in fact, by the entire planet.

Leading off the eight articles included in the section titled Lessons in International Cooperation, Jorge-Pastrana joins with US colleagues to offer a fascinating history of efforts by Cuban and US scientists to transcend political barriers through concerted engagement and joint work. Some of these efforts were heroic, representing the height of scientific ethics and sacrifice. Such a collaboration is illustrated on our cover: in one of the first successful attempts at "science diplomacy," Cuban physician Carlos J. Finlay shared with the US (occupying) Army's yellow Fever Commission the results of his experiments concluding that the mosquito was the vector of yellow fever. The disease had decimated US troops on the island, as well as the Cuban population, and was felling workers on the Panama Canal at an alarming rate. Finlay's generosity, coupled with the willingness of men like the young Johns Hopkins faculty member Jesse W. Lazear, who gave his life in the process of the experiments, made it possible to put an end to this scourge throughout the region.

Three other articles, jointly authored by Cuban and US researchers, address collaborations in communicable disease control, including:

- Arbovirus research, vector control strategies and epidemiological surveillance, reflecting the complementary strengths of Cuban and US institutions, such as the Pedro Kourí Tropical Medicine Institute, the NIH's National Institute of Allergy and Infectious Diseases and the CDC. The authors argue that rapidly emerging threats from arboviral illness, extension of vector habitats, and the two countries' proximity make US–Cuba collaboration not only mutually beneficial, but imperative. US citizens may see such collaboration as all the more urgent, now that it has been reported that conditions in over 75% of counties in the contiguous United States are suitable for reproduction of *Aedes aegypti* and *A. albopictus*, the main mosquito vectors for dengue, chikungunya, Zika and even yellow fever.

- Cuba's decades-long collaboration with WHO working toward global polio eradication, an initiative in which US scientists involved had to tread lightly, because of the US embargo. Cuban findings over two decades have influenced global policy decision-making on new strategies for polio eradication. As WHO's Director of Polio Eradication Michel Zaffran pointed out, an immunity gap anywhere in the world carries the risk of vaccine-derived type 2 poliovirus, and imperils chances of eradicating polio globally.

- Institutional scientific collaboration between the USA and Cuba to help the world move toward TB elimination by 2050. TB control is a priority for both countries, each having low incidence (pre-elimination levels) and robust research capacities. These make collaboration a logical path.

In other areas of joint public health research and results, we share:

- Work by Cuban, US, Barbadian and other scientists to identify biomarkers of long-term impact of early childhood malnutrition. Such biomarkers could help reduce malnutrition sequelae where their burden is highest, since they are detected through EEG, a less expensive and more readily available technology than that offered by more high-tech approaches.

- Insights into the intensive international collaboration, in which PAHO/WHO and US scientists played a role in helping to bring Cuban epidemic neuropathy under control in the early 1990s, at the same time shedding light on other metabolic or mitochondrial optic neuropathies.

- A collaboration between eminent Cuban and US scientific institutions (the Molecular Immunology Center and Roswell Park Cancer Institute) to pursue cancer research and carry out the first US clinical trials for a promising therapeutic lung cancer vaccine developed in Cuba, and now perhaps within sight of US physicians and their patients.

Our Interview this issue is with Dr José Rubiera, the trusted meteorologist who has educated an entire population on weather science. He asserts that cooperation between Cuban and US meteorologists is the "most natural thing in the world" and vital to saving lives in both countries, situated as they are along "hurricane

alley." He also notes the importance of working together to mitigate the impact of climate change. Tragically, Cuba was turned down when it offered disaster-response expertise and capacity for New Orleans after Katrina and again when Puerto Rico was devastated by Hurricane María.

In a Roundtable, Cuban and US scientists—including chemistry Nobel laureate Peter Agre and Cuban dengue expert María Guadalupe Guzmán—make the case for US-Cuba scientific cooperation to overcome political divides to tackle urgent global and regional issues.

While we were in our final production stages, WHO marked World Health Day (April 7) by calling on world leaders to take concrete steps to ensure that "everyone, everywhere can access essential quality health services without facing financial hardship," that is, toward universal health coverage (UHC). At least half of the world's 7.3 billion people still lack full coverage with essential health services and some 100 million people in 2010 fell into extreme poverty (living on $ 1.90 or less a day) because of out-of-pocket health expenditures.

Of course, there can be no UHC without trained human resources, and Cuba is doing its part: its Latin American Medical School (ELAM) provides free education to students from low-income countries and underserved communities in higher-income countries. Some 28,500 MDs from 103 nations have graduated from ELAM since its first class of 2005, 172 of them from the USA. In our second Roundtable, senior editor Gorry shares personal and often moving accounts by several US grads concerning their ELAM experience and where the road is taking them now.

Our thanks to The Atlantic Philanthropies and the Ford Foundation for their generous support for this issue.

We at ***MEDICC Review*** are pleased to congratulate our colleague, Dr Lila Castellanos, on her election as Distinguished Member of the Cuban Academy of Sciences.

In this issue devoted to US–Cuba scientific cooperation, we cannot let Stephen Hawking's death go unremarked. We mourn the passing of a great intellect and a great man, one who trusted implicitly that science could answer the pressing questions critical to humanity's very survival.

We wish to thank our two Guest Editors: Drs Jon Kim Andrus and Pastor Castell-Florit Serrate. Dr Andrus is professor and Director of the Department of Vaccines and Immunization of the University of Colorado's Center for Global Health and Professor at George Washington University. Previously, he served as PAHO Deputy Director; Chief of PAHO's immunization program; and Director of polio eradication in WHO's Southeast Asia Region. Currently, Dr Andrus is co-Chair of the Global Polio Partners Group, and member of the International Monitoring Board for the Polio Transition, PAHO's Technical Advisory Group for Vaccine Preventable Diseases, WHO's South East Asia's Regional Verification Commission for Measles and Rubella Elimination, and WHO's Working Group on the Decade of Vaccines.

Dr Pastor Castell-Florit is Director of Cuba's National School of Public Health and Chair of Cuba's Council of Scientific Societies in Health. During his 45-year career in public health, he has held various posts vital to the development of Cuba's health system. In 2016, PAHO presented him its Award for Health Administration in the Americas, citing his life of service and excellence in the field and his "outstanding leadership and valuable contributions to the management and administration of the Cuban national health system." His two doctoral degrees explore intersectoral action to address social determinants of health. He co-chairs MEDICC's Joint Academic Council.

Today, the world faces immense environmental, economic, health and social challenges that are impossible for one nation—however wealthy or powerful—to tackle alone. The imperative for US-Cuba cooperation in health and science has never been clearer, despite political headwinds out of Washington. The past has important lessons: scientists from earlier generations indeed persisted, and today we reap the benefits of their perseverance. We are confident that the current generation of scientists will follow in their path.

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Neurochemist. Full professor and senior researcher at Cuba's Neurology and Neurosurgery Institute, where she was Deputy Director for Research in 1995–2010. Her main research areas have been demyelinating diseases and blood–brain barrier systems. Dr González Quevedo is currently investigating blood-based biomarkers of brain damage in asymptomatic arterial hypertension and cerebrovascular diseases.

Sergio Jorge-Pastrana
Historian. Executive director of the Cuban Academy of Sciences (ACC), Mr Jorge-Pastrana has published widely on topics to do with science diplomacy and has served as a consultant with several UN agencies. In 2014, he was ACC's signatory for a historic memorandum of understanding on scientific cooperation with the American Academy for the Advancement of Science.

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Health economist with a background in engineering and applied mathematics. Associate professor in the Department of Community and Behavioral Health at the Colorado School of Public Health, University of Colorado, Dr O'Connell's research addresses economic issues related to chronic disease prevention and treatment (particularly among American Indian and Alaska Native populations) and assessment of policies and programs to improve health service access and delivery.

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Physician with higher degrees in biological sciences and mathematics. Dr Valdés is deputy director of the Cuban Neuroscience Center and coordinates the Center's national network of neurophysiology laboratories, as well as the Cuban Brain Mapping Project and the Latin American Brain Mapping Network. He is senior researcher and full professor at the Medical University of Havana, and a member of the Cuban Academy of Sciences; he serves on the Editorial Board of *MEDICC Review.*

Weathering US–Cuba Political Storms: José Rubiera PhD

Cuba's Chief Weather Forecaster

Gail Reed MS

Full disclosure: chief weather forecaster is not his official title, but rather one affectionally conferred on Dr Rubiera by the Cuban people, who look to him not only in times of peril, but also to learn about the science of meteorology. Anyone who has taken a taxi in Cuba during hurricane season (June 1 to November 30), and bothered to ask the driver, will receive a clear explanation about how hurricanes are formed, what the Saffir-Simpson scale is all about, and how the season is shaping up—all courtesy of Dr Rubiera's talent for communication during nightly weather forecasts and special broadcasts. It's no exaggeration to say that he is something of an icon in Cuba, a man people trust.

Now, he is retired as chief of forecasting at Cuba's Meteorology Institute, but he stays on as an advisor, and since 1989 represents Cuba's Meteorological Service as the Vice Chairperson of the World Meteorological Organization's Hurricane Committee for Region IV (North America, Central America and the Caribbean). He also keeps a spot on nightly news and hosts two TV shows of his own: Global Weather and Weather in the Caribbean. And his PhD in meteorology serves him well as full professor at the University of Havana in—what else?—meteorology communications.

Finally, he has been a driving force in Cuba for collaboration with Miami's National Hurricane Center (NHC) and other US meteorologists (in fact, the Chairperson of the Region IV Committee is the head of the NHC).

But, as he says over a cup of rich Cuban coffee, it all started with a two-year-old in a yellow sweater.

MEDICC Review: **How did you first become interested in the weather?**

José Rubiera: It's a bit of a long story, and has to do with my very first memory: I was two, wearing a yellow sweater in my mother's arms, and it was in the midst of the hurricane of 1948. I also recall my uncle giving me a magazine when I was four or five that traced the path of hurricanes through the Caribbean, and then later my brother and I waited up for the hurricane that never passed. It was Hurricane Fox, which made a turn missing our home town near Havana, instead crossing over central Cuba. That was a big one, but we missed it.

My interest continued through high school, and when I got to university, at first there was no meteorology major, so I decided to study physics. Finally they offered a special course in meteorology, and I was one of the students selected, allowing me to graduate in meteorology. I've been dedicated to forecasting; it's what I've always liked, so I did graduate work in the field and in 1991, received my doctorate. The topic was five-day precipitation forecasting, something we didn't really know much about in Cuba then.

MEDICC Review: **When it comes to bilateral collaboration in any field, it's helpful to know a bit about the history of the science in each country, and how collaboration began.**

José Rubiera: Meteorologists exchanging information is the most natural thing in the world. And that's also true for Cuba and the United States.

In the United States, it's worth remembering that it was Benjamin Franklin who first discovered that weather moved, and another father of US meteorology was Thomas Jefferson. In fact, he had a weather vane on his front porch to check the direction of the wind, set up the first network of weather stations in the United States, and even took a thermometer to the signing of the Declaration of Independence.

In Cuba, the first weather service was founded in 1865 by Andrés Poey (son of the famous Cuban naturalist Felipe Poey) who was exiled by the Spanish colonialists to France, where he died. Then, in 1870, Jesuit priest Father Benito Viñes Martorell arrived in Cuba, the same year a hurricane hit the province of Matanzas. Horror-

stricken, he decided to devote his life to studying hurricanes and became the first director of the Belén Observatory in Havana. In fact, in 1875, he was the first person in the world to issue a hurricane warning, keeping all but one ship from sailing out of Havana's harbor (the ship that sailed sank).

He died in 1893, shortly before he was to present his master work in Washington DC, where it was delivered in his stead by another Jesuit priest, Lorenzo Gangoiti, who would later head the Belén Observatory.

Gangoiti is an important figure in the history of weather information exchanges between Cuba and the United States. It was politically a very delicate time, since the US army had intervened in Cuba's independence war, and was occupying the country militarily. Nevertheless, Father Gangoiti warned the US occupation forces that the September hurricane, which had just hit Cuba, was heading for Galveston, Texas. Unfortunately, they paid no attention to him, and the result was the Great Storm of 1900, the deadliest natural disaster in US history.

MEDICC Review: **Another delicate political time has been the period after the Cuban revolution of 1959, with the ensuing US embargo and break in diplomatic ties, until 2015.**

José Rubiera: Yes, but exchange of weather data between Cuba and the United States has never stopped. Even at the lowest point, on the heels of what we call the 1962 October Crisis and the Americans call the Missile Crisis came Hurricane Flora of 1963 *[which caused 1126 deaths and destruction throughout the mountainous areas of eastern Cuba—Eds.]*. I have copies of the messages that Luis Larragoiti Alonso of Cuba's military weather observatory sent to Gordon Dunn, director of the Tropical Meteorology of the US Weather Bureau in Miami, with maps and data obtained about Flora by our helicopters.

Once the Hurricane Committees were created in the World Meteorological Organization, thereafter the US chaired the Region IV Committee, and I have served as vice chair.

MEDICC Review: **I know that one important area of cooperation has to do with the flights of US "hurricane hunter" planes through Cuban airspace.**

José Rubiera: Yes, we flew into the storms until 1991, but thereafter didn't have the planes to do this. The US National Oceanographic and Atmospheric Administration (NOAA) requested and received permission from Cuba to fly their civilian planes through Cuban airspace and into the hurricanes, gathering fresh, more exact data that they shared with us. In the late 1990s, Jerry Jarrell, then head of the National Weather Service Hurricane Center in Miami, even came to Havana with a delegation, the only time one of these hurricane hunter planes actually landed in Cuba.

But NOAA only had two planes, not enough: they needed to be able to rely on the US Air Force's C-130 aircraft. That became a problem, since they didn't want to ask Cuba for permission, and were told that Cuba would say no.

These flights were important to both countries' ability to protect our populations, to save lives with our forecasts, so we played our part and so did Jerry, who assured Washington that Cuba would consider the request. After some back-and-forth on the US side, he and Max Mayfield (who succeeded Jerry), finally convinced their government to make the request, and that's how the C-130 hurricane hunters began flying over Cuba when hurricanes struck.

In fact, in an Orlando, Florida meeting of the Hurricane Committee, the Air Force Lt. Colonel who headed the hurricane hunter squad said that the best country to fly over was Cuba, due to the professionalism of our air traffic controllers.

MEDICC Review**: And what about information from Cuba to the USA?**

José Rubiera: Cuba has 68 first-class weather stations in our national network. This has given us broad coverage to generate precise information, important for the US and the Caribbean, too. For example, in 1994, Tropical Storm Gordon passed between Santiago and Guantánamo Provinces, at the same time unleashing heavy rains in Haiti. In Cuba, we had no deaths, but in Haiti, over 1,000 were killed. Because the storm was a weak one, its center was hard to locate, and both The Weather Channel and CNN were reporting it further north, but our observatory in Cayo Coco showed it right there. Unfortunately, as I reported in the 1995 Region IV Hurricane Committee meeting, this information reached the United States late, because we had to use outdated telex equipment.

At the meeting the NOAA representative said this was an important point, and later, the US finally decided to share satellite technology with us (which later also became obsolete). We now share information in near real time from our radar through Internet. Best would be if it were actually in real time, of course.

MEDICC Review: **How did the renewal of diplomatic relations affect collaboration around hurricane forecasting? And how would you describe the situation now?**

José Rubiera: Among the chief results of restored diplomatic relations was the signing of an MOU in Washington DC in December, 2016, between Cuba's Ministry of Science, Technology and the Environment, our Meteorology Institute and NOAA. It recognized the importance of further integrating the work of our meteorological observation networks and hurricane monitoring, analysis and forecasting. It also referred to data collection, exchange of information and joint research in meteorology, climate change, oceanography and atmospheric contamination.

Because of the recent closing of the US Consulate in Havana, we were unable to send a young specialist in hurricane forecasting to the World Meteorology Organization workshop this April at the US National Hurricane Center, even though all expenses were covered. So this is a problem.

But I'm hopeful that in the not-too-distant future, our relations will not only be maintained but also deepened.

MEDICC Review: **What are the strengths that Cuba draws upon for this collaboration?**

José Rubiera: First, I should say that the United States has an excellent forecasting service. In fact, for example, for Hurricane Katrina, the forecast was perfect. What failed? Communications with the public, making people aware, education, as well as some other aspects. In Cuba, we establish an advisory five days before a storm might arrive, then 72 hours an information stage, then 48 hours an alert, and at 24 hours, alarm. This is a bit more warning than the public receives in the United States, although they have begun to issue their advisories earlier.

And there are other things: Civil Defense is in constant and direct communication with the public at every level, down to the neighborhoods; 80% of evacuees go to the homes of neighbors or relatives, making the move less traumatic than to a shelter; when we have winds of about 90 km per hour, we turn off electricity and gas lines, to avoid electrocution and explosions. Hospitals and other medical services are protected, and if they are hit, they are set up wherever possible. But they remain open. Nonetheless, any loss of life is unacceptable, and so we have to continually work to avoid that . . . sometimes people are negligent. And sometimes, there is simply no collective memory of the last big storm in a particular region, and so people are less inclined to take warnings seriously.

Above all, though, in Cuba people help one another. We may not have Home Depot, but we have communities of people who take responsibility for each other. When there is a disaster, people can feel discombobulated, and that's where that solidarity comes in. I remember in Pinar del Río Province with Hurricane Gustav in 2008, people simply went to work and helped. We saw a school that had been leveled, but the next day, students were back with their teachers, because neighbors had set up makeshift classrooms in their homes, helping the children recover that all-important sense of normal life.

We also have a few advantages: here in Cuba, I can go live on TV for all the time that's necessary and give the public complete explanations, in detail, without sensationalism. In the States, they usually have to be briefer, and not all the weather reporters have the same training. In addition, people in Cuba are educated about hurricanes and tropical storms; in fact, we have a 30-hour course on the subject on one of our educational channels. We also take advantage of psychology: when the TV audience sees me in the studio, they feel things are okay, but when they see me move to the Meteorology Institute, with all the satellite images behind me, then they realize that the situation is getting serious.

MEDICC Review: **And your absence is noticed even more. I remember Hurricane Irma last September.**

José Rubiera: Yes, I was stuck in the Miami airport, and finally reached Havana and went almost directly to the studio.

MEDICC Review: **People in Cuba not only breathed easier, but many Cuban-American friends told me that Miami residents were watching your broadcasts from Cuba, since the storm was threatening Florida, too.**

José Rubiera: Yes, that's what I've been told. With Irma, we had a very serious situation, in which Cuba's entire electrical grid collapsed after the hurricane struck on September 8. But by September 29, 95-98% of services had been restored.

It is painful to see that so many people in Puerto Rico are still without lights after Hurricane María, that hit that island on September 20. We are poor, we are blockaded by the US, but people all do their part, and government prioritizes recovery. I don't see any explanation for the precarious situation Puerto Ricans are living in today. Puerto Rico, a beautiful place, where people are having a terrible time. And the USA is such a rich country…

MEDICC Review: **What would you like to see happen, in terms of greater US-Cuba collaboration, both in emergency situations and to address longer-term issues such as climate change?**

José Rubiera: All collaboration benefits people of both countries. The main purpose of our two weather services is to alert, to sound the alarm, to save lives. So it's vitally important that both countries participate, and as I said, it's also natural, even in the worst moments.

We scientists look for the truth in facts, in data. It is clear that climate change is being caused by human beings, resulting in years such as 2017, one of the hottest in recorded history. The Artic ice is melting, the glaciers shrinking.

Research in the US and elsewhere shows that oceanic temperatures are rising, which means that the intensity of hurricanes will also increase, as will the rains, and sea levels will continue to rise, especially affecting coastal areas and small islands. So we will also see storm surges associated with polar melting and hurricanes themselves. We need to face these facts and work together. Improved relations offer more room for greater collaboration, and more effective results.

MEDICC Review: **These days, what do you enjoy most? Why aren't you really retired?**

José Rubiera: I'd like to do more photography, have a program where I could tell the history of the storms, with live shots of where they passed. I enjoy television. I've never used a teleprompter, but just improvise. I enjoy talking with viewers as if they were family, sitting in my living room. And that's hard to give up. So, why retire, really?

Your Primary Care Doctor May Have an MD from Cuba: Experiences from the Latin American Medical School

Conner Gorry MA

On the 40th anniversary of the Alma Ata Declaration that affirmed health for all a right and primary health care the route to guarantee that right, WHO and PAHO have issued a call to action to convert universal health into reality for the nearly four billion people worldwide lacking full coverage of essential health services. There is some urgency to this movement: WHO estimates the health workforce shortage of nearly 8 million could reach almost 13 million by 2035. And the USA is not exempt: medical associations and special commissions set up to investigate the shortage of primary care physicians, especially "under-represented minority" doctors, have issued report after report on this growing health care emergency. The biggest question looming is: where will the health care providers come from, especially well-trained primary care doctors who want to work for those who need them most?

Part of the answer may be found in Cuba and its Latin American School of Medicine (ELAM), which has graduated some 28,500 MDs from 103 countries since its first class of 2005—including nearly 200 from the USA. Graduates, most from low-income families, are not only admitted for their intellect and academic records, but also for their social commitment,

Conceived in 1998, ELAM provides six years of medical education for its students, including those from the USA. They are asked to commit to practice in shortage areas back home or in similar communities elsewhere. They receive full scholarships from Cuba, thus graduating free of the debt burden that might otherwise drive them into career paths that usually pay higher salaries. From post-earthquake Haiti and Chicago's Cook County Jail, to Honduras' isolated Caribbean coast and Ohio's Transgender Primary Care Clinic, these young doctors are also offering an example to others of their generation.

The innovative program combines community-based, preventive care and a public health approach with clinical skills training. The curriculum incorporates basic sciences as well as clinic and hospital rotations in pediatrics, internal medicine, ob-gyn and other specialties, giving these future doctors practical experience with patients and group problem-solving throughout their medical studies. They also take courses in disaster medicine that include preparedness as well as response.

Today, a higher percentage of graduates from ELAM are working in disadvantaged US communities than those from any medical school in the USA itself, something that has attracted the attention of US medical educators, looking to see how they might increase their contribution to solving the physician shortage in these areas .

The 172 US doctors who have graduated from ELAM have experienced for themselves the hands-on clinical training, emphasis on teamwork, and integrative biopsychosocial approach underpinning Cuba's universal health system. And they have done so while living and studying in a foreign, resource-scarce country, often with no Spanish language skills upon arrival. The steep road to realizing their professional dreams doesn't end upon graduation, however: to practice back home, they must pass the three-step US Medical Licensing Examination (USMLE), plus secure and complete residencies.

Data Snapshot: US Students and Graduates of ELAM

Indicator	Value
Students currently enrolled	72
Graduates	172
Graduates in residency or post residency	84
Graduates working in designated Health Professional Shortage Area (HPSA) and/or Medically Underserved Area (MUA)*	73%
Specialty	**Graduates n (%)**
Family medicine	49 (58)
Internal medicine	21 (25)
Surgery	5 (6)
Pediatrics	4 (5)
Emergency medicine	2 (2)
Neurology	1 (1)
Psychiatry	1 (1)
Triple board	1 (1)

*Those not working in an HPSA or MUA are working in the public sector with underserved communities.
Source: MEDICC data, April 2018, provided by Devon Baird, Director, Academic Programs

MEDICC Review looked to a group of these US graduates to better understand their decision to study medicine in Cuba and how they faced the resulting challenges, as well as the relevance of their Cuban education to their current practice.

***MEDICC Review*: Studying medicine in Cuba is a bold—some would say radical—decision, especially given turbulent US–Cuba relations. What led you to apply to ELAM?**

Parastou Malek (class of 2014): For me, studying at ELAM presented a unique opportunity to learn alongside a very diverse student body. Furthermore, I was desperate to find an effective way to gain the skills I needed to help my community and I knew learning Spanish would allow me to reach a much larger patient population. Previous ELAM graduates also talked about extremely supportive professors who created a friendly and encouraging learning environment for their students. I knew that I had the potential to thrive in such a setting and wanted to experience the difference between the Cuban and US education systems.

Melissa Davis (class of 2011): I believe health care is a human right and that physicians are obliged to bear witness to injustice and advocate for vulnerable populations; I was excited at the opportunity to join other young people with similar aspirations and beliefs. I was also motivated to learn medicine in a relatively resource-poor country so I could apply my knowledge in contexts

Dr Parastou Malek (r) at ELAM's 2014 graduation ceremonies.

besides modern US health care settings. I knew attending ELAM would enable me to practice wherever I wanted in the future without being held back by debt.

Pasha Jackson (class of 2015): Before coming to Cuba, I was a professional player in the National Football League (NFL). Stigmatized by injuries, I floundered from team to team and found my core values of brotherhood, collaborative work and group excellence were drowning—as was I. Inspired by Cuba's examples of global humanitarianism, ELAM fueled my exit from the NFL with renewed hopes for meaningful work within a team environment. In short, ELAM appealed to my altruistic side. I was also excited to refocus on academic interests that were deemed incompatible for high-level athletes.

Rose Lafleur (class of 2009): When I began applying for medical school and interacting with other prospective medical students, I became unsure about my career path—for the first time ever. I couldn't relate to their motivations; their chatter about which specialty made the most money and which schools were most illustrious, bothered me. I didn't hear anything about what motivates me: working with people, the healing aspects of medicine, or the influence a doctor can have on their community. I felt isolated. And sad. Then I heard about ELAM.

Dr Rose Lafleur in her student years at ELAM.

When I requested a brochure, I received a piece of trifolded paper in the mail. On the cover was a picture of a Cuban doctor sitting in the front yard of a farm home, with a couple of chickens around him, auscultating a patient. The brochure contained the basic sciences curriculum and a few words about ELAM's mission. That simple, humble imagery, along with the emphasis on community-oriented health, convinced me that I would find my path in Cuba.

Sarah Hernández (class of 2016): I first heard about Cuba's international medical school during a ten-week University of California study abroad program in Havana. One of my Cuban professors explained how ELAM works and I was instantly attracted to the idea of being trained as a physician in a system that considers health a human right. I felt a tangible excitement, a flame ignite inside of me, when he took me to visit the ELAM campus. Immediately I knew I wanted to study there. ELAM was my first—and only—choice for medical school. I was secure in my commitment to study medicine within a health care system that provides equal access to its entire population.

***MEDICC Review*: Cuba can be a difficult context in which to live and study. Can you describe some of the challenges or culture shock you faced upon arrival?**

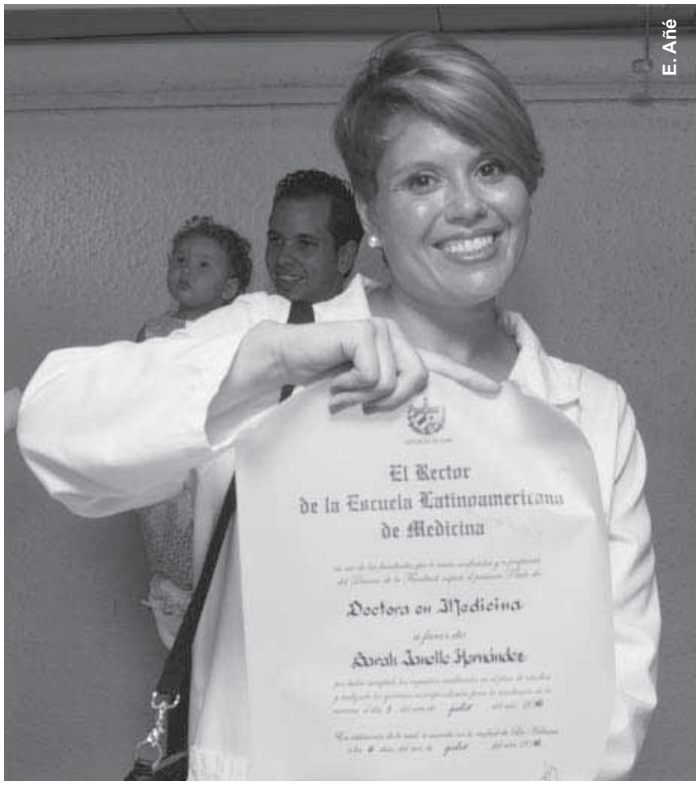
Pasha Jackson: For me, it was a shock living with students largely in their teens. *[most students arrive at ELAM out of high school—Eds.]* I had already completed my undergraduate degree and played professional football for three years when I started at ELAM. Once I moved from the dorms into the community *[All ELAM students spend the first two years on campus and then move to neighborhoods for their clinical years— Eds.]*, I found an interesting juxtaposition between the foreign and familiar. Like Oakland, where I'm from, these were people who were resource poor, but culturally and spiritually rich. This fosters a special type of ingenuity that, for me, represented hope. The real culture shock for me, however, was to be among poor people who were educated, had great access to health care, were free of drug epidemics and most impressive of all, relatively nonviolent.

Parastou Malek: I absolutely experienced culture shock, especially since I lived through a hurricane in my first few months in Cuba. When I arrived in 2008, there was barely Internet, Cubans didn't have cell phones, they didn't own businesses. There weren't that many restaurants and little to buy. The country changed a lot while I was there, but it was still an adjustment.

Sarpoma Sefa-Boakye (class of 2009): Having my first female science professor of African descent like me and the fact that most of my professors looked like me was shocking. I had just finished premedicine at UCLA where I was always the minority; I was actually told by my very first science teacher as a child that I would never make it as a doctor.

Sarah Hernández: My first night I just sat on my bed, silently, looking around blankly, trying to process what was to come. I think the biggest adaptation was the lack of utilitarian items. I longed for more stuff, but it was just stuff I realized, and the Cubans around me were living loving, functional lives with so much less. I was humbled, because I could always obtain necessities—a small care package or by asking someone to bring me something.

***MEDICC Review*: What about studying entirely in Spanish? Did that present difficulties?**



Dr Sarah Hernández on graduation day, 2016.

Sarah Hernández: Although I'm of Mexican-American descent, I didn't learn Spanish as a child and arrived in Cuba with the little I learned in high school. Being immersed in a Spanish-speaking country and medical school, with so many different accents, was mind blowing. Some of my colleagues in the USA whose first language is Spanish aren't fluent in medical Spanish; my ability to speak conversational *and* medical Spanish is such an asset in this context.

Rose Lafleur: I didn't speak a word of Spanish when I arrived in Cuba. And it was hard for me; it took me about two years to speak intelligibly—this made me very shy about trying. I only began communicating well when clinical rotations began in our third year and I had to speak with patients and communicate information to my attending professors.

Pasha Jackson: I spoke very little Spanish when I applied to ELAM. After an evaluation, I was placed in a six-month Spanish immersion course at the school. I was concerned I wasn't learning fast enough but one of my Spanish professors told me it takes roughly five years of dedicated study to become fluent in a language. Indeed, by my fifth year at ELAM, I was freely and independently traveling throughout Havana, engaging in deep, thoughtful conversations, and even giving speeches in Spanish. Increasing my Spanish fluency was challenging, but manageable, thanks to the school's diverse and approachable student body.

Parastou Malek: I only knew very basic Spanish when I arrived, but it came to me a lot easier than the four previous languages I'd learned. I requested a dorm with Latin American students and roomed for two years with students from Uruguay. I also made a huge effort to make friendships outside of the US delegation. I believe my Spanish reached the level it did thanks to the help I received from my Spanish-speaking classmates. Some used to spend hours tutoring me and helping me understand lectures.

***MEDICC Review*: What was the medical training in Cuba like? Are there specific elements or experiences that stick with you?**

Melissa Davis: In third year we began clinical rotations and I wondered how Cuban patients would respond to me as an American. I was surprised at how generous, welcoming and kind they were. I remember once in the hospital, a patient called from across the hall to show a group of us a wound. He wasn't our patient and already had his diagnosis and treatment plan, but he wanted to contribute to our education by showing us his skin lesion.

As third-year students, we were an integral part of the care team and afforded the same respect as doctors. We were never treated as a burden or made to feel like what we did wasn't useful. This made me want to work even harder. Everything we wrote in a patient's clinical record became official after it was signed off by our attending. As an intern in Cuba, I had high expectations both to learn and to teach the students a few years behind me. I didn't realize how formative all of these experiences were at the time, but now when I'm with my students in the USA, I try to make them a part of the team. It's important that they realize they're due the same respect as their superiors—but I also help them understand that with respect comes great responsibility, too.

Rose Lafleur: My medical education and years in Cuba provided me with a deep understanding of the importance of primary care and health education, plus the responsibility patients have for their

Dr Melissa Davis (r) with other US classmates at graduation 2011.

individual health. In fourth year, I did the family medicine rotation and began to truly understand the role of the family doctor. In my practice today, I spend time explaining each patient's condition, detailing where they can look for more information and orienting them about possible complications and how to avoid them.

Coming from the Cuban medical setting where health education is directly linked to outcomes motivated me to start a small nonprofit in Oakland, California, training young people to become health educators. The aim is to provide these young people with employable skills and improve community health outcomes.

Heather Krause (class of 2015): My career in medicine started nearly a decade ago when I trained to be an emergency medical technician in my hometown of Rockport, Texas. Working in disaster medicine is a dream I've nurtured for a long time and the education I received at ELAM prepared me to work in a disaster setting with limited resources. In January 2018, I put my experience and knowledge to use when I joined the New York State Nurses Association medical mission to Puerto Rico.

Dr Pasha Jackson, family medicine resident, Ponoma (CA).

Pasha Jackson: Training in Cuba contributed greatly to my passion for incorporating social determinants into the dominant biomedical culture in the USA. My ELAM education helped reveal the degree to which biological, psychological *and* social spheres of health are inseparable. Since starting my residency program, I've received very consistent feedback from superiors applauding the exploration of my patients' social factors. Cuba's well-known resourcefulness inspires me to explore beyond popular paradigms for integrative solutions to health and wellness. For example, it's quite common for me to coach breathing techniques for anxiety and stress disorders. Often my recommendation of alternative treatments gives my patients a greater sense of confidence in my role as their doctor, strengthening our overall relationship. My time studying in Cuba made me believe in the power of relationship-based medicine, which remains one of my top daily goals and reliable clinical tools.

Parastou Malek: Practicing here in the USA, I do my best to always look at my patients from a biopsychosocial perspective, trying to understand where they are coming from and how I can meet their needs as a physician and as a responsible member of their community. I try to use every opportunity to create good rapport with my patients and gain their trust. I have been taking motivational interviewing training courses in order to find efficient and effective ways to counsel my patients on making lifestyle changes—smoking cessation, diet modification and how to incorporate more exercise, meditation and yoga into their daily routine. Coming from a Cuban context, I try to be as resourceful as possible and I'm mindful of not wasting resources.

Dr Heather Krause (top) with Dr Mercedes Charles, 2017 ELAM graduate

***MEDICC Review*: Can you describe what it was like returning to the USA as a foreign medical graduate and navigating the USMLEs and process for acceptance into a medical residency program?**

Rose Lafleur: I had to re-establish myself completely as a productive, rent-paying individual in a new city. The first year was extremely difficult; I struggled with job security, as well as studying and paying for exams. It wasn't a linear trajectory—but eventually I matched into an internal medicine residency.

Melissa Davis: The USMLE Step 1 exam was the hardest part for me. The Cuban curriculum is designed for group problem solving and relating the concepts directly to our future practice, while the Step 1 questions were more obscure and less clinically relevant. I studied hours a day for several months to pass the exam. Upon starting a family medicine residency, I had to get used to the inordinate number of prescription medication choices and restrictions based on insurance coverage and cost. An even bigger obstacle that still saddens me is the distrust and suspicion directed toward the medical establishment that I sometimes see here but did not experience in Cuba. When people have a negative

Rockport Strong Mobile Medical Unit, Hurricane Harvey disaster relief.

experience with a doctor or in a health care setting, it can be very hard for them to come back. As a result, their chronic conditions go uncontrolled and we see complications which could have been prevented if they'd had access to a trusted family physician. In Cuba the doctors are very much a part of the community and are sought out for advice and guidance.

Sarpoma Sefa-Boakye: Returning home was especially hard for me. I thought the hardest part was going to be taking the USMLEs and getting into residency, but the most difficult part was learning how to work in the US health care system. I did three years of family medicine residency on the US–Mexican border in San Diego and it was hard advocating for my patients in hospitals with very few resources for underinsured patients. Cuba clearly didn't prepare us for that.

Sarah Hernández: Due to the way the Cuban academic calendar is structured, many US graduates have a gap year after graduation, the ten months postgraduation/preresidency. For me personally, it was very difficult socially, psychologically, and especially financially. I went from living in my own apartment back to living with my mother—who graciously took me in, along with my Cuban husband, and our two-year-old son. It was hard to get steady work, since I needed time for the three-month residency interview process, so I took odd jobs, including scanning documents at a law firm; on weekends, I washed dishes at a bar, earning the nickname "Doctor Dishwasher." I even donated bone marrow, white blood cells and blood to cover living expenses and pay for my Step 3 Exam. I was fortunate enough to do a research fellowship at Highland Hospital (in Oakland, California) for three months, which gave me a wonderful transition back into medicine as well as a steady, living wage before I started residency in July 2017.

Parastou Malek: There were so many challenges upon my return—learning how to study for the USMLEs, for example, and then passing them, plus honing my interview skills and connecting with relevant medical programs—it was all really difficult. MEDICC provided endless support through its various programs for ELAM graduates and I don't know where I would be were it not for that. The long hours we're expected to work as residents are especially tough, as is making peace with the broken US health system. On a daily basis I see how the system here can work against patients instead of for them. It is very discouraging and disheartening.

***MEDICC Review*: Are you practicing or in residency now?**

Heather Krause: When Hurricane Harvey hit my hometown in August 2017, my husband and I evacuated in our 24-foot mobile home. As soon as the storm passed, we converted it into a mobile medical unit to provide disaster relief to the affected population; the nearest hospital closed permanently after Harvey. For the next four months, our team of volunteer medical professionals used it as a minor emergency/primary care facility, refilling prescriptions, getting patients started on blood pressure-lowering medications and initiating diabetes treatment. We also did a significant amount of wound care and infection control, and provided services to patients needing care for acute illnesses as well. We treated nearly 400 patients who could not access primary care services due to economic hardship, lack of health insurance

Dr Sarpoma Sefa-Boakye with her parents at graduation in Havana, 2009.

(we saw several patients who lost their insurance plans after the storm) and/or closure of health facilities due to storm damage.

We collected public health data about the patients we treated—the survey was processed by the University of Nebraska Medical Center—and found: 61.5% reported not having a primary care physician; 68% didn't have health insurance; 34% had used the emergency room for primary care services; 73.6% reported their health was negatively impacted by the hurricane; 38% lost their home to hurricane damage; 49.3% had a diagnosed medical condition; 35.7% owed money to a hospital for medical bills. Right now I'm pursuing a master's degree in public health (MPH) at George Washington University's Milken Institute of Public Health.

Sarah Hernández: I am currently a first-year resident at Pomona Valley Hospital Medical Center in Pomona, California, participating in the family medicine residency program. While I'm not exactly sure what my plans are after residency, I am committed to working in diverse, underserved communities. I also foresee myself working with adolescents.

Parastou Malek: At this point, I see myself doing outpatient primary care, mostly. Right now, I'm at the University of New Mexico Community and Family Medicine residency program. I have a variety of interests that I want to explore over the next several years to see what best fits. Stay tuned!

Melissa Davis: I am a clinical assistant professor of Family Medicine at Ohio State University (OSU) and care for a diversity of patients in inner city Columbus. I have some other roles, too. I'm a Teen Clinic physician at the Nationwide Children's Hospital Hilltop and Near East Side Primary Care Centers. In addition to urban family medicine, I have developed a special interest in providing high-quality primary care for transgender or gender nonconforming individuals and see patients weekly at the Transgender Primary Care Clinic at OSU, where we provide comprehensive primary care, including hormone therapy. I enjoy the opportunities here to learn from and teach young health professionals and I also spend six weeks a year supervising residents in the family medicine teaching service. By this summer, I will have obtained my MPH from OSU College of Public Health.

Rose Lafleur: I plan to work as a primary care doctor in a community setting but am also considering ways to insert myself into global public health—thinking globally and acting locally is definitely in my future. At present I'm a first-year resident at Wyckoff Heights Medical Center, a small community hospital in Brooklyn, NY.

Sarpoma Sefa-Boakye: I work as a family medicine physician at a primary care clinic in San Diego county, while also serving as International Medical Director of the Birthing Project USA, which aims to enhance health outcomes for women of color primarily. My goal is to continue promoting the Cuban primary care model through my work both internationally and domestically.

Pasha Jackson: I'm Co-Chief Resident at Pomona Valley Hospital Medical Center's Family Medicine Residency Program in Pomona, California. As for my future plans—I'll have to get back to you on that one!

For more information about ELAM:

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Bridging the Divide: US and Cuban Scientists Speak Up

Gail Reed MS

This roundtable began with world-renowned US and Cuban experts in arboviruses (particularly those transmitted by mosquitoes) but was quickly transformed with the participation of globally recognized scientists in other fields. All have contributed and continue to contribute to the often frustrating efforts to advance bilateral health cooperation, for the benefit of the USA, Cuba and the world. Each from their own vantage point argues why such cooperation can release potential to create scientific synergies capable of addressing some of the most perplexing and urgent global health problems.

MEDICC Review is grateful to them for adding their authoritative and committed voices—as well as their personal stories—to this special issue of the journal. The participants: Peter Agre, Jon Andrus, Juan A. Bisset, María Guadalupe Guzmán, Eva Harris, Eric Martínez and Pedro Valdés. (See brief biographical notes about each at the end of the roundtable.)

MEDICC Review: **How have you been involved in US–Cuba joint scientific work? Have you seen concrete results?**

Pedro Valdés: In 1969, I met Erwin Roy John, who directed the Brain Research Laboratory at New York University (NYU) Medical Center and was one of the first neuroscientists to use digital computers in animal and human brain studies. That year, he facilitated a donation from a group of New York scientists to what was to become, and is now, the Cuban Neuroscience Center.

This collaboration with NYU was stepped up a year later when Cuba produced its first microcomputer, leading to groundbreaking work on computerized EEG analysis for objective evaluation of brain function and dysfunction. In turn, this resulted in a coauthored article in *Science* (See John ER, et al. Neurometrics. Science. 1977 Jun 24;196(4297):1393–410).

This kind of collaboration has continued and expanded with colleagues from University of California (San Diego and Los Angeles), as well as Harvard, and has been essential for developing a population-based approach to hierarchical active screening, implemented in Cuba and several other countries. One important result is a Cuban program for early detection of hearing loss through infant screening, a key contribution to pursuing normal development of children with hearing problems.

Peter Agre: I've had the privilege of interacting with Cuban colleagues in multiple areas of research. Each was outstanding in terms of scholarship and superb in terms of collegiality.

It was a great honor to serve as Honorary President of the 2012 Biotechnology Havana with excellent hosting by Professor Manuel Raíces. I also had the wonderful opportunity to serve as plenary lecturer at Quimicuba 2015, organized by Professor Luis Alberto Montero Cabrera, who has subsequently and brilliantly served as Visiting Professor of Chemistry at Johns Hopkins University. Most recently I was part of a Cuba–AAAS Vector-borne Disease Symposium that included members of the Pedro Kourí Tropical Medicine Institute (IPK) and several US investigators, held in Havana in August 2017.

Jon Andrus: Working under the guidance of Dr Ciro de Quadros, I was a PAHO Regional Advisor for Polio in the Americas. As such, Ciro asked me to coordinate and supervise acute flaccid paralysis (AFP) surveillance in the Americas Region, coordinate the network of polio laboratories, and develop the protocol for certification of polio eradication in the Region.

I had a chance to work with all PAHO member states, including Cuba, on polio eradication issues, especially pertaining to AFP and lab surveillance and the certification committees of each country. I ended up being coauthor of a paper with Cuban scientists, as well as Dr Elizabeth Bell (Mas Lago P, et al. Lessons from Cuba: Mass campaign administration of trivalent oral poliovirus vaccine and seroprevalence of poliovirus neutralizing antibodies. Bull World Health Organ. 1994;72(2):221–5).

During that time, I also worked with Mexican Rotarians from the Yucatán Peninsula to mobilize oral polio vaccine for Cuban children after the disbanding of the former Soviet Union. That way, Cuban children were protected from poliovirus imported from other countries before the Americas' eradication target was achieved.

In 2003, I became Director of PAHO's Immunization team. We conducted reviews of national immunization programs in all countries, including Cuba.

Eva Harris: I've been collaborating with Cuban scientists and participating actively in scientific meetings on the island since 1992. From 1992–2004, I was closely involved with the Genetic Engineering and Biotechnology Center in Havana (CIGB), attending biannual conferences and participating as an instructor in various courses.

While continuing to interact with CIGB, around 2003, I began working more closely with IPK, as my work focused on dengue and other arboviral diseases, aligned with IPK's interests and strengths. In particular, I've collaborated extensively with Dr María Guadalupe Guzmán, who directs dengue research (and more!) at IPK. From 2005 to now, with PAHO's assistance, I have served as an instructor in the International Dengue Course held every two years in Havana, where I give several presentations on different aspects of my work on the virology, pathogenesis, immunology, epidemiology and control of dengue—and now Zika and chikungunya as well.

To support IPK's excellent scientific work, I've facilitated publications and reagents for Dr Guzmán's group, as well as coauthored papers together, including a major review article on dengue published in *The Lancet* that Dr Guzmán invited me to coauthor with her. We have also collaborated on international grants/programs sponsored by the WHO-hosted Special Programme for Research and Training in Tropical Diseases (TDR) and the European Union, including revising WHO Guidelines

for dengue classification and management, as well as various research programs.

María Guadalupe Guzmán: I work in arboviruses, particularly dengue, and now also Zika and chikungunya. Over the years, my research has focused on gaining a deeper understanding of dengue, characterizing the Cuban epidemics, and studying the risk factors associated with the severe form of the disease, as well as diagnosis, vaccine development, pathogenesis and so forth.

At IPK, we've maintained close collaboration over the decades with Professor Scott Halstead, an eminent US scientist in the field, and with other prominent researchers and institutions, resulting in new knowledge and publications. Joint publication, as Eva Harris mentioned, has been particularly important.

We've also developed important collaborative work with the Centers for Disease Control (CDC) of Puerto Rico on aspects of dengue diagnosis and surveillance, more recently applied to Zika and chikungunya, through the good offices of PAHO. Both our institutions are PAHO/WHO collaborating centers, and we have worked together to develop these aspects in the region's laboratories through the PAHO-sponsored lab network, RELDA. This includes proficiency tests, reagent donations, exchange of diagnostic protocols, personnel training, and other collaboration.

One of the lines of work with greatest impact has been US scientists' participation in the International Dengue Course in Havana: they have participated in all 15 editions of the course since the first one was organized by IPK in 1987. We have had professors from universities such as Harvard, University of California at Berkeley, Notre Dame and Massachusetts; and from institutions such as CDC and US National Institutes of Health (NIH).

Eric Martínez: IPK has collaborated with various US universities and research institutes from the nineties through 2005, and even before then, related to infectious diseases, mainly HIV/AIDS and other viral diseases. We worked with colleagues at University of North Carolina at Chapel Hill, University of Texas and the University of Buffalo, among others. IPK personnel were also received at CDC, Harvard and Johns Hopkins University.

In April 2003, Harvard's School of Public Health hosted a forum on dengue, where Drs María Guadalupe Guzmán and I attended as guests of the university, while Drs Gustavo Kourí and Juan Bisset were unable to attend since they didn't receive US visas. Over 100 US participants were at the forum, which was followed by a working session with Professor Paul Farmer and Harvard attorneys he had invited, as he said, to find all legal means to collaborate more with Cuba. Dr Farmer and his colleagues have continued to come to Cuba, their last visit in December 2017 for IPK's 80th anniversary.

Juan A. Bisset: As a newly minted IPK researcher, my first bilateral experience was in 1985 when I received a one-year fellowship from WHO to study at the University of California, Riverside, under Dr G.P. Giorghiou. I was trained in detection of vector insecticide resistance and its mechanisms, and the new knowledge acquired contributed to the development of medical entomology labs in Venezuela, Colombia, Perú, Brazil and other countries in the region. It was also the basis for some 100 publications, and had important implications for decision-making on the correct use of insecticides for vector control, mainly for arbovirus vectors in Cuba.

A second experience was the 2006–2013 collaboration with the University of Notre Dame's Professor David W Severson, who sequenced the *Aedes aegypti* mosquito gene. The first joint WHO-sponsored project with Notre Dame was Molecular Characterization of Insensitive Acetylcholinesterase Mediated Insecticide Resistance in *Aedes aegypti* from Cuba (2006–2007), which was successfully concluded. It broadened our knowledge base, was published and resulted in important conclusions that informed strategies for insecticide use in Cuba. Professor Severson also participated at least twice in IPK's international dengue course. Another IPK–Notre Dame project was funded by CDRF Global and NIH: Genetic Mapping to Identify the Key Loci Involved in Insecticide Resistance to *Aedes aegypti* from Cuba (2013–2014). We made some progress but were unable to finish the work due to problems out of our hands related to US–Cuba relations. Yet, researchers persisted with some other joint studies through 2014.

Generally speaking, US–Cuba scientific cooperation in my experience has been quite fruitful, although not exempt from difficulties, primarily associated with the economic, financial, political and social implications of the US government's blockade on Cuba, which at times overrides the will of research centers in both countries to develop collaborative projects.

MEDICC Review: **In your field, is bilateral cooperation among researchers, academics and/or clinicians important for population health in the US, Cuba and elsewhere? If so, why?**

Peter Agre: The public health of Cubans and citizens of the US and others in the Americas will benefit from close interactions by our scientific leadership. Important trends in infectious disease epidemiology and opportunities in drug development await closer Cuban–US scientific relations.

> **Cuba is seen as the bridge for translating the results of large-scale global brain projects into meaning for the health of people in resource-scarce settings**

Pedro Valdés: Our current collaborations with colleagues in the US (and internationally) are geared toward developing scalable methods for precision brain health. Cuba is seen as the bridge for translating the results of large-scale global brain projects into meaning for the health of people in resource-scarce settings—as discussed with WHO at the first Global Brain Projects meeting. An example of this approach is the multinational study with Harvard of the long-term effects of malnutrition, using EEG technology. *[See article this issue—Eds.]*

Jon Andrus: In communicable disease eradication, infection anywhere is potentially infection everywhere. That's why collaboration is absolutely necessary among all countries of the Americas. This has been important for the Pediatric Dengue Vaccine Initiative (PDVI), but is also critical for measles and rubella. Certainly it also applies to other vaccine-preventable diseases.

María Guadalupe Guzmán: It's very important. In both countries, we have highly rated scientists and academics who can put themselves at the service of other countries as well. And after all, linking wisdom with experience for the good of humanity is precisely work for wise people!

Eva Harris: In the field of arbovirology, the Cuban experience and expertise is critical, since Dr Guzmán's group at IPK and the late Dr Gustavo Kourí are world renowned for their extensive work in this arena. IPK serves as a PAHO/WHO Collaborating Center for Arboviral Disease, and they play a key role in many international corsortia on arbovirology sponsored by PAHO, the European Union and others. IPK has also led, together with collaborators, pioneering work in community-based participatory approaches to dengue control via control of the mosquito vector, an area in which we have worked extensively as well. All this is very important for research and control of mosquito-borne viral diseases, particularly in Latin America, but also Asia and potentially Africa as well.

More broadly, medical and therapeutic advances led by Cuban researchers and institutions have brought critical new drugs and vaccines to the market, where they have made an important impact.

Eric Martínez: The great importance of this collaboration was demonstrated by bilateral meetings in Havana in late 2016. In particular, I'm referring to the US–Cuba technical consultation on arbovirus research, held October 19 at IPK, aimed at prioritizing dengue vaccine development, gaining broader insight into Zika's natural history and pathogenesis, and preparing a document summarizing the main areas for arbovirus research. Its results were analyzed by the US Secretary of Health and Human Services and Cuba's Minister of Public Health in their meetings October 20–21, in the context of a broader PAHO-sponsored Havana forum involving the entire Americas Region, where immediate collaboration on dengue and Zika were discussed.

A few weeks later (November 28–30), a scientific conference was held in Havana on opportunities for arbovirus research collaboration, specifically to share information on recent findings and priorities for future studies, identifying opportunities for expanded cooperation. *[See article this issue—Eds.]*

In January 2017, CRDF Global announced its US–Cuba Collaborative Arbovirus Research Initiative, (funded in collaboration with the National Institute of Allergy and Infectious Diseases), calling for joint proposals from US and Cuban researchers. As a result, IPK proposed seven projects with US partners (four of which were approved), covering such important aspects as prenatal Zika infection, early markers for immune activation against Zika, role of prior immunity in dengue infection, and scalability of lessons learned in community participation strategies for prevention of arboviral diseases, among others.

Juan A. Bisset: One of the approved projects Dr Martínez refers to is with the University of Kentucky, preliminary studies of the use of Wolbachia as a strategy to control residual populations of *Aedes aegypti* and *Aedes albopictus* in Cuba, coordinated by Dr Stephen Dobson (USA) and Dr María Magdalena Rodríguez (Cuba). The results will be important for control of arbovirus vectors uncontrollable by routine methods and most apt to develop insecticide resistance.

Another project, between Cuba and Johns Hopkins University, with principal investigators Dr Jorge Dimopoulos (USA) and Dr María del Carmen Marquetti (Cuba) concerns *Aedes aegypti*'s competence as a vector for Zika and dengue in Havana, the first research to tackle this issue.

More broadly, Cuba has specialists in medical entomology with vast experience in vector control, and since 1981, has implemented a well-organized national vector control program with trained personnel. The US has experts in this field and advanced technology needed to carry out joint studies. Thus the problem at hand is aligned with the experience, expertise and technology of the two countries to be able to demonstrate the benefits of their joint work for science and for human health.

MEDICC Review: **Looking ahead, what projects or areas of bilateral work with colleagues across the Florida Straits do you think are most important for population health in both countries and abroad?**

Pedro Valdés: We can combine the cutting-edge brain research of US and Cuban neuroscientists with translational research to provide diagnostics, preventive interventions and treatment options for the huge global burden of brain disorders. To achieve this, in my opinion, the cooperation must go beyond the stage of simple exchange of information or limited joint scientific actions. Funding must be set aside—and barriers to its use eliminated—to seize these unique opportunity for bilateral impact upon global health.

> **Unfortunately, we often are forced to wait until a crisis emerges, and then we are challenged to establish basic scientific collaborations**

Peter Agre: Unfortunately, we often are forced to wait until a crisis emerges, and then we are challenged to establish basic scientific collaborations. A case in point is the recent emergence of neural injury alleged to have occurred by US Embassy personnel in Havana, for which alarms have been raised without sharing of information by our health experts. Certainly, more would have been achieved by collaborative efforts by Cuban and US neuroscientists than was accomplished by harsh rhetoric by nonscientific politicians.

Eric Martínez: Vector-borne infections such as dengue and Zika are a priority, to which we must now add the risks of yellow fever, chikungunya, West Nile fever and others. We need to look at clinical management to avoid deaths, viral and immunological pathogenicity, vectors and their control, and also epidemiological surveillance.

Work on vaccines is also an interest in both countries, whether to improve on ones currently available or evaluate efficacy of new vaccines through clinical trials, in which Cuba has recognized experience and success, as well as the infrastructure and trained personnel throughout its national health system.

Other infectious diseases also merit joint research, such as HIV/AIDS, in diagnostics—an area in which Cuba has made contributions—evaluation of new therapies, and social aspects of prevention through health education and changes in risk behaviors, particularly in adolescence.

Juan A. Bisset: My hope is that the CRDF Global projects approved for joint research can be carried out successfully and their results published internationally to inform national strategies for disease prevention and control of *Aedes aegypti;* that they generate new opportunities for collaboration and, above all, joint proposals that contribute to the development of science and health in both countries, and produce evidence of value to both science and society throughout the Region.

Jon Andrus: Highly useful areas of collaboration will continue to be the research, including vaccine dose-spacing strategies, and lessons from prevention and control of emerging infections, including arbovirus infections.

Every day, we witness emergence or re-emergence of infectious diseases that respect no borders

María Guadalupe Guzmán: Every day, we witness emergence or re-emergence of infectious diseases that respect no borders. Changes imposed by globalization, together with poverty and social inequities, among other factors, are driving this process. Collaboration among countries is an absolute priority in order to diminish the impact and reverse the effects of challenges posed by this global phenomenon.

So the arena of arboviruses becomes a must for cooperation among Cuba, the USA and other countries, centered on research (development of diagnostic tools, vaccines, basic studies to deepen understanding of pathogenicity or protection against disease, epidemiology, etc.), exchange of personnel, bidirectional capacity-building, technological development, and collaboration aimed at improved surveillance and control.

One essential prerequisite is exchange without restrictions—no restrictions on scientific development or access to technology; exchange visits; two-way training programs; organization of courses, symposia, workshops, and joint studies; or access to funding for research.

Eva Harris: There are enormous opportunities to continue and expand collaborations with our Cuban colleagues to enable their excellent and important scientific research in arbovirology and more broadly, human diseases—leading to therapeutics and vaccines with enormous potential for medical application worldwide, including in the USA. I also think it is essential to end the economic embargo, ease travel restrictions, and enable improved internet communication. Cuba has a large cadre of highly trained and extremely capable scientists and clinicians who should play an even greater role on the world stage than they already do.

ROUNDTABLE PARTICIPANTS

Peter Agre MD PhD is Bloomberg Distinguished Professor at the Johns Hopkins Bloomberg School of Public Health and Johns Hopkins School of Medicine, and director of the Johns Hopkins Malaria Research Institute. In 2003, Dr Agre, physician and microbiologist, and Roderick MacKinnon were awarded the Nobel Prize in Chemistry for discoveries concerning channels in cell membranes. In 2009, Dr Agre was elected president of the American Association for the Advancement of Science (AAAS) and began actively working for relations with Cuban scientists and their institutions. He led a delegation of US scientists to Havana in December 2009 and has made several trips to the island since then. In 2015, he spoke at the Cuban Academy of Sciences on behalf of the Health Advisory Board of the Bloomberg School of Public Health, as it presented the Academy with a plaque commemorating the scientific collaboration between the Cuban physician Carlos J. Finlay and Jesse W. Lazear, of Johns Hopkins University, in their experiments to prove Finlay's original theories on the agent transmitting yellow fever. Their results opened the way to eliminate this scourge in the tropics.

Jon Kim Andrus MD is professor and director of the Department of Vaccines and Immunization of the University of Colorado's Center for Global Health and professor at George Washington University. Previously, Dr Andrus served as PAHO deputy director; chief of PAHO's immunization program; and director of polio eradication in WHO's Southeast Asia Region. He began his global health career as a Peace Corps volunteer, serving as a District Medical Officer in Malawi. Currently, Dr Andrus is co-Chair of the Global Polio Partners Group, and member of the International Monitoring Board for the Polio Transition, PAHO's Technical Advisory Group for Vaccine Preventable Diseases, WHO's South East Asia Regional Verification Commission for Measles and Rubella Elimination, and WHO's Working Group on the Decade of Vaccines. Dr Andrus has published >120 scientific peer-reviewed papers and has received numerous awards for his leadership in immunization in developing countries. He is Guest Editor of this issue of ***MEDICC Review***.

Juan A. Bisset PhD, is a biologist who has worked since 1981 at IPK, where he heads the Vector Control Department. He is also full professor at the Medical University of Havana. Dr Bisset received postgraduate training at the University of California, Riverside, under Dr G.P. Giorghiou, in toxicology and the genetics of insecticide resistance in mosquito vectors, a topic he also pursued at the London School of Hygiene and Tropical Medicine in 1990 and 1992. With the 1997 dengue outbreak in Santiago de Cuba, he began research on control of *Aedes aegypti*. More recently he has become involved in new technologies for arbovirus vector control, including those for dengue, Zika and chikungunya, as well as the use of Wolbachia. Dr Bisset has served as advisor for malaria and dengue control in 7 Latin American countries, received 16 national and international awards, and published 115 scientific articles.

María Guadalupe Guzmán MD PhD DrSc is a virologist at IPK. She has over 30 years' experience working in virology and specifically in dengue and arboviruses. She has directed the PAHO/WHO Collaborating Center for the Study and Control of Dengue since 2005; serves as director of the Center for Research, Diagnostic and Reference Activities at IPK; director of IPK's master's degree program in virology; director of the Cuban project for vaccine development; president of the Cuban Society of Microbiology and Parasitology; and chair of IPK's Scientific Committee. Her work has contributed to knowledge of the pathogenesis, diagnosis, treatment and epidemiology of dengue and dengue hemorrhagic fever, and has developed two new hypotheses concerning dengue. She has been involved in analysis of several dengue epidemics in Cuba and in the Americas region. She is considered an expert by PAHO, WHO, TDR, Dengue Vaccine Initiative, International Council for Science and the European Commision Dr Guzmán has contributed to training of Cuban and Latin American scientists in virology and arboviruses, and has coordinated 15 international dengue courses at IPK. Currently, she coordinates the network of arbovirus laboratories in the Americas region and is a Distinguished Member of the Cuban Academy of Sciences, and a member of the Third World Academy of Science. Dr Guzmán has authored >300 papers, short communications and books. She is the author of four patents and is a past member of the Foundation Council of the Global Forum for Health Research and a past PDVI board member.

Eva Harris PhD is a professor at the University of California, Berkeley, in the Division of Infectious Diseases at the School of Public Health, and director of the Center for Global Public Health.

She has developed a multidisciplinary approach to study the molecular virology, pathogenesis, immunology, epidemiology, clinical presentation and control of dengue, Zika and chikungunya. She has worked in close collaboration with several Latin American countries, particularly Nicaragua, for nearly three decades. In 1997, Dr Harris received a MacArthur Award for work over the previous decade on programs to build scientific capacity in developing countries and address public health and infectious disease issues. Dr Harris was named a Pew Scholar for her work on dengue pathogenesis; received recognition from the Minister of Health of Nicaragua for her contribution to scientific development; and was selected as a Global Leader for Tomorrow by the World Economic Forum. In 2012, she was elected councilor of the American Society of Tropical Medicine and Hygiene and received a Global Citizen Award from the UN Association.

Eric Martínez MD PhD is a pediatrician dedicated to teaching and research on pediatric infectious diseases, particularly dengue, for over three decades. As a PAHO consultant, he has worked in 18 Latin American and Caribbean (LAC) countries during epidemics or as a participant in courses and seminars on dengue. He was one of the lead writers of the clinical management in WHO's Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control (2009) and PAHO's Dengue: Guidelines for Patient Care in the Americas (2010). He was the LAC countries' coordinator of the DENCO (dengue control) International Project (clinical diagnosis section) resulting in a proposed new dengue classification, now recommended by WHO. He is also a member of WHO's Data Security Monitoring Board for New Polio Vaccines (Polio Initiative). For many years, he was Deputy Director and Director of two pediatric university hospitals in Havana and headed the Cuban Ministry of Public Health's Department of Medical Research. A decade ago, he joined the IPK teaching staff, focusing mainly on postgraduate education. He also chairs IPK's Research Ethics Committee. Author of >100 scientific papers, Dr Martínez has edited 6 books on dengue in Havana, Dominican Republic, Bogotá, Buenos Aires and Rio de Janeiro. He is a member of the Pan American Society of Infectology and the International Society of Infectious Diseases.

Pedro Valdés MD PhD DrSc is the deputy director general for research of the Cuban Neurosciences Center, which he cofounded in 1990. His work includes statistical analysis of electrophysiological measurements, neuroimaging (fMRI, EEG and MEG tomography), nonlinear dynamic modeling of brain functions, as well as software and electrophysiological equipment development. He has been active in promoting brain mapping, setting up international collaborations and societies, and the Cuban and Latin American Brain Mapping projects, participating actively in the Organization for Human Brain Mapping (OHBM) since 1998, having served on its program committee. In 1979 he received postdoctoral training on neurometrics and computational techniques and biophysical modeling of brain electrical activity with Professor E. Roy John at the Brain Research Laboratory of New York University, USA. Dr Valdés is full professor at the Medical University of Havana, member of the Cuban Academy of Sciences and the Latin American Academy of Sciences. He is also Distinguished Professor of Neuroinformatics of the Key Laboratory for Neuroinformation, University of Electronic Science and Technology of China, where he also heads the Joint China–Cuba Laboratory for Frontier Research in Translational Neurotechnology. Dr Valdés serves as OHBM program chair and is a member of ***MEDICC Review's*** Editorial Board.

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Promoting Scientific Cooperation in Times of Diplomatic Challenges: Sustained Partnership between the Cuban Academy of Sciences and the American Association for the Advancement of Science

Sergio Jorge-Pastrana, Marga Gual-Soler PhD, Tom C. Wang PhD

ABSTRACT

Scientific research cooperation between Cuba and the USA has a long history that dates back to the 19th century. For the past 200 years, the two countries' relationship has been subject to complex economic, political and social forces. In the second half of the 20th century, the Cuban revolution and the subsequent escalation of the US government embargo impacted every aspect of Cuban life. While science was no exception, scientific interactions never ceased. Over the past decade, scientific cooperation—led and facilitated by scientific organizations such as the Cuban Academy of Sciences, the American Association for the Advancement of Science and others—has steadily increased to address ever more critical issues facing both countries. Science and global health diplomacy were key to reestablishing a trusting and productive relationship of mutual and global benefit after the USA and Cuba restored diplomatic relations in 2015. However, recent changes in Cuba policy by the new US administration are jeopardizing these opportunities for increased scientific cooperation, which are in the best interests of people in both countries.

KEYWORDS International cooperation, academies and institutes, Cuba, USA

HISTORICAL CONTEXT

Science in Cuba and the USA developed in parallel following the process started earlier across the Atlantic with the European Enlightenment. Thus, by the time national scientific and cultural institutions were being established in the USA, the same was happening in Cuba. Nascent learned societies, such as Cuba's Academy of Sciences (then called the Royal Academy of Medical, Physical and Natural Sciences of Havana, the first academy of sciences established outside of Europe)[1] and the Smithsonian Institution early on established links for engagement in discussion, exchange of papers and materials, and sometimes parallel quests for new knowledge in both countries (letters exchanged beginning in the 1840s between Joseph Henry, First Secretary of the Smithsonian and Felipe Poey, a founding member of Cuba's Academy, are kept in the Smithsonian Archives).[2] While these links were somewhat frail, archives in both countries reveal that even then, US and Cuban scientists' interests went beyond country borders and found echoes in the activity of partners abroad, building friendships that continued in international scientific conferences to which both contributed papers and debates.

The most prominent scientific cooperation between the USA and Cuba during this early period was joint work by Cuban academician Carlos J. Finlay and Jesse Lazear of Johns Hopkins University, destined to prove Finlay's theories presented 20 years earlier on the mosquito as the vector for yellow fever transmission.[3] This in turn paved the way for needed sanitation efforts and eradication of this scourge, not only in Havana but also in Panama (where construction of the Canal was constantly delayed by epidemics that crippled the workforce), and in many tropical areas afflicted by cyclic vector-borne disease crises with every rainy season.

IMPORTANCE US–Cuba cooperation is essential. The two countries share emerging health and environmental challenges, and it is in both countries' interests to continue scientific engagement and knowledge exchange. Experience proves that commitment by their scientific communities can overcome political barriers.

This collaboration may be cited as an early example of science diplomacy for several reasons. Internationally, Finlay first presented his thesis on vector transmission at the 5th International Sanitary Conference in Washington, DC in February 1881. The meeting was convened for diplomats and physicians to discuss international spread of communicable diseases and epidemics. Finlay contributed to the discussion by explaining yellow fever transmission from sick to healthy subjects and his novel theory that the mosquitoes were the vector. Several months later, he presented his further-refined ideas to the Cuban Academy, results that were independently confirmed by Lazear, a member of the US military's sanitary commission headed by surgeon Major Walter Reed. Reed and other members of his commission initially favored the hypothesis of miasmatic contagion, but Finlay shared the results of all his previous experiments with the commission, enabling Lazear to independently corroborate his conclusions.

All this was accomplished in the difficult diplomatic situation provoked by the US military occupation of Cuba, in which the sanitary commission itself was part of this foreign intervention. Finlay was a local scientist attempting to contribute his discovery to end the continuous epidemics threatening Cubans, the US soldiers and the entire region, but his thesis contradicted the scientific understanding of the US commission's head and most of its members. In their rigorous pursuit of truth through science, Finlay and Lazear became "scientific diplomats," their complementary, confirmatory results overcoming political odds to solve a terrible public health problem.

Soon after the 1959 Cuban revolution, nearly 100 years after the Cuban Academy was established, the political divide between the USA and Cuba started to grow, leading to severed diplomatic relations. A cascade of divisive events ensued: an economic, trade and financial embargo that has escalated since 1961–62, the Bay of Pigs invasion, and the 1962 Missile Crisis. Relations that still existed among scientists virtually disappeared during those confrontational times. The Academy, reestablished after 1962 as

the Cuban Academy of Sciences (ACC), with a broader scope and a mandate to foster research institutes, promoted studies in basic research and descriptions of Cuba's natural environment. Basic research in the fields of mathematics, physics, chemistry, geography, geology, geophysics, astronomy, meteorology, zoology, botany, and oceanography, as well as agricultural sciences, engineering and social sciences, were initiated by groups within the ACC.[1]

In the 1960s, Albert Sabin, best known for his research on polio and a pioneer in vaccine diplomacy, attempted to forge an agreement between ACC and the US National Academy of Sciences. Sabin received multiple invitations from Cuban public health officials during the early 1960s, but escalating hostility between the USA and Cuba made a high-profile visit by such a famous US scientist nearly impossible. However, when the US Department of State announced an easing of travel restrictions in 1965, in which medical researchers were included in the humanitarian exception to the travel ban, Sabin seized the opportunity to visit Cuba to promote greater cooperation in combating vector-borne diseases, hoping to serve as an interlocutor between senior officials in the two countries.[4]

By the 1970s, some links were reestablished between Cuban and US scientific institutions. Talks between ornithologists led by directors of the national zoos eventually produced bilateral visits between ACC and the Smithsonian Institution. The first memoranda of understanding (MOU) were signed by Cuban and US institutions in April 1980 when Dillon Ripley, Secretary of the Smithsonian, visited Havana. However, relations cooled once again with rising Cold War tensions in the following decade, effectively stifling the budding joint scientific endeavors and any hope to pursue normal relations among scientific colleagues.

Nevertheless, some researchers persisted in their efforts. Scientists from the National Museum of Natural History, the American Museum of Natural History, as well as several university and biomedical research centers, continued to partner with scientists in ACC institutes and some of the newly established biotechnology research facilities. Despite practical challenges to collaborative research, a steady increase in scientific discussion and jointly authored papers and books[5] continued to prove that, even in that difficult political environment, scientists sought and found ways to cooperate.

During the most tense periods, opportunities for increased cooperation were often facilitated by multilateral organizations in which the USA and Cuba were both members. For example, after facing bureaucratic barriers involving US Customs enforcement, Havana's Pedro Kourí Tropical Medicine Institute, with PAHO's assistance as intermediary, transported strains of dengue virus from Cuba's 1981 epidemic for further study at the US National Institutes of Health (NIH). Several months later, in collaboration with PAHO and WHO, Cuba hosted the first international course on dengue, launching a new era in international cooperation on dengue-related research, education and innovation that has benefited both Cuban and US researchers for over 30 years.[6]

In the 1990s, after the end of the Cold War, new opportunities for increased cooperation appeared, again facilitated by multilateral organizations such as the Inter-American Institute for Global Change Research (IAI) of which both Cuba and the USA were founding members.[6] At its creation in 1992, IAI was envisaged as an instrument for scientists and decision makers in the Americas to jointly frame, understand and tackle critical cross-border and regional issues associated with global change and their socioeconomic implications. The 19 member countries that formed the intergovernmental organization would fund collaborative research, training and policy-relevant communication. Thus, the IAI provided a multilateral forum for the USA and Cuba to interact scientifically when bilateral collaboration was not possible.

Also at that time, links were reestablished, or new ones established, between ACC and several US research institutions such as the American Museum of Natural History, the Social Sciences Research Council, the New York Botanical Garden (in 1994 ACC signed an MOU with the New York Botanical Garden, its signatories Brian Boom and Sergio Jorge Pastrana), and a growing number of US universities. Meanwhile, cooperation in the social sciences increased continuously through annual meetings of the Latin American Studies Association.

However, diplomatic and economic obstacles due to the continued US embargo on Cuba limited these collaborations' scope and reach. Although there were exceptions for certain types of medical and academic exchanges, US sanctions restricted Cuban researchers' ability to buy scientific equipment and access certain international grants, and limited US researchers' ability to use US government research funds and to co-organize meetings with Cuban counterparts.

It was under these difficult conditions that the American Association for the Advancement of Science (AAAS) and ACC intensified their cooperation.

BILATERAL COOPERATION IN THE 21ST CENTURY: ACC AND AAAS

In 1992, William T. Golden, then an AAAS officer (described by *The New York Times* as "a main architect of American science policy in the 20th century"),[7] visited Cuba and participated in events commemorating an ACC anniversary. During the trip, he explored initial possibilities for establishing permanent links between the two institutions. This was followed in 1996 by a meeting between AAAS President Rita Colwell and the Cuban delegation to the General Assembly of the International Council for Science in Washington D.C. After these initial explorations, Colwell led the first AAAS delegation to Cuba in 1997. The visit focused on understanding the development of biomedical sciences and the biotechnology industry in Cuba, but also led to broader recommendations, including calls on US and Cuban authorities to ease restrictions on scientific travel.[8,9]

In 1998, AAAS published a report by Edward Kaufman and Elisa Muñoz that documented substantial hurdles for scientists wishing to travel between the USA and Cuba.[10] From then through 2002, AAAS sought to support scientists' rights to such travel, through its Latin American and Caribbean Program and its Human Rights Program, The project provided an online clearinghouse for information about cases where scientists were prevented from traveling to scientific conferences and meetings at partner institutions in the two countries.

At the turn of the 21st century, AAAS, ACC and other counterpart institutions devoted joint efforts to increasing scientific cooperation

within the Caribbean region. At the 2002 AAAS Annual Meeting in Boston, an ACC delegation was invited to present opportunities for cooperation at a roundtable. In attendance were Golden, Colwell, Pastrana and Guadalupe Guzmán (the latter from Cuba's Pedro Kourí Tropical Medicine Institute in Havana), who were all involved in previous efforts to increase cooperation. By this time, scientific communities in both countries had already recognized for over a decade the importance of increased cooperation for the benefit of both societies.[11]

The second decade of the 21st century brought intensified efforts by AAAS and ACC to achieve more systematic cooperation. Starting in 2009, led by Nobel laureate and then AAAS President Peter Agre and AAAS Chief International Officer Vaughan Turekian, and carried forward by successive AAAS leaders (including another president, Gerald Fink) a series of scientific meetings and delegation visits culminated in April 2014 with a historic MOU between the two organizations, signed by AAAS CEO Alan Leshner and ACC Executive Director Sergio Jorge Pastrana.[12]

This formal agreement opened a path for increased and continuous cooperation in several priority areas of biomedical research that were of common interest and were recognized as paramount in both countries. Moreover, the series of visits leading up to the MOU involved other US scientific institutions (effectively broadening interaction between potential US and Cuban partners) and included Frances Colón, acting Science and Technology Adviser to the US Secretary of State; Colón was the highest-level US science diplomat to visit Cuba in an official capacity before the 2015 restoration of diplomatic relations.

By December 17, 2014, when US President Barack Obama and Cuban President Raúl Castro announced the beginning of a process to normalize bilateral relations[13] and brought hope for easing cooperation to both scientific communities, strong links among scientific leaders of both countries were already firmly in place.

Under the ACC–AAAS MOU, three USA–Cuba bilateral workshops have been held on neurosciences,[14] cancer immunotherapy[15] and vector-borne diseases[16] to foster interactions between leading researchers in both countries that could lead to increased and long-term programs of joint research. Individuals and institutions involved in these workshops have continued to maintain contact and interact, but they could benefit from an improved climate for cooperation that would allow for joint funding applications, research mobility, joint training, and shared laboratory instruments and techniques. To this end, in 2016 the AAAS Center for Science Diplomacy launched a pilot Cuban Biomedical Fellows Program, funded by the Richard Lounsbery Foundation in the USA, as the first structured exchange program supporting early- and mid-career Cuban biomedical scientists to conduct research visits to top US laboratories, with the expectation that this would lead to long-term collaborations between leading Cuban and US research institutions.

CURRENT SITUATION AND PROSPECTS

Reestablishment of diplomatic ties between the USA and Cuba in 2015 and ensuing policy revisions by the Obama administration prompted expanded scientific cooperation and new types of cooperation, by general authorization for joint commercial as well as non-commercial medical research and, for the first time, for Cuban-developed medications to enter normal FDA regulatory channels. The US Department of the Treasury also granted licenses for clinical trials in the USA of specific Cuban medications.[17,18] The US NIH had also initiated a small number of relatively small grants to be administered by CRDF Global,[19] a US NGO that implements international scientific cooperation programs. The latter would have helped foster long term programs of bilateral scientific cooperation.

In addition, the US Department of Health and Human Services[20] and National Oceanic and Atmospheric Administration together with the Ministries of Health and of Science, Technology and Environment, their Cuban counterparts, signed intergovernmental MOUs to pursue scientific cooperation in public health and environmental sciences, including joint monitoring of coral reef ecosystems to better understand the consequences of climate change in the shared marine ecosystems across the Florida Straits, and an MOU particularly focused on cancer research.[21] Although the basis for joint research had already been laid by individual scientists and their institutions, for the first time in five decades, many nongovernmental organizations on both sides saw opportunities for regular cooperation. Long-term scientific cooperation emerged in key areas of mutual interest; more than half of the agreements signed during this brief period were preceded by earlier contacts between scientists trying to find ways for constructive cooperation. Those relations were maintained through challenging times by the shared interests of individuals and institutions. This proved once again, as evident many times in the past, that scientists and their discussions have been essential for gaining understanding among nations of different political, cultural and social environments.

Today, three years after restored diplomatic relations, the atmosphere for cooperation is once again uncertain. In October 2017, the new US administration halted rapprochement with Cuba, implementing revised policies that, while not explicitly targeting science, severely limit travel and logistical aspects of traveling between Cuba and the USA. The administration's decision to close its consular services for Cubans at the US Embassy in Havana means that Cubans must travel to a third country to apply for a US visa.[22] These moves will likely discourage both sides from pursuing joint research, a deterrent to scientific cooperation.

During these uncertain times, a new kind of relationship continues to be built between scientists of the two countries that, though close geographically, have been as widely separated for more than half a century as if they were on different continents. Scientific communities in both countries have repeatedly reinforced the need to continue to find ways to promote collaboration that could contribute to addressing shared national and regional challenges.

Such cooperation is essential: Cuba and the USA are inextricably linked. The two nations share emerging health and environmental challenges, and their common backyard is an ocean filled with limited resources. During difficult times in the history of the US–Cuba relationship, scientists have worked to keep partnerships alive in the face of changing and often destructive policies. It will be in both countries' interests to continue US–Cuban knowledge exchange and facilitate deeper engagement between scientists to benefit people in Cuba, the USA and well beyond. Scientific institutions of both countries will undoubtedly continue to promote and defend scientists' rights to share their knowledge and experience in the search for new truths vital to solving urgent problems faced by the two countries and the planet as a whole.[23]

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Cuban Epidemic Neuropathy: Insights into the Toxic–Nutritional Hypothesis through International Collaboration

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ABSTRACT

From 1991 to 1993, an epidemic of optic and peripheral neuropathy—the largest of the century—broke out in Cuba, affecting more than 50,000 people. Initially the main clinical features were decreased visual acuity, central and cecocentral scotomas, impaired color vision and absence of the papillomacular bundle. Later, peripheral and mixed optic–peripheral forms began to appear. Due to the magnitude of the epidemic, the Cuban government requested help from the international community at the 46th World Health Assembly in 1993. PAHO and WHO immediately responded by sending a mission of international experts. Several hypotheses regarding the pathogenesis of Cuban epidemic neuropathy were put forward including: toxic, nutritional, genetic and infectious. The authors refer to extensive studies by researchers sponsored by the Cuban government and PAHO/WHO, joined by scientists from several other countries, including the USA. This paper describes their multidisciplinary work, particularly devoted to investigating the hypothesis of a primary toxic–nutritional cause of the epidemic. Clinical aspects, such as case definition and clinical description, were vital issues from the start. Cuban physicians who first examined patients received a clear impression of its toxic–nutritional origin, later confirmed by international experts. Research then focused on the mechanisms contributing to damage under the toxic–nutritional hypothesis. These included injuries to the mitochondrial oxidative phosphorylation pathway, nutritional deficiencies, excitotoxicity, formate toxicity and dysfunction of the blood–brain barrier. It was expected that the results of such international collaboration into this major health problem would also shed more light on mechanisms underlying other nutritional or tropical myeloneuropathies.

KEYWORDS Optic neuritis, optic neuropathy, peripheral neuropathy, neurotoxicity syndromes, disease outbreaks, international cooperation, Cuba

INTRODUCTION

The outbreak of optic and peripheral neuropathy in Cuba at the beginning of the 1990s affected more than 50,000 persons throughout the country.[1] The epidemic followed an abrupt economic crisis due to the collapse of the socialist bloc (1989–1991) and the tightening of the US embargo, which led to severe food shortages and greater physical demands on the population (motor-driven transportation was at a near standstill). These deprivations were the underlying factors in what became the largest epidemic of neurological disease in the 20th century.[2]

The first cases were reported in Cuba's westernmost province, Pinar del Río, towards the end of 1991: patients presented bilateral vision loss, suggesting a diagnosis of retrobulbar neuritis. As case numbers continued to climb, in April–June 1992, Cuba's Ministry of Public Health (MINSAP) sent a multidisciplinary commission to examine the patients in the field. Visual deficits described included decreased visual acuity and color perception, and/or central or cecocentral scotomas, with a normal fundus or slight temporal pallor of the optic nerve. In some cases, neurological impairments such as a predominantly sensory peripheral neuropathy and hearing loss were observed. Cuban scientists began investigating the possible etiology and hypothesized that the cause was probably multifactoral, with emphasis on nutritional and toxic factors,[3] without ruling out a possible viral contribution, based on virologists' findings from cerebrospinal fluid (CSF) studies.[4]

IMPORTANCE Cuban epidemic neuropathy research exemplifies how intensive and widespread international collaboration can help solve important health problems, in this case, shedding light on other metabolic or mitochondrial optic neuropathies.

After months of research, two types of neuropathy were defined: an optic form (characterized by subacute onset of the symptoms and signs previously described) and a peripheral form, a predominantly sensory neuropathy, with posterior spinal cord involvement in some cases, with or without concurrent optic neuropathy. The optic form was more prevalent in men, the peripheral form in women. Both forms were often accompanied by weight loss and fatigability. Incidence rates were 926.7 per 100,000 population for persons aged 45–65 years and 290.9 per 100,000 for persons aged >65 years, lowest in children aged <15 years, 4.2/100,000.[3] The epidemic spread from west to east with the highest incidence rates in Pinar del Río Province (1332.8/100,000) and lowest in Guantánamo, Cuba's easternmost province (65/100,000). Risk was associated with smoking; lower body mass index; and lower intake of animal protein, fat, and foods containing B vitamins. Beginning 1993, Dr Hector Terry Molinert (then MINSAP's Vice Minister for Epidemiology) and his team proposed distribution of vitamin supplements (including B vitamins) to the entire population. After this was implemented, the epidemic began to decline as of May 1993.[3] At first, the disease was named Cuban epidemic optic neuropathy, but as peripheral nervous system involvement became apparent, a more general term was applied: Cuban epidemic neuropathy (CEN).[5]

Due to CEN's scale as a public health problem, the Cuban government requested help from the international community at the 46th World Health Assembly in 1993. Among the first to arrive in Cuba to investigate the outbreak through the US-based International Peace for Cuba Appeal were Norah Lincoff and Michio Hirano, who examined patients between May 4 and 11,

1993, and soon published their impressions of the epidemic.[6] Almost simultaneously, PAHO and WHO responded by sending missions May 16–26 and June 16–24, 1993, briefed on arrival by Cuban experts in nutrition, toxicology, ophthalmology, neurology and epidemiology. The missions' objectives were mainly to review and analyze available information regarding CEN's clinical and epidemiological features and possible causes, and to recommend and collaborate in research areas that could be useful to determine etiology and eventual control. US scientists from various clinical and scientific backgrounds who participated in the PAHO/WHO missions published a detailed account in 1997.[7]

The information gathered by Cuban and international experts who visited the country from May 1993, was presented at the International Workshop on Cuban Epidemic Neuropathy, held in Havana in July 1994. At that time, the main conclusion was that inflammatory or infectious origins were unlikely. Morphologic changes were consistent with an axonal neuropathy, similar to that observed in toxic–metabolic, or nutrition deficiency conditions. The Workshop emphasized the need to continue investigating and to design further studies with a multidisciplinary and multicenter approach.[8]

The Role of International Collaboration A vast program was established between MINSAP, PAHO/WHO, Orbis International, CDC, US NIH and other international organizations to investigate CEN's causes. Experts from Cuba, the USA and Venezuela collaborated in studying CEN's clinical, toxicologic and neurochemical characteristics in order to understand its underlying mechanisms. The authors' experience reported in this paper are related to joint work carried out in patients in Pinar del Río during the epidemic period and later in development of models of low-dose chronic methanol administration in experimental animals.

OBJECTIVES

1. Describe the clinical ophthalmological and neurological characteristics of the CEN epidemic in patients residing in Pinar del Río Province.
2. Propose a pathophysiological hypothesis for CEN etiology.

Justification The CEN investigation was started early in 1992 by Cuban scientists and continued from May 1993 in collaboration with scientists mainly from the USA, but also from the United Kingdom, Venezuela, Russia and elsewhere. The need to identify the possible causes or contributing factors generating this unique disease outbreak led to an extensive research network that would eventually investigate various hypotheses about the epidemic's origins.

Participating institutions Researchers from Cuba's Neurology and Neurosurgery Institute (INN) studied CEN in Pinar del Río Province during the first quarter of 1992. Rosaralis Santiesteban Freixas (RSF), head of the Neuro-Ophthalmology Department, and Santiago Luis (SL), neurologist and Director of the Institute, carried out extensive clinical examinations of CEN patients, while Alina González-Quevedo (AGQ) and Ileana Alfaro, of the Neurochemistry and Neuroimmunology Laboratory, conducted serum and CSF studies.

Alfredo Sadun (AS) was a member of the PAHO/WHO delegation (at the time, professor of ophthalmology and neurosurgery at the Doheny Eye Institute, University of Southern California, Los Angeles, USA). He travelled to Cuba in May and September 1993 to perform clinical assessments on a small number of CEN patients. In 1994, he visited Cuba twice again, the second time accompanied by Janis Eells (JE), professor of pharmacology and an international expert in methanol toxicity at the Department of Pharmacology and Toxicology, University of Wisconsin–Milwaukee, USA.

Two years later, after the epidemic had subsided, Dr Lucimey Lima (LL), an expert in basic retinal and optic nerve neurochemistry, participated in a scientific meeting in Cuba and subsequently joined the research group.

Mechanisms Collaboration with US colleagues began in 1993–1994 under the aegis of a larger cooperation effort between MINSAP and PAHO/WHO. Financial support came from PAHO, Orbis International, and US NIH. Collaboration with Venezuelan colleagues in 1997–2002 was supported by grants and fellowships from Venezuela's National Foundation for Science, Technology and Innovation (Grant S1-2001-903) and the Scientific and Technological Research Council (Grant S1-723, fellowship from Project PI-3277, scholarship PI-98-3277).

Activities

- **April–June 1992:** clinical and physical ophthalmological examinations in Pinar del Río Province, neurological examinations of patients, serum and CSF sample collection
- **May and September 1993**: clinical and physical ophthalmological examination of 20 patients in Pinar del Río, reassessment of patients in September, analysis of methanol content in sample of home-brewed rum from Pinar del Río
- **1994:** formate and folate analysis of serum and CSF samples stored at INN, histological analysis of four sural nerve and one optic nerve biopsy from CEN patient
- **1995:** development of a rat model of chronic methanol intoxication by AS (in USA) and rat/human comparative histological studies
- **1998–2000:** development of a rat model of chronic methanol intoxication by AGQ (in Venezuela) and neurochemical studies

Ethics Studies conducted in human subjects and animal experimentation were approved by the ethics committees of Cuba's INN and the Venezuelan Institute of Scientific Research and were conducted according to the Declaration of Helsinki for experimentation in human subjects and animals.[9] Participants gave written informed consent.

ANALYSIS

In response to Cuba's request and PAHO/WHO's call, several cooperative initiatives were planned and carried out jointly by US, Latin American and Cuban researchers.

Clinical findings Researchers from Cuban institutions started investigating the neuropathy outbreak from its onset in Pinar del Río Province. RSF carried out ophthalmological examinations, for which a protocol was established in April–May 1992. As a result, visual impairment was described as follows:[10,11]

- Bilateral decreased near and far visual acuity, not corrected with lenses
- Impaired red–green color vision on the Ishihara test[12]
- Bilateral and symmetrical central and cecocentral scotomas, especially for red and green, in tangent field testing
- Normal fundus examination or slight temporal optic disc pallor

The first cases were mainly men aged 25–64 years, heavy smokers and/or alcohol consumers, who complained of blurred vision, light sensitivity and weight loss. This, together with the ophthalmological findings, pointed to an initial diagnosis of tobacco–alcohol amblyopia.[13]

In May–June 1992, more Cuban experts visited Pinar del Río (biostatisticians, epidemiologists, neurologists and nutritionists, among others). By then, the morphology of visual evoked potentials was also found to be altered, displaying a bifid p100 wave. Neurological signs and symptoms were also detected in some patients with optic neuropathy, consistent with a predominantly sensory peripheral neuropathy: hearing loss, deep tendon hyperreflexia indicating corticospinal tract involvement, and increased urinary frequency, urgency in urinating and in some cases urinary incontinence.

Three forms of neuropathy were identified: optic, peripheral and optic–peripheral. Later, cases were also reported in other provinces with an apparent pattern spreading from west to east. House-to-house surveys and case–control studies in Pinar del Río reported vision improvement in most cases when patients were treated with B-complex vitamins. The multidisciplinary commission's hypothesis was that the epidemic stemmed from toxic–nutritional causes. Although a viral contribution was not ruled out at the time, the epidemiological pattern was inconsistent with that of a communicable disease.[13]

Venezuelan neuro-ophthalmologist, Rafael Muci, a PAHO/WHO expert who participated in the mission to Cuba in May 1993, had shown Cuban researchers the use of red-free light for fundus examination, permitting visualization of loss of nerve fiber layers in the retina. In December 1992, his expertise had been requested by Cuban neuro-ophthalmologists cognizant of the need to demonstrate anatomical correlates of functional damage to the papillomacular bundle observed in visual field studies.

Alfredo Sadun and his colleagues conducted extensive neuro-ophthalmological and psychophysical examinations and interviews on 20 patients upon his arrival to Cuba with the PAHO/WHO delegation in May 1993. Several common features and patterns were subsequently determined, recommended and accepted by the Cuban epidemic task force for a new case definition.

Diagnosis required evidence of nerve fiber layer loss in the papillomacular bundle and any three of the following five symptoms and signs: subacute bilateral vision loss, dyschromatopsia, saccadic smooth pursuit, central or cecocentral visual field defect and impaired contrast sensitivity. Cuban ophthalmologists were trained by Muci in the new recommended case definition and in use of neuro-ophthalmological (red-free funduscopy) and psychophysical tests (threshold Amsler grid testing)[14] required to diagnose epidemic optic neuropathy. This considerably reduced the number of false positives.[5]

Neurochemical studies and experimental models Among the first laboratory studies conducted early in the outbreak were serum and CSF analyses to assess the possibility of immune-mediated inflammatory optic neuropathy. The results did not support this hypothesis, since only a minority of patients exhibited intrathecal IgG synthesis. These findings and CEN's epidemiological and clinical features made an infectious process unlikely.[15] Increased blood–CSF barrier permeability was observed in approximately 30% of cases, blood–CSF damage being more frequent within 16 to 60 days of disease onset and disappearing after 120 days. Blood–CSF barrier dysfunction was more prevalent in patients with severe neurological impairment but was not found to be related to severity of ophthalmological damage. These results were later confirmed in a larger sample of patients. Considering that the most favored hypothesis for CEN origin was toxic–nutritional, it was suggested that blood–brain barrier dysfunction could be associated with metabolic derangements and/or neurotoxicity.[16]

Although previous epidemiological studies indicated that intake of essential amino acids in CEN patients was below 70% of recommended values,[17] we found levels of essential amino acids were generally preserved, except for a selective reduction of taurine and threonine.[18] Serum albumin levels were also preserved.[15] Taurine, a sulfur containing neutral β amino acid, was of particular interest because of its important CNS trophic function, especially in the retina and optic nerve, as well as its antioxidant properties.[19] Taurine was lower in patients with more severe ophthalmological impairment, but was not associated with severity of polyneuropathic manifestations, indicating that taurine deficiency could play a role in the optic form's pathophysiologic mechanisms.[18] Although endogenous taurine synthesis occurs in the liver and brain (pyridoxine required as a cofactor), the human body has limited capacity to synthesize it. Thus, vitamin B6 would be considered an essential amino acid in situations of widespread vitamin deficiency. Furthermore, animal products are the main sources of taurine in humans, and these were very scarce in the Cuban diet in the early 1990s.

CEN patients' CSF displayed accumulation of glutamate and aspartate (excitatory amino acids), suggesting that excitotoxicity could also be involved in the disease's pathophysiology.[18]

In the search for toxins that may have triggered CEN, noncommercial (home-brewed) rum samples acquired in Cuba by AS were tested in the USA, revealing methanol levels from 0.87% to 1%.[5] Although this amount would not lead to acute methanol intoxication, prolonged exposure, especially in the presence of folate deficiency, could lead to formate accumulation and subacute impairment of visual function. Furthermore, it should be noted that physiological levels of methanol are present in the blood, from environmental exposure and derived from diet through normal metabolic processes. Methanol and/or formate can be found in some foods, including fruits, vegetables, juices (mainly orange, grapefruit and tomato), fermented beverages, aspartame sweetened foods, beans, honey and roasted coffee.[20]

In order to investigate folate and formate levels in CEN patients, JE traveled to Cuba in 1994 with AS and contacted the INN's Neurochemistry Laboratory, which had stored serum, and CSF samples from CEN-confirmed patients in Pinar del Río. Formate analysis was conducted at INN and samples were transported to the USA for folate analysis. Marked folate deficiency was detected in more than 50% of samples analyzed, and serum formate

accumulation in 25%. Folate concentration was inversely correlated with severity of optic neuropathy, while formate concentration was directly correlated.[21] Although it is unlikely that classic methanol poisoning (which produces an acute formate acidosis) could have significantly contributed to the entire epidemic, consumption of ethylic alcohol containing small amounts of methanol was a risk factor for developing the disease.[5] It should be emphasized that this study included patients from the same region where the home-brewed rum samples had been taken, and 55% were alcohol drinkers; thus chronic formate toxicity may have contributed to triggering the disease in some patients.[22] Gay's Isle of Youth study concluded that smoking and alcohol consumption did not by themselves account for disease occurrence but reinforced the effects of dietary deficiencies.[23]

At this point in the investigation of CEN, the need emerged to develop animal models matching some characteristics of the Cuban patients, especially the possibility of chronic low-level methanol exposure in the presence of folate deficiency. The rationale was to combine folate deficiency with chronic methanol toxicity so as to increase formate production to match serum levels observed in CEN patients. Two models were developed independently by Cuban researchers. One was an experimental model of chronic methanol administration in rats with dietary folate deficiency.[22] Analysis of optic discs disclosed prelaminar axonal swelling anterior to the lamina cribrosa, indicating axoplasmic blockage at this level. Ultrastructural examination revealed early axonal degeneration and a relative abundance of mitochondria, many of which were swollen and with disrupted cristae. These histopathologic features matched very closely those observed in the optic disc of a CEN patient who died of unrelated causes. Due to the selective action of formic acid as an inhibitor of mitochondrial function,[24] these results supported the hypothesis that impaired mitochondrial oxidative phosphorylation produced axoplasmic blockage.

The second model was developed in rats with chronic low-level methanol administration and folate deficiency induced by methotrexate, where accumulation of aspartate (an excitotoxic amino acid) was detected in the optic nerve,[25] results which paralleled the increased levels of aspartate and glutamate in CEN patients' CSF,[18] suggesting participation of excitotoxic mechanisms.

Pathophysiological mechanisms underlying CEN Very early in the investigation, striking clinical similarities with Leber hereditary optic neuropathy (LHON) were recognized and later discussed with international experts, leading to the search for mutations in patients.[26,27] However, later it was definitively demonstrated that CEN was not associated with LHON.[28] As the main pathogenic mutations of LHON affect subunits of the mitochondrial complex in the respiratory chain, it was suspected that CEN was possibly affecting mitochondria on an acquired basis.[29]

Clinical, epidemiological, neurochemical and experimental studies revealed possible mechanisms underlying CEN, most likely resulting from insults to the mitochondrial oxidative phosphorylation pathway from severe nutritional deficiencies (folic acid and other B-complex vitamins), leading to impaired detoxification mechanisms and thus to chronic accumulation of exogenous and endogenous toxins (formate from methanol metabolism, and/or exposure to cyanide from dietary products and cigarette smoke).[22] Furthermore, in CEN's pathophysiological mechanism, where oxidative stress was definitely the "conductor of the orchestra," three interrelated processes may have been present: excitotoxicity, blood–brain barrier dysfunction and formate toxicity. Additionally, a selective taurine deficiency may have complicated the picture due to its abundance in the retina and well-known antioxidant and neuroprotective properties.[30]

CONCLUSION

Cuban epidemic neuropathy research exemplifies how intensive and widespread international collaboration can work to solve important health problems, in this case, further shedding light on other metabolic or mitochondrial optic neuropathies. US–Cuba cooperation, under the PAHO/WHO umbrella, was key to developing, pursuing and generating evidence to support the nutritional–toxic hypothesis of CEN etiology.

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US and Cuban Scientists Forge Collaboration on Arbovirus Research

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ABSTRACT

After December 17, 2014, when the US and Cuban governments announced their intent to restore relations, the two countries participated in various exchange activities in an effort to encourage cooperation in public health, health research and biomedical sciences. The conference entitled Exploring Opportunities for Arbovirus Research Collaboration, hosted at Havana's Hotel Nacional, was part of these efforts and was the first major US–Cuban scientific conference in over 50 years. Its purpose was to share information about current arbovirus research and recent findings, and to explore opportunities for future joint research. The nearly 100 participants included leading arbovirus and vector transmission experts from ten US academic institutions, NIH, CDC, FDA and the US Department of Defense. Cuban participants included researchers, clinicians and students from Cuba's Ministry of Public Health, Pedro Kourí Tropical Medicine Institute, Center for Genetic Engineering and Biotechnology, Center for State Control of Medicines and Medical Devices and other health research and regulatory organizations. Topics highlighted at the three-day meeting included surveillance, research and epidemiology; pathogenesis, immunology and virology; treatment and diagnosis; vector biology and control; vaccine development and clinical trials; and regulatory matters. Concurrent breakout discussions focused on novel vector control, nonvector transmission, community engagement, Zika in pregnancy, and workforce development. Following the conference, the Pedro Kourí Tropical Medicine Institute and the US National Institute of Allergic and Infectious Diseases have continued to explore ways to encourage and support scientists in Cuba and the USA who wish to pursue arbovirus research cooperation to advance scientific discovery to improve disease prevention and control.

KEYWORDS Arboviruses, flavivirus, Zika virus, chikungunya virus, dengue virus, research, disease vectors, Cuba, USA

INTRODUCTION

On December 17, 2014, when the US and Cuban governments announced their intent to restore relations, US President Barack Obama emphasized the implications of rapprochement for health cooperation.[1] Prior to this announcement, a group of US scientists and policy experts, sponsored by the American Association for the Advancement of Science (AAAS), traveled to Havana in April 2014 to meet Cuban scientists, physicians and policy makers; visit research and public health facilities; discuss opportunities for further interaction; and sign a memorandum of understanding between the Cuban Academy of Sciences and the AAAS to launch further exploration of mutual health research interests.[2]

In August 2015, the Cuba's Pedro Kourí Tropical Medicine Institute (IPK) sponsored the 14th edition of its research and training conference, the International Dengue Course, which it has organized in Havana since 1987. Participants included dengue viral disease scientists from the US National Institutes of Health (NIH) and CDC. In October 2015, Cuban scientific leaders attended, for the first time, the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) in New Orleans, where they participated in a US–Cuban information-sharing symposium organized by the NIH's Fogarty International Center, the ASTMH and PAHO.[3–4] This symposium, Cuba–U.S: Building Bridges Through Science and Global Health, was followed by an unprecedented visit by the participating Cuban scientists to the NIH in Bethesda, Maryland. During the visit, NIH leadership explored opportunities for chronic and infectious disease research collaborations with Cuba.[5]

IMPORTANCE Cuba's experience in arbovirus research and health strategies for mosquito control complement US CDC's strengths in research and epidemiologic surveillance. Rapidly emerging threats from arboviral illness, extension of vector habitats, and proximity make US–Cuba collaboration not only mutually beneficial, but imperative.

Following further official contacts and reestablished diplomatic relations, Cuba's Vice-Minister of Public Health, Dr José Ángel Portal Miranda, visited the USA early in 2016. He included NIH and other agencies of the US Department of Health and Human Services (HHS) on his itinerary. In June, following the historic visit of President Obama to Cuba in March 2016, where health research was again highlighted as a key area for expanded cooperation, Cuba's Minister of Public Health, Dr Roberto Morales Ojeda, visited Washington DC to meet with HHS Secretary Sylvia Burwell. During this visit, the two leaders signed a memorandum of understanding to establish cooperation in public health, health research and biomedical sciences, specifically calling for collaboration to confront Zika, dengue, chikungunya and other arboviruses.[6] Also during this visit, leadership from Cuba's Ministry of Public Health (MINSAP), IPK, and the NIH's National Institute of Allergy and Infectious Diseases (NIAID), agreed on the value of convening a scientific meeting to explore arbovirus research collaboration opportunities, given the emerging potential threat of Zika, dengue and chikungunya in the southern USA and the Caribbean region. A bilateral scientific planning committee was established with representation from NIH, CDC and the US FDA to assist the IPK in conference planning.

Also significantly, on October 17, 2016, the US Department of the Treasury's Office of Foreign Assets Control (OFAC) issued a regulatory amendment that authorized (under general license) expanded US–Cuban engagement in commercial and noncommercial joint medical research and training.[7] Furthermore, during the same week (October 19) a preliminary US–Cuban arbovirus research meeting was held in Havana, in conjunction with a PAHO-organized regional arbovirus control

meeting (October 20–21).[8] HHS Secretary Burwell attended the PAHO regional meeting and used the opportunity to visit Cuban health facilities and research institutions. She also signed another memorandum of understanding with MINSAP to foster cancer research cooperation.[9]

COLLABORATION

After two years of preparations, IPK, MINSAP and other Cuban health agencies and research centers, together with government and academic scientists from the USA, convened the first major US–Cuban scientific conference in over 50 years. The conference, Exploring Opportunities for Arbovirus Research Collaboration, was held at the Hotel Nacional in Havana (November 28–30, 2016). Its purpose was to share recent findings from arbovirus research and explore future joint research opportunities.

The nearly 100 participants included leading arbovirus and transmission vector experts from ten US academic institutions, NIH, CDC, FDA and the US Department of Defense. Cuban participants included researchers, clinicians and students from MINSAP, IPK, Center for Genetic Engineering and Biotechnology, Center for State Control of Medicines and Medical Devices, and other health research and regulatory centers. Topics highlighted at the meeting included surveillance research and epidemiology; pathogenesis, immunology, and virology; treatment and diagnosis; vector biology and control; vaccine development and clinical trials; and regulatory matters. Concurrent breakout discussions focused on novel vector control, nonvector transmission, community engagement, Zika in pregnancy, and workforce development.

Presentations on arbovirus epidemiology noted that it took a decade for dengue to spread and reach 1.5 million cases in the Americas Region. However, with ever-increasing travel, urbanization and mosquito vector expansion, the more recent chikungunya and Zika epidemics reached these prevalence levels in a much shorter period.

Other presentations described Cuba's robust, well-organized infectious disease surveillance system. The system is based on a network of clinics and hospitals, relying on a provider base of 8 physicians and 8 nurses per 1000 population. Cuba's long-standing program to limit vector-borne diseases stresses community involvement in vector control and includes year-round nationwide coverage aimed at eliminating mosquito breeding foci.

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An active surveillance system includes a network of laboratories and a national reference center (IPK) that has a decades-long history of arboviral disease diagnosis. Many of these laboratories utilize state-of-the-art nucleic acid detection and serological assays to diagnose the island's most imminent threats—dengue, chikungunya and Zika viruses. Diagnosticians exchanged topical information on new assays, with a focus on evolving techniques that improve specificity where cross reactivity between flaviviruses—including dengue, West Nile, yellow fever and Zika—remains a problem.

The scope of Cuban arbovirus research was presented in detail, particularly IPK's basic, translational and applied research programs, which include those focused on viral epidemiology, host factors influencing viral pathogenesis, virus evolution and molecular biology, vaccine and antiviral development, and environmental studies on mosquito control.

Because of their central role in arbovirus transmission to humans and their expansion into new geographic areas in the region, *Aedes aegypti* and *A. albopictus* were extensively discussed. The history of Cuba's successful programs to control *A. aegypti* in the 1980s was presented, with a sobering coda on its current resurgence throughout the country.

Vaccines were another active focus of the conference with an emphasis on development and clinical evaluation of new dengue and chikungunya vaccines, and ongoing early efforts to develop Zika vaccines. The NIH investigators reviewed encouraging early clinical studies of a chikungunya virus-like particle vaccine and of a live-attenuated, recombinant tetravalent dengue vaccine. Cuban scientists described promising preclinical testing of a subunit dengue vaccine developed to protect against all four serotypes.

Antiviral therapeutics were discussed, including their potential role as short-term preventive interventions during arbovirus outbreaks where registered vaccines are unavailable. Discussions of retesting and repurposing established therapeutic drugs led to conclusions that this approach to emerging arbovirus outbreaks deserves further evaluation. Researchers reviewed the current use of arbovirus animal models and emphasized the need for well-characterized models for the clinical syndromes of microcephaly and Guillain–Barré that appear to be linked to Zika infection. Throughout the meeting, participants identified numerous fields for potential collaboration, and many expressed a desire to pinpoint specific areas of joint research where collaboration might be initiated to address critical questions related to basic understanding of arboviruses and their vectors. US scientists recognized Cuba's strong track record in arbovirus research and control, making the prospect of collaboration attractive, with substantial opportunities for synergy.

ANALYSIS

Shared concern about mosquito-borne diseases is spurring cooperation among Cuban and US scientists. The conference helped build on the two countries' strengths in research capacity and experience, to initiate new collaborative research studies, which should have important implications for more effectively preventing and addressing arboviral infections in both countries, the Americas Region and the world. Following the conference, IPK and NIAID have continued to explore ways to encourage and support scientists in Cuba and the USA who wish to pursue arbovirus research cooperation to advance scientific discovery to benefit population health.

One of the most important results was CRDF Global's US–Cuba Collaborative Arbovirus Research Initiative, 2017 (jointly funded with NIAID), which considered proposals from US and Cuban scientists working jointly in arbovirus research. IPK and US institutions submitted seven joint research grant proposals, four of which were approved and are due to start in 2018. One of these, involving IPK and the University of California at San Diego, will focus on the role of OSBPL10, RXRA and other lipids participating

in the RXRA metabolic pathway in maturation, replication, assembly and secretion of dengue virus. Another two projects will address entomological studies; one, with Johns Hopkins University, will aim to determine factors influencing *A. aegypti* competence as a vector for dengue and Zika viruses in Cuba; the other, with the University of Kentucky, will be devoted to the use of *Wolbachia* in control of residual populations of *A. aegypti* and *A. albopictus* in Cuba. A final project, with the University of North Carolina at Chapel Hill, will evaluate changes in antibody expression in Cuban individuals after primary dengue infection.

As noted by many leaders since reestablishment of diplomatic relations, health and scientific cooperation can provide a foundation for US–Cuba relationship building. The severity of arboviral diseases' potential outcomes (including for infants and pregnant women, not all of which sequelae are well understood), the increased rapidity with which recent outbreaks have evolved, the anticipated climate-change driven extensions of vector habitats,[10] and the fact that only 90 miles separate Cuba from the USA, make the rapidly emerging threats of Zika, dengue, chikungunya, and other arboviral diseases in the Gulf and Caribbean region fertile ground for collaborative arbovirus research that would broadly benefit public health in both countries. Furthermore, jointly planned, managed and executed infectious disease research can provide a model for other US–Cuba scientific cooperation. As the top infectious disease research institutes in their respective countries, IPK and NIAID remain committed to helping lead the way. Because IPK is a PAHO/WHO collaborating center for dengue and other arboviruses, (and in fact is the dengue lead in the Arbovirus Diagnosis Laboratory Network of the Americas), its experience in research and participation in health strategies for mosquito control are vital to the USA and other countries, complementing CDC's strengths in research and epidemiological surveillance.

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Case Study in International Cooperation: Cuba's Molecular Immunology Center and Roswell Park Cancer Institute

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ABSTRACT

In 1961, the USA severed diplomatic relations with Cuba, and in 1962 an embargo was imposed on trade and financial relations with that country. It was not until five decades later that the USA and Cuba would reestablish relations. This opened the way for the New York State Trade Mission to Cuba in April 2015, during which Cuba's Molecular Immunology Center and Buffalo, New York's Roswell Park Cancer Institute signed a formal agreement that would set in motion biotechnology research collaboration to address one of the most important causes of death in both countries. Significant research from Cuba led to this groundbreaking collaboration. The purpose of this paper is to discuss the development of this cooperation, from the Molecular Immunology Center's initial investigations, through the opening of a phase I clinical trial at Roswell Park Cancer Institute with therapies developed at the Center. This cooperation was responsible for the first clinical trial for CIMAvax-EGF involving advanced-stage non-small cell lung cancer patients in the USA. A license was also approved by the US Department of the Treasury's Office of Foreign Assets Control authorizing a commercial partnership for development of biotechnology products, combining the cancer research efforts of both institutions. This unusual collaboration between Cuba and the USA—the US economic embargo and travel restrictions not withstanding—opens good prospects for expanded medical research between the two countries. While political and logistical challenges remain, the shared mission and dedication of these Cuban and US scientists points the way towards relationships that can lead to development, testing, approval and use of promising new therapies for cancer patients.

KEYWORDS Biotechnology, clinical trials, cancer vaccines, cancer immunotherapy, non-small cell lung cancer, NSCLC, Cuba, USA

INTRODUCTION

Before 1959, the USA and Cuba were active trading partners. In 1961, the US government severed diplomatic relations with Cuba, and a year later declared an economic, trade and financial embargo on the country. It was not until December 17, 2014, that Presidents Barack Obama and Raúl Castro agreed to resume bilateral relations and to reopen embassies in their respective capitals.[1] Years prior to the Obama presidency, the American Association for the Advancement of Science, the New America Foundation and others had supported scientists' travel between Cuba and the USA. Unfortunately, this support was not enough to thaw relations between the two countries.[2]

Renewed relations, however, opened opportunities for growth along multiple pathways for joint efforts in biomedical research and other fields.[3] In April 2015, New York Governor Andrew Cuomo led a state trade mission to Cuba, during which a formal agreement was signed between the Molecular Immunology Center (CIM) in Havana and Buffalo's Roswell Park Cancer Institutes (RPCI), to further develop CIM's cancer vaccines.[4] The formal agreement, based in several years of conversations between the two institutions, paved the way for new medical collaborations with potential benefits for people in both countries and abroad.

IMPORTANCE This collaboration is a unique opportunity to share resources and enhance access to knowledge and technology for both Cuban and US scientists and institutions. Such cooperation can bring forward new, effective therapies derived from biotechnology to benefit cancer patients in the USA, Cuba and internationally.

However, as bilateral contacts between Cuban and US professionals move ahead, the embargo and the travel restrictions remain in place. US regulations permit only certain activities under general or specific license from the US Department of the Treasury's Office of Foreign Assets Control (OFAC), as well as certain categories of US travel to Cuba.[5] Travel by Cubans to the USA has recently become more difficult, due to restrictions imposed by the new administration in Washington,[6] and it remains to be seen what effects these might have on joint scientific and medical research efforts.

DEVELOPMENT OF CUBA'S HEALTH SYSTEM, BIOTECHNOLOGY AND CLINICAL TRIAL CAPABILITIES

Prior to 1959, Cuba's health care facilities were concentrated in the cities. From then on, the country began to implement a new, single health system, free and universally accessible to its population, and 100% publicly funded.[7] In the early 1960s, the Faculty of Medicine was reopened at the University of Havana, and shortly after, medical education was extended to all provinces. Thereafter, the number of physicians, nurses, and other health care workers rapidly increased, expanding access to care throughout the country. By 1970, there were 53 hospitals in rural areas.[8]

The public health budget also provides training to physicians and addresses public health issues, including programs for health promotion and education. Several national programs were developed around maternal–child health, older adult health, sexually transmitted and other infections, as well as chronic conditions and prevention of toxic habits such as smoking and alcohol consumption. Since the early 1980s, primary health care was given a particular boost with the creation of the neighborhood-based family doctor-and-nurse program, complementing multispecialty community polyclinics,

as well as secondary and tertiary care, to improve individual and population health outcomes.[8] Between 1960 and 2010, the transformation of Cuba's health system was accompanied by reductions in infant mortality, low birth weight rates, and infectious and parasitic disease mortality, as well as increases in life expectancy—to the extent that Cuba achieved health indicators similar to and in some cases better than those of the USA.[8]

Before 1959, Cuba relied heavily on imported medicines from other countries such as the United States—the USA being one of the world's largest manufacturers of medicines and medical devices.[3] Once the US embargo was imposed, drugs from the USA could no longer be exported to Cuba. In turn, no Cuban products such as medications, could be purchased from Cuba for US patients. The embargo was tightened twice in the 1990s, both times with international, extraterritorial implications. First, among other things,the Cuban Democracy Act passed by Congress in 1992 prohibited trade by Cuba with subsidiaries of US companies abroad, and then in 1996 the Cuban Liberty and Democratic Solidarity Act threatened to impose penalties on institutions and countries that invested in or partnered with Cuba. These policies had negative impacts on health and US–Cuba cooperation in medicine and medical research.[5,9]

Despite privations due to economic constraints, the Cuban health system has been widely recognized internationally for its practices and outcomes. Unfortunately, isolation from the USA has not allowed Cuban products to compete in the US domestic market or its significant contributions in the fields of medicine and biotechnology to be recognized in the United States. These contributions include effective vaccines against meningitis B and hepatitis B. While licensing agreements were negotiated with major pharmaceutical companies such as Glaxo–Smith–Kline, to explore bringing Cuban biotechnology in North America and Europe, they were never fully implemented.[10]

Government support for health care and medical research remains generous in Cuba. Health care was a major countrywide priority under then-President Fidel Castro, who also placed great emphasis on research and knowledge development. This is reflected in the fact that Cuba started biotech research and production as early as 1982. The world's first biotech company (Genentech) opened in the USA in 1976; Cuba's Center for Biological Research, producing both natural and recombinant interferons, opened in January 1982. While there were financial constraints, science was valued enough to receive the needed funds to stay current as biotechnology research expanded worldwide.

Today, Cuba's globally recognized BioCubaFarma Enterprise Group consists of 31 enterprises and 8 commercial companies with over 20,000 employees and 62 manufacturing facilities. BioCubaFarma enterprises produce 525 of the 849 medicines included in the Essential Drugs List of Cuba's Ministry of Public Health, has been granted over 800 sanitary registrations abroad and exports to 48 countries.[11]

Given its experience in biotechnology and drug development, Cuba is well equipped to participate in clinical trials within the FDA regulatory framework. In 2007, Cuba's National Clinical Trial Registry went live and four years later became the first WHO-accredited primary registry in the region. Cuban clinical trials adhere to international good clinical practice standards. Cuba completed 150 clinical trials between 1992 and May 2016, with increased approval of study protocols since 1996. Their first large-scale multicenter clinical trial was begun in 1996, involving 52 hospitals in testing recombinant streptokinase for treatment of acute myocardial infarction. After successful completion, the Cuban-developed drug was registered and is now sold in over 25 countries. As of May 2016, Cuba was conducting 30 clinical trials abroad in 18 countries.[12]

Bilateral cooperation in cancer research: the work of US and Cuban institutions *RPCI* was founded in 1898 under the vision of Dr Roswell Park. Dr Park, a practicing surgeon, held the view that cancer would become a leading cause of death, and thus was intent upon making RPCI the first institution in the world that focused entirely on cancer and cancer research. He believed in translational research as a means to bridge basic laboratory science, clinical cancer research and patient–population health.[13]

With the help of Dr Edward Butler, a grant was proposed to develop the first cancer research laboratory, originally called the New York State Pathological Laboratory of the University of Buffalo, the embryo of RPCI. In 1974, RPCI became the first NCI-designated comprehensive cancer center. It also received accreditation through the Joint Commission on Accreditation of Healthcare Organizations and became a member of the National Comprehensive Cancer Network. With this affiliation, RPCI gained the ability to deliver the most promising, cutting-edge therapies through collaborations with other institutes around the USA.[13]

CIM was founded in Havana in January 1991 and its present venue inaugurated in 1994. The founding group had been working on cancer immunology since 1979 at the Cuban National Institute of Oncology and Radiobiology. Research on the role of epidermal growth factor (EGF) in cancer started in 1981, and Cuban authors published their first paper worldwide describing the presence of EGF receptors in human breast cancer in 1984.[14] CIM now operates four manufacturing facilities and has >1100 employees. It exports products to over 30 countries and has filed 750 patents abroad, including in the USA. CIM researchers have produced over 500 peer-reviewed scientific papers. In 1995, clinical trials began in Cuba to study CIM-developed CIMAvax-EGF, a cancer vaccine designed primarily for advanced stage non-small cell lung cancer (NSCLC) patients.[15] This vaccine targets the EGF that can drive growth of NSCLC and other cancers. After trials were completed successfully and CIMAvax-EGF was approved and registered by the Cuban regulatory authority, it has become available to Cuban patients in the public health system since 2011.[16] This novel vaccine led the way for collaboration between CIM and RPCI.

Development of CIMAvax-EGF Vaccine The first phase I/II open-label trial was conducted at the Medical–Surgical Research Center in Havana in 1995, involving ten patients with malignant tumors at various locations. The vaccine was further developed for NSCLC therapy, since a response due to overexpression of the EGF receptor (EGFR) was seen in primary NSCLC tumors.[17]

CIMAvax-EGF vaccine induces antibodies against EGF. Through EGF immune deprivation, the immune system is able to decrease circulating EGF and prevent binding of the ligand to EGFR, the

EGF receptor. In turn, this disrupts proliferation of cancer cells. After vaccination, studies have shown inverse correlation between circulating EGF and antibody response.[16]

Currently, the vaccine has been tested in more than 5000 advanced NSCLC patients and has proven to be safe. During phase II studies, the vaccine was administered after first-line platinum-based doublet chemotherapy. The studies showed the vaccine was safe and produced anti-EGF antibodies. Patients that received the vaccine also showed a trend to increased survival, with those who reached an antibody response of ≥4000 showing better survival.[17,18]

A phase III randomized trial evaluated the vaccine with best supportive care vs. best supportive care alone. This trial included all patients who had achieved stable disease, partial or complete response upon receiving first-line platinum-based doublet chemotherapy. The study included 270 participants in the vaccine group and 135 participants in the best supportive care group (control). Most common adverse events included mild or moderate injection site reactions along with fever, headache, malaise, chills and vomiting. The vaccine increased overall survival in the study population: average survival was 10.8 months for the vaccinated group vs. 8.9 months for the control group. The vaccinated group also showed a 5-year survival rate of 14.4% vs. 7.9% for controls. In the vaccine group (patients completing 4 vaccine doses) the median survival time was 12.4 months (95% CI, 10.42–14.45) vs. 9.4 months (95% CI, 7.53–11.33) in the control group (composed of patients surviving for at least 6 weeks). Five-year survival was 16.6% for patients who received 4 vaccine doses versus 6.2% for unvaccinated patients.[19]

Prolonged use of the vaccine was found to be safe in NSCLC patients. Repeated vaccinations were shown necessary to maintain low levels of circulating EGF and a high anti-EGF antibody response. Patients with high EGF serum levels at baseline had better survival (14.7 months) than unvaccinated patients with similar EGF serum concentrations (8.6 months). Interestingly, 5-year survival was 23% for vaccinated patients with high EGF serum levels at baseline whereas no patients in the control group were alive by that time.[19,20]

After completion of the phase III trial, a phase IV trial began to evaluate administration of the vaccine in a primary care setting. Vaccine safety was reconfirmed, and the primary care setting allowed for better access to the vaccine and increased compliance with administration. Clinical trials are now running to confirm EGF as a predictive biomarker for the vaccine's efficacy.[20]

Cancer research collaboration: external conditions, motivation, process, results New collaboration between the USA and Cuba facilitated sharing resources that otherwise would not have been available to institutions in countries that were previously isolated from each other. While there is always room for mutual learning, working together more often creates new knowledge that can benefit both countries' populations.

Additionally, Cuba's closed-loop approach to medical research closely aligns with Roswell Park's mission. That is, rather than focusing on scientific results alone, both have adopted the approach that their medical investigations should bring results that translate into development and manufacture of new products that meet population health needs. Success in exporting these new products closes the loop, providing a monetary incentive and sense of responsibility to continue research. This closed-loop approach, already in place in Cuba, motivates scientists to develop more innovative and advanced products.[21]

In 2011, scientists from CIM visited RPCI, taking the first steps toward collaboration in drug development. After many discussions at international conferences, it took two years for an agreement to be drafted providing for CIM's cancer vaccines, including CIMAvax-EGF, to be tested in US patients at RPCI. This was the start of a collaboration that holds the promise of bringing these novel therapies to US physicians and their patients.

In 2013, RPCI received an OFAC license for clinical trials in the USA of two CIM cancer vaccines and three of its immunomodulatory drugs. Within months, the necessary protocols and legal agreements were under development between CIM and RPCI. During New York state's trade mission to Cuba in April 2015, RPCI and CIM signed the formal agreement to work together and agreed upon the importance of such collaboration across borders to further test CIM vaccines. A year later, an investigational new drug application to the US FDA was approved for the first phase I trial of CIMAvax-EGF with the checkpoint inhibitor, nivolumab (Opdivo), in patients with late-stage, advanced NSCLC.

Bilateral collaboration in clinical trials RPCI opened the first clinical trial testing the CIMAvax-EGF vaccine combined with nivolumab in late 2016. The estimated enrollment for this phase I/II trial is 136 participants. Currently the estimated study completion date is June 2021. The trial's primary objectives are to evaluate the safety of the combination of the vaccine and nivolumab, determine overall survival, and assess antibody titers and EGF levels.[22]

Thousands of requests from around the world were received to participate in the trial. An inquiry form was issued by RPCI to determine eligibility for enrollment. Questions included were, among others, the patient's diagnosis, prior therapies and willingness to participate in the trial. If the patient seemed eligible according to basic disease characteristics and history of treatment, they were individually contacted about possible enrollment. A total of 959 potentially eligible participants, families, friends, health care providers and caregivers were given detailed information about the trial between October 2016 and November 2017. Inquires came from 47 US states and over 48 countries. More than half were from family members and over a quarter were self-referrals.

While eligibility and the number of patients who can enroll in a clinical trial remain tightly controlled, the cancer community has shown interest in the new therapies available through the RPCI–CIM collaboration. RPCI expects the same positive feedback from the community when the next US clinical trial opens with another therapy developed at CIM, nimotuzumab, a monoclonal antibody that recognizes EGFR, approved since 2005 for use in Cuba's National Health System.[12] Thus, the opening of the phase I/II CIMAvax-EGF vaccine clinical trial at Roswell Park is only the beginning, and should lead to FDA approval for future general use and sale of such products developed in Cuba.

ANALYSIS: OPPORTUNITIES AND CHALLENGES

The thaw in relations between the USA and Cuba during the Obama administration expanded opportunities for researchers to network and form collaborations, but those opportunities are limited and subject to reversal.

In October 2016, an executive order by President Obama prompted OFAC regulatory changes that enable engagement with Cuba on joint medical research projects—both commercial and noncommercial—under general license. These include the opportunity to obtain approval from the FDA for pharmaceuticals originating and developed in Cuba. The general license also allows US grants to be awarded to Cuban nationals engaging in scientific research.[23,24]

While a specific OFAC license has been issued for the collaboration between RPCI and CIM, political hurdles remain. Under OFAC policy, the license provides approval for only preclinical and clinical research using products developed in Cuba. While OFAC regulations under the Obama presidency opened the way for Cuban-origin products to go through the entire regulatory process, receive approval if safe and effective, and be marketed, it is unclear as of this writing if this ruling will hold up in the current climate—a clear disincentive for US companies to invest in trials or become involved in such collaborations, no matter how potentially beneficial to US patients.[24]

Such uncertainties plague the future of US–Cuba collaboration in cancer research under the change in US administration. While under the Obama administration, the two countries were able to advance in establishing scientific links, it is uncertain whether the Trump administration will go along the same lines or will erect barriers to those ties.

However, even in these circumstances, joint efforts by CIM and RPCI bring new hope to lung cancer patients by offering them the results of efforts to obtain new and more effective therapies. The OFAC license for CIM's and RPCI's joint work paves the way for other academic institutions and companies to engage in bilateral collaboration to develop new therapies, also needed to limit or eliminate toxicity currently seen with other cancer treatments. These new agents may also lead to more cost-effective care for cancer patients and for those suffering other life-threatening diseases.

Because of this multiyear effort, greater collaboration in research is also expected to accelerate development of new agents, both those developed at CIM and at RPCI, with the goal of benefiting patients with cancer in both countries. These hold the promise of obtaining therapies that would not otherwise be available to US patients, and future discoveries will benefit from cooperation, each partner providing assistance to the other to complement areas of strength and fill the gaps in each other's knowledge. In the best interests of both countries and populations, these new channels of collaboration should be preserved.

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Cuba's Scientific Contributions to Global Polio Eradication

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ABSTRACT

Cuba eliminated polio in 1962 and was among the first countries to do so. Since then, only 20 cases of vaccine-derived paralytic poliomyelitis have been reported. Because Cuba used oral poliovirus vaccine exclusively in two mass campaigns usually in February and April each year, Sabin viruses were detected only within approximately 6–8 weeks after each annual campaign. This made Cuba a very attractive site to study the epidemiology of poliomyelitis in a tropical country without risk of secondary transmission of Sabin viruses for a large part of each year, an advantage over countries that used oral poliovirus vaccine continuously throughout the year in routine immunization programs. This report summarizes the unique scientific collaboration between Cuba's Ministry of Public Health and WHO, with participation by US scientists, in the global effort to eradicate polio.

KEYWORDS Poliomyelitis, disease eradication, disease elimination, oral poliovirus vaccine, Sabin vaccine, inactivated poliovirus vaccine, Salk vaccine, Cuba, WHO

INTRODUCTION

In 1988, when the World Health Assembly resolved to eradicate poliomyelitis by the year 2000,[1] Cuba had achieved elimination over 25 years earlier and managed to remain polio free despite substantial travel by its population to polio-endemic countries. Two mass vaccination campaigns conducted in 1962, achieved very high coverage and eliminated wild poliovirus from Cuba.[2] In 1994, the entire Western Hemisphere was certified as polio free by PAHO's International Commission for the Certification of Eradication of Poliomyelitis.[3]

The rest of the world started to institute sensitive surveillance for acute flaccid paralysis, a clinical presentation that includes paralytic poliomyelitis, and started to plan for mass-campaign use of oral poliovirus vaccine (OPV) for eradication. Cuba and its Ministry of Public Health (MINSAP) expressed their willingness to contribute to these efforts by cooperating in expanding the scientific foundation for polio eradication and implementing related clinical trials and other evaluations.

Cuba already had an excellent health infrastructure for conducting scientific research, including clinical trials. Principal investigators, including the heads of the national poliovirus laboratory housed in the Pedro Kourí Tropical Medicine Institute (IPK), participated in such studies. IPK and its Ethics Committee reviewed and approved the clinical trials; while the Center for State Control of Medicines and Medical Devices approved vaccines for use in the studies, as well as study protocols. All trials were also approved by WHO's Ethics Review Board and the National Expanded Program on Immunization was also engaged. More recently, MINSAP established a field site for clinical trials with vaccines in Camagüey Province, in eastern Cuba. Thus, with MINSAP and Cuban government support, the necessary infrastructure was put in place for studies and clinical research jointly prioritized by MINSAP and WHO.

IMPORTANCE Collaboration between Cuba and WHO has been vital for the Global Polio Eradication Initiative. Cuban research findings over two decades have influenced global policy decision-making and made it possible to design innovative strategies for polio eradication.

This report summarizes the WHO–Cuban polio research collaboration, from the first scientific study concerning poliovirus eradication (1994) to the present. Many other studies that are part of this joint effort have been published previously.[4–16]

SCIENTIFIC PROJECTS

Cuba's part in the continuing collaboration with WHO has focused on issues relevant to policymaking for the ongoing global polio eradication effort. It has concentrated particularly on looking for answers to scientific questions that could not be answered elsewhere, taking into account Cuba's unique OPV vaccination program, carried out only twice annually, usually in February and April. Specifically, research has addressed several aspects of OPV and inactivated poliovirus vaccine (IPV), such as immunogenicity, adverse reactions and complications, persistence of Sabin virus in populations, the immunogenicity schedule and its affordability, number of doses needed, evaluation of new vaccines and devices, and booster response.

Studies completed and published *OPV immunogenicity* This study evaluated the seroprevalence of serotype-specific polio antibodies following 2, 4, and 6 OPV doses in Cuba. Results confirmed that 3 OPV doses were not sufficient to achieve high seroprevalence against all three serotypes in Cuba. This suggested that in other tropical zones, additional doses would be needed to ensure high population immunity.[4]

Assessment of intussusception risk after OPV This study was designed to address a concern that OPV could cause intussusception, which was found to be a problem with the first licensed rotavirus vaccine in the USA. No increased risk of intussusception after OPV vaccination was observed among Cuban infants,[5] alleviating concerns raised globally.

Vaccine-associated paralytic poliomyelitis (VAPP) In this study all cases of reported acute flaccid paralysis between 1963 and 2006 were analyzed to determine if they were associated with vaccine administration, after interruption of wild poliovirus circulation had been achieved in 1962. The study showed that VAPP risk was not elevated and was comparable to that reported in other countries.[6]

Sabin virus persistence in populations and the environment after mass OPV campaigns A series of studies attempted to characterize persistence of circulating Sabin virus after mass

vaccination campaigns, using stool surveys, seroprevalence surveys and environmental sampling. Collectively, results demonstrated limited persistence, approximately 2–3 months, following a mass OPV campaign.[7,8] Finding such limited circulation, even in a tropical developing country, helped influence endgame policy development for WHO's global eradication program.[17]

IPV schedule immunogenicity This clinical trial assessed immunogenicity of a 2-dose IPV schedule (at 2 and 4 months) versus a 3-dose schedule (at 6, 10 and 14 weeks). Both schedules provided similar seroconversion rates, >80% for all three poliovirus serotypes. This study,[9] and one in Puerto Rico[18] demonstrated that immunogenicity of early IPV administration are greatly reduced by maternally derived antibody. Because the study included an unvaccinated control group, it was able to assess the contribution of two- and three-dose IPV schedules on limiting poliovirus excretion after a trivalent OPV challenge dose, compared with the unvaccinated control arm. The results demonstrated no differences between groups in excretion prevalence seven days after challenge, confirming early reports from higher-income countries. However, the IPV group's virus titer was approximately 0.5 log10 lower than that of the control group.[9] The findings were subsequently confirmed in other studies in developing countries,[19–21] which demonstrated IPV does not induce mucosal immunity per se, but may accelerate development of such immunity, in line with other studies showing that IPV-vaccinated subjects excrete for shorter periods than nonvaccinated individuals.[22,23]

Affordable IPV This study, in conjunction with another in Oman,[24] evaluated the immunogenicity of fractional-dose IPV administered intradermally by needle-free jet injector (Biojector 2000). A fractional dose contains only one fifth of the IPV antigen contained in a full dose, enabling limited supplies to go farther. The study once more confirmed low immunogenicity of IPV when given in an early schedule (at 6, 10, and 14 weeks of age), suggesting maternally derived antibody interference with vaccine immune responses, highlighted by the large difference in immunogenicity between the fractional-dose group and the full-dose control group in this early schedule.[10] Nevertheless, it demonstrated feasibility of using needle-free jet injectors to administer IPV, and suggested that optimal immunogenicity may be achieved by starting IPV later in life and allowing a longer interval between doses.

Priming after IPV This clinical trial was an outcome of the previous study and addressed two questions. First, if the schedule starts later (here at four months) and the interval between doses is longer (here also four months) can the immunogenicity of a fractional- or a full-dose schedule be improved? Second, what does a single dose do in terms of immune response, defined as seroconversion and priming? The study demonstrated that 2 doses can seroconvert >90% of vaccinees to all 3 serotypes with a 4- and 8-month schedule. In addition, it elucidated for the first time the relative contribution of priming following a first dose of IPV. Although seroconversion to poliovirus type 2 was 47% and 63% following a fractional dose or full dose, respectively, of IPV, >90% of vaccinees that did not seroconvert, responded with a priming immune response.[11] This study was instrumental in development of recommendations for a single dose of IPV following withdrawal of Sabin poliovirus type 2 from trivalent OPV and for an immunization schedule using two fractional doses. Subsequently, IPV priming was confirmed by studies in Bangladesh and in several Latin American countries.[18,19,25]

Devices for intradermal administration of fractional-dose IPV Several devices were evaluated to facilitate intradermal administration of fractional-dose IPV, including jet injectors: Biojector 2000 (Bioject, USA), Bioject ID Pen (Bioject, USA), Tropis (Pharmajet, USA). These studies compared devices' usability and ability to induce immune response with administration by BCG needle and syringe, and full-dose IPV administered intramuscularly. Three dimensions were assessed: immune response indicated by seroconversion or by increase in antibody titers; quality of injection (bleb formation, liquid leaking); and vaccinators' and parents' preferences for administration method. These evaluations demonstrated that, with one exception, ability to induce immune response with the devices was comparable to that using BCG needle and syringe administration. There was no clear association between immune response and bleb size or quantity of liquid leaking from dermal injection sites. Ergonomic assessment stimulated further engineering improvements of at least one device.[12,13] As reported previously, health care providers and parents preferred needle-free devices by an overwhelming majority.[13,24]

New vaccine evaluation (IPV produced from Sabin strains) This study evaluated immunogenicity and reactogenicity of two formulations of Sabin IPV, a plain and an adjuvanted vaccine, with conventional Salk IPV as a control. Between 90% and 100% of subjects responded with either seroconversion or a 4-fold boosting of antibody titers. No serious adverse events were reported during the six-month followup period.[14] A followup study evaluated antibody decay 21–22 months after initial vaccination and reported that it was similar in all 3 study groups.[15] These studies provided further confidence in Sabin IPV development efforts.

Booster response following fractional-dose IPV This study was designed to demonstrate noninferiority of fractional-dose compared with full-dose IPV. There were no significant differences in booster response 7, 28 and 56 days after a first or second dose vaccination. The study concluded that fractional-dose IPV induced a booster immune response similar to that of full-dose IPV, and that fractional-dose IPV could stretch available supplies when needed in an outbreak response situation.[16] The earlier fractional-dose study[11] and followup studies provided the scientific basis for recommending a fractional-dose IPV schedule.[26,27]

Studies in progress Several studies and evaluations are continuing and are expected to yield important new findings to further guide policy decision-making for the Global Polio Eradication Initiative. These studies will help clarify the role of IPV in mucosal immunity and provide information on intramuscular fractional-dose IPV, specifically:

- mucosal immunity following IPV,
- cross-immunity following bivalent OPV and IPV versus IPV alone,
- disappearance of poliovirus type 2 in sewage after the switch from trivalent to bivalent OPV,

- intramuscular fractional-dose IPV given at 4 and 8 months, and
- pilot introduction of one needle-free device to administer fractional-dose IPV. This pilot will help guide policy decisions for such devices, especially in Cuba.

LOOKING FORWARD

Cuba has proven a useful resource and partner for polio eradication, acting as an incubator for testing new ideas and approaches. The WHO–Cuban collaboration, lasting for over 20 years, has been vital for the Global Polio Eradication Initiative, making it possible to design innovative strategies, especially for the polio eradication endgame[17] and for immunization policy development worldwide.[28] Collectively, MINSAP and the global community need to ensure that this resource, including associated infrastructure, is protected, in order to be able to conduct clinical trials that meet and surpass the highest ethical and scientific standards.

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Seeking Biomarkers of Early Childhood Malnutrition's Long-term Effects

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ABSTRACT

Protein–energy malnutrition affects one in nine people worldwide and is most prevalent among children aged less than five years in low-income countries. Early childhood malnutrition can have damaging neurodevelopmental effects, with significant increases in cognitive, neurological and mental health problems over the lifespan, outcomes which can also extend to the next generation. This article describes a research collaboration involving scientists from five centers in Barbados, China, Cuba and the USA. It builds on longer-term joint work between the Barbados Nutrition Study (which, over a 45-year span, has extensively documented nutritional, health, behavioral, social and economic outcomes of individuals who experienced protein–energy malnutrition in the first year of life and healthy controls from the same classrooms and neighborhoods) and the Cuban Neuroscience Center (which has developed low-cost brain imaging methods that can be readily used in low income settings to identify biomarkers for early detection and treatment of adverse consequences of childhood malnutrition).

This collaboration, which involved Barbadian, Cuban and US scientists began in the 1970s, when quantitative EEG techniques were applied to EEG data collected in 1977–78, at which time study participants were aged 5–11 years. These EEG records were never fully analyzed but were stored in New York and made available to this project in 2016. These data have now been processed and analyzed, comparing EEG findings in previously malnourished and control children, and have led to the identification of early biomarkers of long-term effects of early childhood protein–energy malnutrition. The next stage of the project will involve extending earlier work by collecting EEG recordings in the same individuals at ages 45–51 years, 40 years later, and comparing findings to earlier data and to these individuals' behavioral and cognitive outcomes. Quantitative EEG biomarkers of the effects of protein–energy malnutrition may help identify children at greatest risk for early malnutrition's adverse neurodevelopmental effects and inform development of targeted interventions to mitigate the long-term adverse effects of protein–energy malnutrition in developing countries.

KEYWORDS Protein–energy malnutrition, electroencephalography, EEG, biomarkers, neurosciences, Barbados, Cuba, USA

INTRODUCTION

Protein–energy malnutrition (PEM) is caused by insufficient protein and calorie consumption, resulting in impaired protein synthesis. Its most severe clinical forms are marasmus and kwashiorkor. Marasmus is characterized by markedly low weight for age, dehydration, chronic diarrhea and stomach shrinkage. Kwashiorkor is characterized by fluid retention, extended abdomen, irritability, and failure to grow and gain weight.[1]

Globally, malnutrition continues to impact large numbers of children aged less than five years in low-resource settings. While low weight-for-age levels have been reduced to 22.9% over the past decade, 155 million children aged <5 years have low stature for age, and 52 million have low weight for age, with more than half of these children living in South Asia.[2] PEM not only causes physical and metabolic changes, it also causes long-term cognitive and behavioral problems that can persist over the lifespan and across generations. Thus, it is important to study its effects on the central nervous system using the latest technologies and to develop targeted interventions that can reverse or reduce these adverse consequences.

IMPORTANCE This 45-year study—ongoing—was made possible by collaboration among Barbadian, Cuban and US scientists. It is the first to use quantitative EEG to assess early childhood malnutrition's long-term neurocognitive effects and identify biomarkers of increased risk for related sequelae, supporting improved targeting of preventive efforts. Since EEG is relatively inexpensive and available, this is particularly promising for developing countries.

PROBLEM AND SCOPE

For more than four decades, the Barbados Nutrition Study (BNS) has followed individuals who suffered from PEM in their first year of life and a control group matched by age, sex and handedness, to examine the consequences of infant PEM for health status, cognition and behavior over the lifespan.[3–5] Malnutrition studies, including BNS, suggest that early childhood malnutrition can have lifelong impacts, even affecting subsequent generations.[6–9] Improved public health measures have helped increase the number of childhood survivors of PEM, but resulting health, cognitive and behavioral problems often persist. For example, diabetes and attention deficit disorders are four times more common in people who suffered from malnutrition as infants.[6]

Early biomarker identification of children at greater risk of impaired health, cognition and behavior following PEM can facilitate effectiveness of interventions to prevent such adverse outcomes. While two modern neuroimaging techniques—MRI and positron emission tomography—can be employed, both are costly and not easily attained in countries with limited economic resources.[10] In contrast, EEG is a portable, noninvasive and relatively inexpensive technique that can potentially be used for this purpose.

Quantitative EEG (qEEG) is based on the spectrum of signals obtained from electrodes placed on the scalp and may detect abnormalities by comparing signals from the EEG logarithmic spectrum to reference data, through statistical parametric mapping, using covariates such as age.[11] The development of electrophysiological source imaging allows for a tomographic version of the qEEG with good tridimensional resolution. The Cuban Neuroscience Center (CNEURO) has developed hardware and software to advance qEEG use in a wide range of settings.[12]

COLLABORATION

This paper describes a collaboration that began in 2016 to identify brain biomarkers of early childhood malnutrition and their association with impaired cognitive and behavioral outcomes. Scientific partners in this research effort are CNEURO, the Chester M. Pierce MD Division of Global Psychiatry at the Massachusetts General Hospital (MGH), the Center on the Developing Child at Harvard University, the Barbados Nutrition Study, and the Joint China–Cuba Lab of the University of Electronic Science and Technology of China.

Objectives The main purpose of the current study is to identify neural markers of early childhood malnutrition using qEEG and to apply a model of disease progression or accumulated risk of brain damage to test qEEG predictive capacity. Using archival BNS data, our model will include data on several childhood adversities that commonly co-occur—malnutrition, poverty, maternal depression and child maltreatment. We will also collect qEEG data in BNS study participants who are now aged 45–51 years and will compare these findings with qEEG data from 1977–78, when participants were aged 5–11 years. Cuban MEDICID neurometric equipment will be utilized in Barbados for this purpose.

Our research to date has identified two candidate biomarkers: increased delta and theta activity and decreased alpha-wave on EEG, an electrophysiological pattern we observed in children with histories of PEM but not in controls with healthy neurodevelopment. These EEG findings contribute to an analytical framework that includes measures of clinical, cognitive and behavioral outcomes assessed in childhood and subsequently over a span of four decades in the same cohort. In order to refine neural markers identified by qEEG and deepen our understanding of childhood malnutrition's long-term effects**,** we also plan to incorporate MRI to detect structural brain changes and near-infrared spectroscopy to gain additional information about brain function and dynamics.

Lastly, the project includes plans to use qEEG in other low resource settings where our research team has established collaborations.

JUSTIFICATION

This collaboration began in the early 1970's with BNS and members of the New York University Brain Lab, led by Professor E. Roy John. Lab members, including Drs Pedro Valdés Sosa, Leslie Prichep and others, published an article on computer-assisted neurometrics in *Science* in 1977[13] and a subsequent *Science* report [14] using BNS control-group data from 1977–78. However, a comparison of these data in both PEM and control groups has not yet been published.

Janina R. Galler cofounded the BNS (with Sir Frank C. Ramsey) and has studied its participants (some of whom are now in their sixth decade) and their 2nd- and 3rd-generation offspring continuously since the early 1970's. Her link with Cuba dates to 1973 when her collaboration with Prof. John began. From 1976, Dr Galler served as a UNDP advisor to the Cuban Ministry of Public Health, and in 1985, she was a keynote speaker at the first Pan American Pediatric Congress in Havana. More recently, CNEURO and BNS have come together in a joint mission to enable improved multidisciplinary nutrition studies in the Caribbean (centered in Barbados and Cuba) and pave the way for similar studies elsewhere in the Americas and in Africa, with potential benefits for population and health strategies. CNEURO will be setting up a qEEG laboratory in BNS over the next several months to further these efforts.

PARTICIPANTS

Participating institutions in the initiative are CNEURO, BNS, MGH, Harvard University's Center on the Developing Child, and the Joint China–Cuba Lab for Frontiers Research in Translational Neurotechnology at the University of Electronic Science and Technology of China.

BNS This study was established to document the effects of early childhood malnutrition in Barbadian children born between 1967 and 1973, when severe malnutrition was a major public health problem on the island (no longer the case). In 1977, the BNS selected 129 children with clinically diagnosed moderate to severe marasmus (PEM marasmus group) who were aged 3 months to 1 year and met the following inclusion criteria: birth weight >2500 g, no pre- or postnatal complications, no brain injuries, and Apgar score >8.[3–5] The children were included in a national intervention program that followed all malnourished children in Barbados from birth to age 12 years and provided routine medical care, subsidized food, home visitation, nutrition education for their primary caretakers and twice-weekly preschool education.[15] None of the children in the PEM group experienced a further episode of malnutrition.

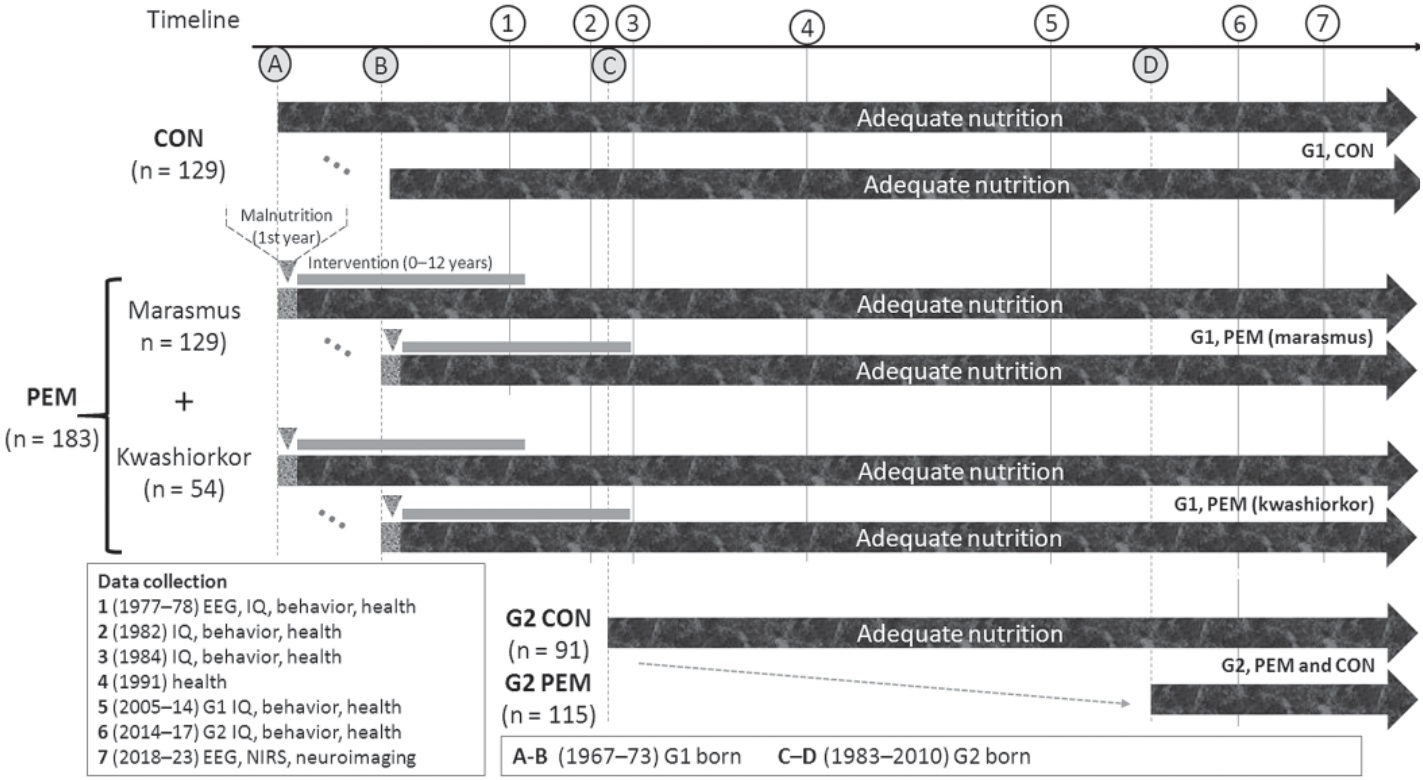
For each child in the PEM (marasmus) group, the study recruited a classmate of the same age, sex and handedness who met the same inclusion criteria but did not have a history of malnutrition (control group). In 1984, a third group of children with documented kwashiorkor during the first year of life was incorporated into the study (PEM kwashiorkor group).

Over the past 45 years, the BNS has collected medical, epigenetic, neuropsychological, behavioral, academic performance and social data.[3–9] Since 1973, systematic followup has been conducted on all study participants (generation 1), their parents (generation 0), and their immediate descendants (generation 2).[16] Household standard of living, maternal depression, child maltreatment and other adverse conditions were also documented.[17,18]

BNS has continued to actively study 56% of the original group of participants recruited in 1973–76, and 75% of eligible participants who still reside in Barbados have been in seven waves of data collection over 45–51 years. Currently 206 immediate descendants of the original cohort (now aged 6–30 years) are being studied. This research has been supplemented with multidisciplinary studies in animal models of protein–energy malnutrition.[19] For these reasons, BNS is a unique longitudinal study of individuals with histories of early childhood malnutrition. For a detailed description of the several waves of data collection see Figure 1.

Between 1977 and 1978, EEGs were recorded in participants from control and PEM (marasmus) groups, but only results from the controls were published as part of a normative, cross-cultural study of childhood qEEG. The effects of early malnutrition on qEEG from this study have not yet been

Figure 1: Barbados Nutrition Study data collection waves



CON: controls G1: generation 1 G2: generation 2 NIRS: near-infrared spectroscopy PEM: protein–energy malnutrition

published, nor has the possibility of identifying biomarkers been fully explored.

MGH The original and largest teaching hospital of Harvard Medical School, MGH is considered one of the top five hospitals in the USA. The Chester M. Pierce MD Division of Global Psychiatry is one of the first US programs for global mental health and serves as a site for global mental health expertise and a source of collaboration in international efforts aimed at reducing the global burden of mental illness.

Center on the Developing Child at Harvard University The Center focuses on the development of children who have experienced adverse conditions early in life. Its areas of work are childhood nutrition, global health, early toxic stress, and brain development. The Center seeks transformational improvements in lifelong learning, behavior and both physical and mental health among children facing adversity.

CNEURO Valdés-Sosa and other founders of CNEURO were the first in Cuba to conduct computer-assisted assessment of brain disorders, using a computer donated by US scientists in 1969. By 1970, they developed the first Cuban computer for EEG analysis. In the early 1990s, Cuba was the first country to systematically introduce qEEG into its public health system.[20] Few research centers in the world have been as influential as CNEURO in quantitative analysis of electrical activity in the brain.[21,22]

In Cuba, CNEURO coordinates the neuroscience programs of the Ministry of Science, Technology and the Environment, which includes other research centers, universities (including the two with which the Cuban authors of this paper are associated), hospitals and health centers. This leadership extends beyond Cuba to other parts of the Caribbean, Latin America and Asia.[23] CNEURO has developed successful national programs for hierarchical screening in Cuba and Ecuador to identify and treat problems related to brain functioning.[10]

Joint China–Cuba Lab for Frontier Research in Translational Neurotechnology Currently PAVS directs the laboratory at the University of Electronic Science and Technology of China, which has developed program packets for preprocessing and analysis of EEG data obtained from BNS (both control and PEM groups) in 1977–78. The lab continues to develop qEEG tomographic tools for this purpose.

Financing The collaboration's initial activities were financed by participating institutions, as detailed in memoranda of understanding. Subsequently, the Nestlé Foundation for the Study of Problems of Nutrition in the World, headquartered in Lausanne, Switzerland, provided funding. NIH funding supports the ongoing BNS intergenerational study of childhood malnutrition, which includes collection of epigenetic, health, neuropsychological and behavioral data.

ACTIVITIES

The aims of this new collaborative study are to collect EEG data in adults aged 45–51 years who were tested 45 years earlier (1977 –1978) and to confirm the predictive value of the qEEG for malnutrition effects over the lifespan and across

generations by identifying biomarkers, a unique opportunity provided by BNS.

Table 1 summarizes the initiative's main activities. Activities 1–4 are nearly complete. Activities 5–7 are ongoing and will be partially financed by a grant from the Nestlé Foundation.

Recognizing that childhood malnutrition occurs in the context of poverty and other adversities, we propose to employ a model of progressive brain damage that could reveal the independent and combined effects of accumulated risk from exposure to a variety of childhood adversities, including malnutrition, poverty, maternal depression and child maltreatment. Finally, comparisons of EEG data collected four decades ago in childhood with more recent adult data in the same cohort will facilitate identification of neural markers of early childhood malnutrition and its long-term and intergenerational effects on brain, cognition and behavior.

Estimates of power spectral density at frequencies between 0.78 Hz and 19.14 Hz, with a 0.39 Hz frequency-step, as part of quantitative analysis were applied to the preprocessed information. Statistical analysis, was conducted, correcting for multiple comparisons using permutations. Significant differences were found between groups, using ANCOVA specific to the channel and frequency curve (19·48), according to regression by age. Differences were demonstrated between EEG data of PEM and control participants, which can predict functional differences between PEM and control participants. In this first analysis of qEEG, biomarkers are present as bands in the low frequencies (delta and theta) of the EEG and are specific to the group that experienced PEM in the first year of life.

The current study will recruit a subgroup of original research participants (50 PEM and 50 controls) to undergo repeat testing, including EEGs, at ages 45–51 years. BNS has proven experience in recruiting and tracking participants, and in performing behavioral, cognitive and health assessments. CNEURO staff has vast experience in field work, EEG recordings, and analysis of electrophysiological data, which will facilitate our goal of identifying neural biomarkers of early malnutrition.

As part of this collaboration, 137 EEG records (54 PEM and 83 controls) were located out of a total of 258 (129 PEM and 129 controls) obtained in 1977–1978 in Barbados. Following review by two specialists (who recommended discarding records with evidence of sleep during testing), a total of 108 valid EEG records (46 PEM and 62 controls) remained, with 19 derivations from the 10–20 international system, sampled at 100 Hz. EEG data were preprocessed to automatically reduce electromyographic and electrooculograpic artifacts, using independent component analysis.

Articles describing new findings and newly identified biomarkers will be published at all stages of this initiative to facilitate development of targeted interventions for children suffering from early childhood malnutrition. The first article is being prepared for submission in 2018.

Ethics Written informed consent was provided by all BNS participants under the oversight of the MGH IRB (IRB Protocol 2015P000329/MGH). All BNS research was approved by the Barbados Ministry of Health. MGH participants were compensated for travel and time taken off from work. Future data collection and research will follow similar ethical guidelines, as established by the Declaration of Helsinki and International Committee of Medical Journal Editors guidelines.[24,25]

RESULTS AND BENEFITS

A report on the results of analyses of childhood EEGs from 1977–78 is currently in preparation. Software packages have been used to prepare qEEG data for preprocessing and analysis. A model of disease progression or accumulated risk of brain damage is being developed to identify the mechanisms whereby PEM during the first year of life may affect neurodevelopment and impair cognition and behavior over the life span and across generations.

During the project, participating centers will benefit from training in electrophysiological methodologies, field methods, longitudinal data collection, and technology transfer and staff training. As translational research, it will ultimately benefit public health systems where the findings obtained here are applied.

Table 1: Barbados Nutrition Study collaborative activities, 2017 forward

Activity	Year	Location	Products/Comments
1. Locate and transfer 1977–78 childhood EEG recordings	2017	USA	EEG database (raw)
2. Recover EEG data: change format, preprocessing, preliminary analyses	2017	Cuba, China	EEG (preprocessed) database, MATLAB programs
3. Statistical analyses comparing PEM and CON using qEEG, search for biomarkers	2017	Cuba, China	Toolboxes in MATLAB to process EEG data Article submitted to *Frontiers in Neuroscience* special issue, Energy Efficient Neural Code in Individual Neurons and Brain Circuits
4. Define accumulated risk model	2017	Cuba	Model in discussion
5. Create facilities for adult EEG recording and analysis	2018	Barbados	Infrastructure, BNS staff training, G1 subject recruitment
6. Record EEGs and NIRS in PEM and CON adults	2018	Barbados	Creation of new longitudinal and multimodal database
7. Analysis of qEEG (comparing 1977–78 and 2018 recordings)	2018	Cuba	Article published
8. Recruit participants (PEM and CON) and conduct MRI, cognitive and behavioral tests	—	—	Multimodal databases
9. Refine qEEG biomarkers	—	—	Biomarkers refined, article published
10. Field tests	—	Africa	Health recommendations, article published

BNS:Barbados Nutrition Study CON: control group G1: generation 1 NIRS: near-infrared spectroscopy PEM: protein–energy malnutrition group qEEG: qualitative electroencephalography

As the project evolves, biomarkers will be refined with data from near-infrared spectroscopy and magnetic resonance imaging that will also be collected in selected study participants. Lastly, field testing can be extended to other low-resource settings, such as African countries with high malnutrition prevalence and with which scientific collaboration already exists.

This is the first time that qEEG has been used to evaluate the effects of early childhood malnutrition on the central nervous system and to identify biomarkers to objectively assess children at greatest risk for neurodevelopmental delays and disabilities in developing countries and to assist in the development of targeted interventions for high-risk children in these settings.

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A Collaboration to Teach US MPH Students about Cuba's Health Care System

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ABSTRACT

In 2011, the US Department of the Treasury changed its regulations to allow US students to participate in short-term education programs in Cuba. Beginning in 2012, and each year thereafter, Cuba's National School of Public Health and the Colorado School of Public Health have jointly taught a class on the Cuban public health system. The program goals are to provide US students with an opportunity to learn about the Cuban national health system's focus on 1) prevention and primary health care services; 2) financial and geographic access to services and health equity; 3) continuum of care across the home, family doctor-and-nurse offices, polyclinics and hospitals; 4) data collection at all levels to understand health risks, including outbreaks, and to guide resource allocation; 5) assessing patients' health and risks using a comprehensive definition of health; 6) multisectoral collaborations between the Ministry of Public Health and other Cuban agencies and organizations to address population health risks; 7) disaster preparedness, response and recovery; and 8) provision of international health assistance. The class incorporates information about health systems in Latin American and other Caribbean countries to provide context for understanding the Cuban health system.

The course includes: 1) seminars, online readings and discussions before travel to Cuba; 2) seminars at Cuba's National School of Public Health, visits to Cuban national health institutions at all levels, from community-based family doctor-and-nurse offices and multispecialty clinics (polyclinics) to internationally recognized national health institutions, and guided visits and activities about Cuban culture and history during their 12 days in Cuba; and 3) followup course work upon return to the USA in which students integrate what they learned into their final class reports and presentations. During time spent planning, implementing and revising the program, both institutions have learned from each other about global health teaching methodologies and have laid a foundation for future teaching and research collaborations. To date, 49 individuals have participated in the program.

KEYWORDS Medical education, public health system, collaboration, Cuba, USA

INTRODUCTION

Cuba is known for implementing a public health model based on universal health coverage, equity and efficient resource allocation.[1–5] With a focus on prevention and primary care, Cuba has achieved health indicators that match or exceed those of countries with substantially more resources.[1–5] Many ask how Cuba has been able to accomplish this.

In 2011, the US Department of the Treasury changed its regulations on travel to Cuba to allow US students to participate in short-term education programs in that country.[6] Since 2012, Cuba's National School of Public Health (ENSAP)[7] and Colorado School of Public Health (CSPH)[8] have jointly taught an annual class on public health in Cuba comparing it with approaches in other Latin American and Caribbean countries.

What can US students learn from studying the health system of a country where the government provides and finances health services and the average GDP is significantly lower than that of the USA? Furthermore, what are the benefits to Cuban and Colorado faculty who participate in the program? This paper addresses those questions and decribes ongoing collaboration between our two schools of public health.

IMPORTANCE Collaborative course development and teaching methods are key in this course, which provides opportunities for students and faculty members to learn about the way key health services and policies, curricula and teaching strategies are organized and implemented in Cuba.

COLLABORATION

Antecedents It would not have been possible to establish the program in 2012 without previously established relationships and collaborations. Dr O'Connell traveled to Cuba multiple times between 2001 and 2011, many of the trips associated with a community nonprofit, the Boulder–Cuba Sister City Association (Boulder, Colorado has a sister-city relationship with the municipality of Yateras in rural Guantánamo Province). During these trips, she learned about the Cuban public health system and worked on projects supported by the Cuban Ministry of Public Health (MINSAP) and the Sister City Association. Those efforts led to development of oral health educational materials and an oral health program for children, known as Alerta Feliz. Three MINSAP oral health experts created the program in partnership with Dr O'Connell and an artist from Guantánamo Province.[9] In 2008, Dr O'Connell participated in the International Congress on Health Economics, held in Havana, and initiated discussions with ENSAP colleagues about possible collaboration. During this period, representatives from the US nonprofit, Medical Education Cooperation with Cuba (MEDICC) were invited to give seminars on the Cuban public health system at the University of Colorado to increase knowledge of key elements of Cuba's public health system among administrators, faculty and students. CSPH is part of the university system and was interested in increasing global health opportunities for its students.

Program The program was designed to foster MPH students' understanding of factors that influence public health and public health administration in Cuba and other countries in Latin America and the Caribbean. It highlights Cuba's focus on:

- prevention and primary health care services;
- financial and geographic access, and health equity;

- continuum of care across settings that include the home, family doctor-and-nurse offices, polyclinics and hospitals, in both urban and rural areas;
- data collection at all levels to understand health risks, including outbreaks, and to guide resource allocation;
- *dispensarización*, or continuous assessment and risk evaluation, assessing patients' health using a comprehensive definition of health that includes patients' and families' physical, mental, economic and social status, and tailors followup protocols accordingly;[4]
- multisectoral collaborations between MINSAP and other Cuban agencies and organizations to address population health risks;
- disaster preparedness, response and recovery; and
- international collaborations that include providing public health services, training, consultation and disaster relief throughout the world.

Program readings, seminars and assignments include information on health systems in Latin American and other Caribbean countries to provide context for understanding the Cuban health system. At the end of the course students must be able to describe these countries' population health status; assess scientific evidence relevant to health, health service delivery and outcomes; assess differences between health service delivery models; analyze policies, resources and other factors that contribute to health; and engage with Cuban faculty, students, health administrators and providers to develop understanding of these health systems.

Justification Future health professionals in the USA can gain valuable insights from examining Cuba's health service delivery model, which focuses on prevention and primary care, evidence-based approaches, and rigorous data collection to understand and address health risks, and which has produced impressive health outcomes, despite ongoing economic difficulties and limited resources.[3−5]

Participating institutions and their contributions *Program Logistics* ENSAP and CSPH personnel are responsible for organizing course content at their respective institutions.[7,8] ENSAP coordinates provision of ENSAP seminars and site visits in Havana, while Cienfuegos Province's MINSAP personnel coordinate site visits in Cienfuegos. ENSAP faculty participate in site visits in Havana and Artemisa, and ENSAP faculty members travel with the class to Cienfuegos. Cienfuegos and Artemisa were chosen because they have achieved high standards in health services organization and for logistic reasons, because they are close to Havana. ENSAP faculty provide information on specific topics addressed and their relevance to other components of Cuba's health system. Their perspectives as national and international health experts as well as Cuban community members are invaluable.

CSPH oversees Colorado-based academic content and arranges travel logistics for students and accompanying faculty. Course content is revised by ENSAP and CSPH faculty and MINSAP personnel. For example, ENSAP and MINSAP identify opportunities to revise seminars and schedule other site visits. A CSPH anthropologist has added content to improve student understanding of demographic, social and economic factors that contribute to population health.

Collaboration mechanisms *Compliance with Cuban and US government regulations and academic requirements* Each year ENSAP and the University of Colorado's Office of International Studies (OIS) update their program agreement via a signed letter. Additionally, the course's educational objectives and content satisfy CSPH requirements for MPH academic competencies and credits. MINSAP, ENSAP and CSPH organize program logistics and activities to ensure compliance with Cuban and US government regulations. ENSAP and MINSAP oversee compliance with Cuban regulations, including arranging for US students to have Cuban academic visas. CSPH and OIS provide logistical support and oversight to ensure compliance with US regulations and mitigate risks associated with travel. As part of this effort, CSPH and OIS personnel review information on Cuba from the US Department of Treasury's Office of Foreign Assets Control, US Department of State, and *International SOS*.[10]

Activities *Program Description* To achieve the program's objective, the Cuba health program is organized as a semester class, with academic learning occurring in Colorado and Cuba. The three-credit course starts in the spring semester, spans 12–14 weeks and ends in the summer semester. This schedule allows for travel to Cuba to occur after spring semester ends.

In Colorado, students apply to participate in the program. The application process includes an interview to ensure the class supports students' academic goals. This is particularly important as the program cost, which students pay, includes tuition and costs associated with student and faculty travel (airfare, lodging, transportation, meals, etc. in Cuba). Additionally, since most students are employed, many must use vacation time to take days off from work.

Below we describe the types of students who participate in the program and academic activities in Colorado before travel to Cuba, during the 12 days in Cuba, and in Colorado upon return.

Program participants include students from a wide range of personal and professional backgrounds and experience; this diversity contributes to their learning. Most participants are students enrolled in the MPH degree program at CSPH. Students may also be enrolled in other University of Colorado academic programs in the Schools of Medicine, Nursing, Pharmacy, Public Affairs, Liberal Arts, and Business, some of whom are dually enrolled in CSPH to obtain an MPH. Most students are employed as health professionals at local and state departments of health, health provider organizations (e.g., hospitals, clinics); as clinicians (e.g., physicians, nurses); or as administrators at university research centers or other health organizations. Thus far, four faculty from University of Colorado programs other than CSPH have participated.

Before the trip, students attend 3 seminars and complete 10–12 online educational modules that include readings, discussions and other academic content. Seminars and modules describe aspects of the public health system and MINSAP's relationship to other governmental organizations. Modules address provision of services for specific populations such as pregnant women, children and elders; communicable diseases such as diarrheal disease, tuberculosis and HIV/AIDS; and chronic conditions such as diabetes and cardiovascular diseases. Other topics include workforce development, vector control (e.g., *Aedes aegypti* mosquito), vaccine and medication production, natural and traditional medicine, and an overview of Cuba's history and economy.

The course's central assignment is a comparative report on how Cuba and another country in Latin America or the Caribbean address a specific public health topic. Table 1 provides an overview of topics selected to date. Before the trip, students write a short report on Cuba's strategies for addressing their topics. The Colorado coursework provides a basic understanding of Cuba's health system and a foundation for more in-depth exchanges with Cuban faculty, students, health providers and the community during the trip.

Table 1: Public health topics addressed in student reports and presentations*

Area	Topics	Students n (%)
Maternal and child health	Reproductive health Maternal health Child health	8 (18)
Communicable diseases	Tuberculosis HIV/AIDS Diarrheal diseases	8 (18)
Chronic diseases	Hypertension Cardiovascular disease Diabetes Cancer (e.g., breast, cervical)	14 (31)
Health infrastructure	Physician training Vector control (e.g., *Aedes aegypti*) Disaster preparedness Biotechnology Traditional and natural medicine	10 (22)
Other	Aging Smoking prevention Domestic violence	5 (11)
All topics		45* (100)

*of 49 participants (no reports or presentations from the 4 participating faculty)

The trip to Cuba includes a full-time schedule (typical schedule in Table 2). During the first three days, students engage in activities to learn about Cuba's history, economy and culture, and how social determinants of health influence service provision. The schedule includes seminars at ENSAP that build on the learning that occurred in Colorado. ENSAP faculty address the school's educational programs; Cuba's health care system principles, services, and transformations over time; workforce development; health statistics and disease surveillance; health promotion; research on current health priorities (including economic studies) and disaster preparedness. Faculty are national experts in their fields and students benefit from their experiences in Cuba and internationally.

Students have opportunities to interact with Cuban health professionals who deliver services on site visits to national health institutions in Havana and health providers in other provinces. During the visit to the Latin American Medical School,[11] students learn about Cuba's role in training physicians from other countries, as well as Cuba's history of international assistance. Researchers at the Pedro Kourí Tropical Medicine Institute[12] provide information on their collaborations overseas and Cuba's history of managing HIV/AIDS, tuberculosis and dengue. Students learn of US collaborations with BioCubaFarma (which specializes in pharmaceutical and biotechnology research, development, production and marketing)[13] and with the Genetic Engineering and Biotechnology Center[14] from representatives who describe development and production of commonly used medications and vaccines, as well as innovative medications used in Cuba and exported.

Students start their five-day stay in Cienfuegos Province at the Medical University of Cienfuegos, where faculty provide an overview of provincial population health status, health services and medical training programs. In Cienfuegos City, students visit four key health care providers: a family doctor-and-nurse office (CMF), a polyclinic, a maternity home and a seniors' day center. One day is spent in a rural municipality to observe how primary health care services are delivered there. During these urban and rural site visits, students learn how health care facilities coordinate services between various levels of care while addressing their communities' environmental and occupational risks, including those associated with vector control and disasters.

During seminars and site visits in Cuba, students obtain information on the specific health topics each is researching. Because students have basic background information, we all benefit by their insightful questions about those topics. One program highlight for class instructors is the seminar scheduled toward the end of the trip when students give presentations on their topics (synthesizing information they obtained before and during the trip), discuss their findings and ask remaining questions. Cuban health care providers and community members also participate in the seminars, offering their perspectives and contributing to the question-and-answer period.

Accompanying CSPH faculty members are particularly intent on developing critical thinking among students by encouraging them to ask key questions, not only about the achievements and advances but also about the challenges Cuba's health system faces in for taking a deeper look into both Cuba's and comparison-country health systems.

When students don't have a scheduled activity, they learn about public health through interactions with Cubans in the community and by exploring their surroundings. For example, they are able to obtain a community perspective on the complexities of specific health issues (e.g., nutrition, exercise, aging), hurricane preparedness and mosquito control. Upon return to the USA, students incorporate what they learned in Cuba in their final reports, in which they share highlights of their comparisons between the two countries selected, during presentations given in the last class seminar, a few weeks after their return.

Although each activity makes its unique contribution to the course, CMF visits considerably expand students' understanding of primary health care. Students directly observe one of the few health care systems that has fully implemented community-based primary health care. They learn first hand from family doctors and nurses about services delivered in their neighborhoods in collaboration with other providers, have an opportunity to walk through a neighborhood with a family doctor to conduct a home visit and discuss a variety of health topics with doctors, nurses and patients.

Outcomes To date, 49 individuals have participated in the program (45 students, 4 faculty). Students demonstrate their understanding of factors influencing public health and resource allocation for health services through verbal communication, online discussions, class presentations and written reports. As described above, the central course assignment is a report on how Cuba and another country in Latin America or the Caribbean address a specific public health issue. A grading rubric is shared with students and used to give

Table 2: Typical activity schedule in Cuba

Day		Time	Program activities
Day 1	Friday	All day	Travel to Cuba
Day 2	Saturday	All day	Historic and cultural sites in Havana
Day 3	Sunday	All day	Historic and cultural sites in Havana and surrounding area
Day 4	Monday	Morning	Seminars at ENSAP
		Afternoon	Site visit: Latin American Medical School
Day 5	Tuesday	Morning	Seminars at ENSAP
		Afternoon	Site visits: Pedro Kourí Tropical Medicine Institute, Genetic Engineering and Biotechnology Center, BioCubaFarma
Day 6	Wednesday	Morning	Site visit: Artemisa (health services in elementary schools)
		Afternoon	Seminars at ENSAP
Day 7	Thursday	Morning	Travel to Cienfuegos
		Afternoon	Seminar: Medical University of Cienfuegos (provincial health status and services)
Day 8	Friday	Morning	Site visits: CMF and polyclinic*
		Afternoon	Site visit: seniors' day program
Day 9	Saturday	Morning	Site visit: rural municipality (primary health care services)
		Afternoon	Explore rural area
Day 10	Sunday	All day	Historic and cultural sites in Cienfuegos and Trinidad
Day 11	Monday	Morning	Site visit: maternity home
		Afternoon	Seminar: student presentations Travel to Havana
Day 12	Tuesday	All day	Travel to USA

*In Cuba's National Health System, primary health care is delivered in family-doctor-and-nurse offices (CMF) and multispecialty community polyclinics to which CMFs report.[4]
ENSAP: National School of Public Health

them written and verbal feedback on drafts. The rubric and feedback support students' ability to demonstrate competencies related to program objectives; the vast majority of students demonstrate high competency levels. More information about the course and types of student assessment used to determine their course grade may be obtained on the CSPH website.[15]

Students provide comments about the course throughout the class and through course evaluations. In morning planning and afternoon debriefing sessions during the trip, students have opportunities to discuss program activities and make suggestions. At the end of the course, students submit anonymous evaluations that include open-ended questions and use of a 5-point scale (1 = *needs much improvement*, 5 = *excellent*) to provide feedback on specific class components. To date, the overall course rating is 4.6.

At the end of each year, MINSAP, ENSAP and CSPH personnel involved conduct an informal evaluation of program activities and the institutions' respective contributions to program objectives. We revise the Cuba program based on faculty and student evaluations. Online course content now includes a greater emphasis on economic evaluation and resources allocated to health service provision, because of the importance assigned these issues in Cuba. ENSAP faculty now include more practical applications of key Cuban public health concepts, programs and outcomes in seminars. Over the years, we have incorporated new site visits. For example, in 2017, students visited Artemisa Province to learn about provision of health education and preventive dental services in elementary schools.

ANALYSIS

Program challenges and benefits Although we encountered many challenges developing and implementing the program, due in part to political differences between our two countries, we addressed them with support from our academic institutions, aided by flexibility, persistence, good humor and friendship. As health professionals, we stayed focused on our mutual interest in providing an educational program about a health care delivery system with notable outcomes. Based on our experiences collaborating on this education program and the oral health project, we appreciate the importance of ongoing communication between US and Cuban colleagues to improve understanding of each institution's goals and objectives, address all aspects of the collaboration, comply with US and Cuban regulations, and become aware of and allow time to address changes.

Students encounter challenges related to language and costs. Students who do not speak Spanish or Portuguese are not able to access health information published in Cuban and other academic journals. However, much information on Cuba's health system is available in English language journals (e.g., *The Lancet, American Journal of Public Health, MEDICC Review*) and in reports from PAHO, WHO and other international agencies. Although translation is provided for seminars and site visits, opportunities for additional conversations in small groups are more limited for these students.

Over the years, Colorado and Cuban faculty have identified opportunities for additional collaborations, based on faculty expertise and interests and a desire to expand opportunities for students at both institutions. A challenge limiting such activities is the availability of financial support; e.g., Colorado students wishing to pursue additional educational activities (e.g., independent studies, practicums, capstone projects) require funding for travel in addition to Cuban and Colorado institutional approvals. Nonetheless, such activity is occurring.

In addition to earning credits toward their degree programs, students benefit from the program in numerous ways in the short and long term. Some students' academic programs include a global health concentration and learning from this program will contribute to their future studies and work. For example, a doctoral student is using knowledge obtained from the class in her dissertation research. The program gives future US health professionals opportunities to engage with Cuban faculty and health care providers on Cuba's health system model and provision of specific services. Despite differences between the US and Cuban health systems, many lessons learned from Cuba are applicable to addressing US health needs. Students learn about home visits, comprehensive health assessment and cross-sectoral coordination of services—concepts that are increasingly being applied in the USA to address a broad array of health issues, including mental health.

MINSAP, ENSAP and CSPH have also derived benefits from this collaboration, including academic exchanges in both countries that facilitate learning about health systems and research methods. For example, funds were secured to support three ENSAP faculty

visits to the University of Colorado, where they gave seminars and discussed their research and education programs with peers. Additionally, CSPH faculty have given papers and participated in roundtables at international health conferences held in Cuba and have had exchanges on qualitative and quantitative research methods (including those associated with economic studies) with ENSAP faculty.

Through in-person meetings and email, ENSAP and CSPH faculty have collaborated with MINSAP as the Alerta Feliz oral health education program is revised and deployed to other locations. During the 2017 site visit to Artemisa Province, Colorado students learned about research on the Alerta Feliz program conducted by dentists in ENSAP's master of health economics program. The research objective was to improve children's oral health practices, using Alerta Feliz program concepts and materials. CSPH faculty are advisors to this work, providing information and guidance on research methods and oral health.

An important limitation of this endeavor is the course's short duration, which limits the number of field activities and topics covered. This is partially offset by pre- and postcourse assignments required of participants.

A key message of the course is that experiences and methods cannot be extrapolated from one scenario to another but must be critically assimilated. Political, economic and cultural factors influence strategies to implement programs and policies and modify intervention effects.

ENSAP and CSPH faculty learn educational methods from each other. For example, ENSAP learned methods for integrating practice and research into student seminars. Furthermore, ENSAP faculty and MINSAP personnel have an opportunity to deepen their understanding of Cuba's health system through the program activities and engagement with each other, as well as CSPH faculty and students. Throughout the trip, CSPH faculty improve their Spanish language skills and conversely, Cuban faculty improve their English.

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Prospects for US–Cuba Cooperation in Gastroenterology, Hepatology and Liver Transplantation

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ABSTRACT

Gastroenterology, hepatology and liver transplant exchanges between the USA and Cuba have mainly consisted of scientific events and short visits. This has facilitated Cuba's inclusion in recognized scientific organizations, familiarity with Cuba's biotech products for treatment of liver disease, and access by Cuban professionals to the highest level of scientific information for clinical practice. It has also given health professionals in the US a more accurate picture of Cuba's health sector. The results of the Global Alcoholic Liver Disease Survey, which included Cuba and was designed and coordinated in the USA, opened doors to joint research and scientific publications. Until now, there have been no protocols for ongoing cooperation to enable bilateral clinical trials or continuing professional development in diagnostic, therapeutic and surgical techniques for hepatology and liver transplantation. There are many mutually beneficial research prospects in these areas. What has been accomplished to date, described in this article, is encouraging and sets the stage for future collaboration.

KEYWORDS Hepatology, liver transplant, health, medicine, science, Cuba, USA

INTRODUCTION

Chronic liver disease is a serious global health issue. Global deaths due to hepatic cirrhosis increased from some 676,000 in 1980 to >1,000,000 in 2010, and the mortality rate increased by 10.3% between 2005 and 2015. Average prevalence of autopsy-detected hepatic cirrhosis is ≤10%, but this is likely an underestimate, since one third of patients are asymptomatic for many years. The main causes of cirrhosis are alcohol, nonalcoholic fatty liver disease and viral hepatitis, which occur in all countries, regardless of geography or level of economic development. These diseases have enormous health and social costs, including direct health care expenses and indirect costs from productive years of life lost. It is estimated that viral hepatitis causes 53% of hepatic cirrhosis and 54% of liver cancers.[1–3]

In the USA, the burden of chronic liver diseases is substantial and has been increasing. The National Health and Nutrition Examination Survey, conducted between 1999 and 2010, estimated cirrhosis prevalence at 0.27%, or 633,323 adults. Diabetes, alcohol abuse, hepatitis B and C, male sex and old age were independently associated with cirrhosis. The first three factors contributed to 53.5% of cases.[4] Age-adjusted mortality from chronic liver disease and cirrhosis increased from 9.6 per 100,000 in 1999 to 10.2 per 100,000 in 2013 (with more marked increase in the group aged 55–64 years), making it the 12th leading cause of death in 2013 (1.4% of all deaths).[5] Research and interventions to improve patient health are needed.

In Cuba, cirrhosis and chronic liver disease have been the 9th and 10th leading causes of death in the last 20 years; taken together, they have the second highest mortality rate among digestive disease, after colon cancer, and are a major hospital discharge diagnosis.[6] The main causes of chronic hepatitis and cirrhosis in Cuba are the same as in other countries in the Americas Region: viral infections (particularly hepatitis C) and alcohol.[7] Although hepatitis B (HBV) is a leading cause in many countries, it is not in Cuba, where incidence and prevalence of hepatitis B have been decreasing because of a national program to vaccinate at-risk groups and people aged <25 years.[8]

IMPORTANCE Progress in hepatology and liver transplantation has helped Cuba overcome great health challenges. Unique models have been established for future collaborations that will benefit both countries.

Cuba uses a multidisciplinary and intersectoral approach to finding scientific and technological solutions to resolve, or at least mitigate, the problem of chronic liver disease. The biotech and medical/pharmaceutical industries have been key to providing products and technological resources.[9]

Hepatology, which is relatively new in Cuba, has seen advances in diagnosis, research, and clinical and surgical practice. Various lines of research have resulted from scientific exchange between gastroenterologists and researchers from the former Western Havana Scientific Pole (a group of institutions, now under BioCubaFarma, dedicated to the full research and development cycle aimed at promoting biotechnological development and advanced technologies to resolve health and nutrition problems, while generating revenue for Cuba from competitive products).[10] Joint research beginning in the 1980s led to Cuban production of interferon (in its various forms) for treatment of viral hepatitis B and C, and the hepatitis B vaccine, HeberbiovacHB,[11–13] which helped reduce incidence and prevalence of liver infections.

Other research explores the natural history of hepatic cirrhosis, hepatocellular carcinoma, viral hepatitis, nonalcoholic fatty liver, alcoholic liver disease, autoimmune liver diseases and inherited diseases, and new technologies are being invented to improve their diagnosis.[14–19] Liver transplantation began in Cuba in 1986 but was discontinued in the early 1990s. Since the national liver transplantation program in Cuba was restarted in 1999, >400 liver transplants have been performed, over 80 of them in patients aged <18 years.[20] Although scientific policies are a priority in Cuba and important resources are being invested for

health research, the US economic embargo and other factors have created severe economic limitations, so such scientific and technical cooperation and exchange activities with developed nations with resources in topics of shared interest are welcome opportunities.

COLLABORATION

Cuba's Ministry of Public Health and the US Department of Health and Human Services have agreed to collaborate on health issues. This new stage of bilateral diplomatic relations, which were reestablished in 2015, motivated joint medical research in multiple areas.[21] The countries' geographical proximity is well suited for exchange projects, programs, and health strategies to benefit both populations. Several US scientists have called for lifting restrictions imposed on Cuba, mainly in the areas of health and science.[22,23]

Collaboration in gastroenterology, and specifically hepatology, predated renewal of diplomatic relations. It has focused on developing Cuban hepatologists' and transplantologists' technical skills in US settings, sharing areas for learning and discussion with US professionals about medical and gastroenterology practice in Cuba, and Cuba's National Health System (NHS). Exchange began in 1996 with visits by US gastroenterologists from Boston and Portland (ME) to explore Cuban gastroenterologists' research and their clinical and procedural advances (Table 1), having limited previous knowledge of Cuban medicine and gastroenterology, acquired through visits supported by the US Presbyterian Church.

To date, activities have been focused on two main categories: short visits by Cuban gastroenterologists to prestigious US institutions, and participation by specialists at conferences held in both countries with joint clinical and endoscopic work (Table 1). The short visits offered the Cubans new knowledge and skills through the expertise of highly qualified professionals in gastroenterology and digestive endoscopy. As part of the exchange, US specialists donated endoscopic equipment and supplies to Cuban services.

At the same time, Cuba shared its advances in biotechnology for treating acute and chronic viral hepatitis C with a Cuban biotech product, recombinant interferon alfa-2b, produced by the Genetic Engineering and Biotechnology Center.[24–26] Results were presented at the First Boston-Cuba Gastroenterology Conference (1999).

The first contact between US and Cuban liver transplantation specialists was facilitated in 2009 by Global Links (a Pittsburgh-based nonprofit organization that provides large-scale humanitarian medical aid) and consisted of a visit by professionals from the pediatric transplant team at William Soler University Children's Hospital in Havana to an equivalent service in the USA (Table 1).[27]

One important result of these exchanges was the inclusion of Cuba's Gastroenterology Institute in the Global Alcoholic Liver Disease Survey (GLADIS),[28] which was coordinated by Dr Ramón Bataller (then of the Division of Gastroenterology and Hepatology at University of North Carolina at Chapel Hill). This research, conducted in 2015, explored possible clinical and etiological differences among patients with chronic liver disease. The research involved 3000 patients from 16 gastroenterology and hepatology centers in 23 countries. The study also collected anthropometric, etiologic and clinical data on 100 patients admitted consecutively with early liver disease (not cirrhosis or decompensated disease) seen as outpatients and 100 patients who were hospitalized for liver disease.

The 2017 Hepatology Symposium in Havana attracted renowned US academics, opinion leaders and experts, most of whom were members of the American Gastroenterology Association, American Association for the Study of Liver Disease (AASLD), American College of Gastroenterology, European Association for the Study of Liver Disease, or the American Society of Transplantation (Table 1). Relationships established at this conference enabled a Cuban delegation to attend The Liver Meeting (Table 1), a key AASLD event and the main conference in the field of hepatology, which each year brings together over 9500 hepatologists from around the world.

Table 1: Exchanges between Cuba and the USA since 1996 in gastroenterology, hepatology and liver transplantation

Year	Type of activity	Country	Actions/Results
1996	US gastroenterologists visit Hermanos Ameijeiras Clinical–Surgical Teaching Hospital	Cuba	Presentation of scientific results Planning of new meetings in both countries for collaboration
1998	3rd Cuban–US gastroenterology conference	Cuba	Joint endoscopies Agreements granting Cubans short US placements
1999	Short placements of Cuban specialists at Lahey Hospital Medical Center and Beth Israel Medical Center	USA	Endoscopies, rounds, joint endoscopic retrograde cholangiopancreaticography
1999	1st Boston–Cuba Gastroenterology Conference	USA	Discussion of scientific results with Cuban biotech products
2009	Short placements of Cuban hepatologists and transplant specialists at Children's Hospital of Pittsburgh (University of Pittsburgh Medical Center)	USA	Knowledge about new procedures, treatments, managing intensive therapy, hepatology, anesthesiology, immunology, emergency room and abdominal organ transplants
2015	Global Alcoholic Liver Disease Survey (GLADIS)	Cuba	Inclusion of Cuba in US-coordinated, international, multicenter research on alcoholic liver disease
2017	2017 Hepatology Symposium	Cuba	Exchanges on liver transplantation: handling complications, results from living-donor transplants and variants, new immunosuppressive therapies. For liver disease: HBC treatment and results of direct-acting antivirals, management of hepatocellular carcinoma, nonalcoholic fatty liver disease, alcoholic liver disease
2017	The Liver Meeting	USA	Presentation of experience and impact of Cuba's HBC prevention and treatment program. Inclusion of Cuba in IC–HEP Council

HBC: hepatitis B and C IC-HEP: International Coalition of Hepatology Education Providers

The support of organizations dedicated to providing the latest information and facilitating clinical education on liver disease to health professionals was critically important for these exchanges, including the International Coalition of Hepatology Education Providers, the Liver Health Connection and the Chronic Liver Disease Foundation, as well as Cuba's Gastroenterology Institute and the Cuban Gastroenterology Society.

ANALYSIS

Cuba's NHS guarantees free and universal health care. The system is pyramidal, based on primary care, where family doctor-and nurse offices and multispecialty polyclinics focus on disease prevention and promotion of health, referring patients to secondary-specialty care when necessary. Tertiary care institutions conduct research and handle more advanced techniques and procedures,[29] including liver transplants.

These characteristics of the Cuban health care system offer excellent opportunities for large-scale collaboration and research projects. Doctors and researchers are well-trained and qualified, suported by a national network of health care facilities with a uniform structure and a consolidated hospital management system that offers diagnostic and therapeutic options under ethical principles established by accredited ethics committees in all institutions. This structure favors obtaining reliable data regarding morbidity and mortality rates for different diseases, as well as other health statistics. Reliable records are kept of all research conducted.[30]

In this context, Cuba offers favorable conditions for clinical trials in patients with chronic liver conditions (such as viral hepatitis, nonalcoholic fatty liver disease and alcoholic liver disease) who have not received specific antiviral treatment or have not responded favorably to antivirals available in Cuba. There have been no clinical trials to date involving both countries. Such trials would be beneficial for assessing direct-acting antivirals for treatment of chronic hepatitis C infection (including patients with end–stage kidney disease) and certain forms of ablative treatment of hepatocellular carcinoma, in which the USA has experience.

The First Boston–Cuba Gastroenterology Conference allowed US specialists to appreciate Cuban advances in gastroenterology and hepatology, with use of Cuban therapeutic biotech products. This led to the first inclusion of Cuban doctors in the American Gastroenterology Association. For their part, Cubans updated their knowledge of technological and scientific developments in gastroenterology and increased clinical and endoscopic skills vital to quality practice.

The 2009 visit by Cuban transplantologists to the pediatric transplant unit in the Children's Hospital of Pittsburgh (University of Pittsburgh Medical Center) did not lead to changes in medical or surgical protocols in place in Cuban transplantation services since 2004, but did bring about smaller changes in procedures for deep vein thrombosis prophylaxis and pediatric anesthesia. The focus of Cuba's medical system and its advances in hepatology, hepatobiliary surgery and pediatric transplantation were presented. Another highlight of the experience was the opportunity for Cubans to meet Dr Thomas Earl Starzl, known as the father of modern transplantology, who performed the first liver transplant; his innovations in surgery, immunology and immunosuppression revolutionized the field.[31]

GLADIS showed that referrals of patients with liver disease to specialty care varied significantly by country. Referrals of alcoholic patients occurred in more advanced stages than for patients with viral or nonalcoholic liver disease. Specific patterns were recognized in Cuban patients on diagnosis and referral to specialized services. Patients with autoimmune hepatitis, HBV and HBV+HCV coinfection were diagnosed in early stages, while alcoholic liver disease, alone or associated with HCV, was diagnosed in advanced stages, mostly with complications of hepatic cirrhosis.[28] Early diagnosis of liver disease from HBV infection is associated with Cuba's viral hepatitis prevention and control program in primary care, which includes actions in surveillance, awareness promotion, vaccination and prevention in general. The program's impact on controlling hepatitis from HBV has been documented.[32–34] However, despite preventive actions, HCV is still a leading cause of advanced liver disease and liver transplantation in Cuba.[35]

Alcoholism is a mounting challenge in the Americas, which has higher levels of alcoholism, on average, than the rest of the world.[36] According to Cuba's 2014 Multiple Indicator Cluster Survey, 46.5% of men and 19.2% of women aged 15-49 years report consuming alcohol in the past month.[37]

Including Cuba in GLADIS was a progressive step in addressing alcohol-related liver disease; its results warn of the threat of a disease that starts silently, goes unnoticed, and ends fatally due to complications. Early detection and timely referral to specialized centers are needed for these patients, as part of strategies that can be shared in collaboration between Cuba and the USA.

US specialists participating in the 2017 Hepatology Symposium learned how Cuba's health care system is organized, and about hepatology and liver transplantation work in Cuba. They also became familiar with progress in biotechnology and pharmaceuticals, closely linked to progress in hepatology, and learned about Cuba's national health care programs, such as those for viral hepatitis prevention and control, immunizations, HIV/AIDS, and others that connect the NHS with biotechnology institutions This exchange was enriched with an opportunity to visit institutions dedicated to hepatology and liver transplantation in Cuba, such as the Gastroenterology Institute and the Medical–Surgical Research Center.

Cuba's inclusion for the first time in The Liver Meeting was an opportunity for delegates to highlight Cuba's experience in and impact on the prevention and treatment of hepatitis B,[35] presenting the current state of hepatology in Cuba and outlining prospects for future collaboration. These meetings between Cuban and US specialists also facilitated Cuba's incorporation into the Latin American Association for the Study of the Liver (ALEH) and the International Coalition of Hepatology Education Providers, two leading organizations in the study of liver disease. The Chair of the Cuban Gastroenterology Society attends meetings of ALEH's Board of Directors.

These exchanges are a good starting point for Cuba's inclusion in leading scientific organizations, for sharing knowledge of Cuban biotech products for treatment of liver disease, and for Cuba to become a partner in multinational research on liver disease. In this regard, such contacts must be further developed to open

doors to joint US–Cuba research and publication of scientific articles with authors from both countries within an official framework of cooperation. Professionals from both countries dedicated to researching liver disease and liver transplantation would benefit from continuing and expanding training through exchanges at high-level institutions, as well as skill development in cutting-edge diagnostic, therapeutic and surgical techniques.

CONCLUSIONS

Progress in hepatology and liver transplantation has helped Cuba overcome great health challenges. The US–Cuban exchange has contributed to new knowledge for both countries. Cuban professionals have gained access to high-level scientific information and clinical practice, while their US colleagues have learned and seen evidence of the development of the health sector in Cuba. This has helped resolve doubts and deepen understanding of Cuba's reality and prospects for research in this area, sowing the seeds for future collaboration.

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Moving Closer to Tuberculosis Elimination through Institutional Scientific Collaboration: Opportunities for Cuba and the USA

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ABSTRACT

Global efforts to eliminate tuberculosis by 2050 continue to challenge health systems. In countries with low reported tuberculosis incidence, such as the USA (3.1/100,000 population) and Cuba (6.9/100,000), differences in classification by income level and health systems' overall organizational structure are evident. However, the two countries' low tuberculosis incidence, geographic proximity, robust research capacity and shared health priority for tuberculosis elimination provide fertile territory to strengthen collaboration for tuberculosis control in clinical, laboratory and community settings. Two tuberculosis symposia in Cuba—one at the Cuba Salud Convention in 2015 and the other at the International Forum on Hygiene and Epidemiology in 2016—were instrumental in stimulating dialogue on continued efforts towards eliminating tuberculosis by 2050. In this article, we describe tuberculosis burden in the USA and Cuba, critically analyze strengths and challenges experienced in areas of low tuberculosis incidence and provide recommendations for future institutional collaboration to support tuberculosis elimination and improved population health.

KEYWORDS Tuberculosis/epidemiology, *Mycobacterium tuberculosis*, prevention, communicable disease control, disease eradication, disease elimination, international cooperation, Cuba, USA

INTRODUCTION

Globally, tuberculosis (TB) is the main infectious cause of death, with an estimated 10.4 million new cases and 1.7 million deaths in 2016.[1] An estimated one third of the world's population has asymptomatic *Mycobacterium tuberculosis* infection.[1] Over the past decade, although advances in diagnosis and treatment access, availability and effectiveness have improved TB patient outcomes, there have been no major strides towards global TB elimination. Continued emphasis on understanding the influence of political and social determinants of health on physical, psychosocial and individual health of TB patients will be crucial for TB elimination.

Three biological and social challenges in *M. tuberculosis* control persist and hinder TB elimination. First, both multidrug-resistant TB (MDR-TB), defined as *M. tuberculosis* strains that are resistant to isoniazid and rifampicin, and extensively drug-resistant TB, defined as MDR-TB resistant to any fluoroquinolone (e.g., levofloxacin, moxifloxacin) and at least one of three injectable second-line drugs (amikacin, capreomycin, kanamycin), have challenged successful treatment regimen delivery and outcomes. This human-made phenomenon is attributed to inadequate treatment by health care providers and lack of patient adherence to treatment regimens. An estimated 490,000 new MDR-TB cases were reported in 2016.[1]

Second, persons diagnosed with latent tuberculosis infection (LTBI) have an increased risk of developing active TB (TB reactivation), with a 5%–10% lifetime risk.[2] One third of the world's population is thought to harbor LTBI; it is from this pool of infected persons that active TB cases emerge. Mathematical models of TB elimination all point to the need to address LTBI in order to have any prospect of eliminating TB this century.[3]

Third, nosocomial spread of TB is also a major driver of TB transmission, especially to persons with immune deficiencies (e.g., HIV/AIDS) or living in impoverished and overcrowded conditions (e.g., displaced populations or refugees, residents of correctional facilities or homeless shelters). Such persons frequently experience social stigma or exclusion, stress and anxiety, and demonstrate reduced health-seeking behaviors.[4] Moreover, health care workers, who have increased occupational risk of *M. tuberculosis* exposure, may be employed in health institutions with poor TB infection control practices.

Despite these general challenges, low-incidence countries, characterized by TB incidence of <100 cases per million population, have sustained TB control efforts.[5] Pragmatically speaking, obstacles to TB elimination in low-incidence countries are primarily: a) limited government support, such as inadequate health budgets; b) frequent periodic TB outbreaks in vulnerable groups (e.g., in correctional facilities, homeless shelters, health institutions); and c) need for early identification of susceptible individuals with LTBI and at risk of developing active TB.[5] Rapid responses are essential to address these challenges and act promptly to mitigate TB outbreaks and disease propagation in the community.

WHO reported 274,000 TB cases (27/100,000 population) in 2016 in the Americas Region.[1] Although the TB targets of the 2015 Millennium Development Goals were met, TB continues to be a major public health issue in Latin America and the Caribbean.[6] In 2016, two neighboring countries reported low TB incidence: USA (3.1/100,000 population) and Cuba (6.9/100,000 population).[7] Yet, although these two countries are in the TB pre-elimination stage (<10 TB cases per million population/year), further progress

IMPORTANCE The USA and Cuba—both characterized by low tuberculosis incidence, geographic proximity, robust research capacity and shared health priority for TB elimination—can strengthen institutional scientific collaboration to contribute to achieving tuberculosis control and elimination by 2050.

will be required to reach TB elimination (<1 TB case per million).[8] While the USA and Cuba differ in terms of total population and allocated budgets for their National TB Programs (NTP), their comparable levels of estimated TB incidence coupled with TB control as a shared national priority provide a framework for future scientific TB collaboration and partnerships. Table 1 presents estimated indicators of TB burden, treatment and NTP financing for both countries in 2016.[7,9] National surveillance programs have reported variation in TB incidence within each country. Table 2 displays TB incidence in 2015 and 2016 for US states and Cuban provinces reporting ≥3 cases per 100,000 population.[10,11]

Table 1: Reported TB cases, treatment and national budgets, USA and Cuba, 2016

Indicator	USA	Cuba
Total population, 2016 (millions)	322	11
Country income level	High	Upper middle
TB burden, 2016		
Incidence rate (per 100,000 population)	3.1	6.9
Mortality rate (per 100,000 population)	0.03	0.09
Number of reported new and relapse cases (total)	8814	689
Number of MDR-TB cases (total)	130	16
New cases (%)	1.5	2.2
Previously treated cases (%)	5.6	4.2
TB treatment coverage*, 2016 (%)	87	87
TB treatment success rate, 2015 (%)		
New and relapse cases	83	83
Previously treated cases, excluding relapse cases	77	50
TB financing, 2016		
National TB budget (US$ million)	142	27

*new and relapse TB cases notified and treated, divided by estimated incident TB cases
MDR: multidrug-resistant TB: tuberculosis
Sources: references 7,9

Continued discussions of global TB burden prompted the World Health Assembly to adopt the WHO End TB Strategy in 2014, and shift the dialogue from "stopping TB" to "ending the TB epidemic."[5] This strategy emphasizes a holistic approach, adopting multisectoral interventions for community health and society, with three main pillars: 1) enhanced patient-centered prevention and treatment (e.g., early diagnosis and treatment of high-risk groups); 2) national policies and supportive systems (e.g., political commitment, community engagement and appropriate health policies); and 3) targeted research and scientific advances (e.g., discoveries to identify innovative strategies and approaches).[5]

Considering this holistic approach with its pillars, collaborative scientific teams are key to advancing the technical agenda and making progress towards TB elimination. In this report, we propose that the USA and Cuba—which have low TB incidence, geographic proximity, robust research capacities, and shared health priorities aimed at TB elimination—can strengthen scientific collaboration for TB control in clinical, laboratory and community settings. Considering TB control efforts in the USA and Cuba, we aim to critically analyze the strengths and challenges experienced in these two low-incidence countries and provide recommendations for future institutional collaboration that can contribute to TB elimination and improved population health.

Table 2: Tuberculosis incidence ≥3/100,000 population[a], USA and Cuba, 2015–2016

Jurisdiction	2015 n (rate)	2016 n (rate)
USA[b] (state or district)		
Georgia	320 (3.2)	(<3.0)
Arkansas	90 (3.0)	91 (3.0)
Minnesota	(<3.0)	168 (3.0)
Florida	602 (3.0)	639 (3.1)
New Jersey	326 (3.6)	294 (3.3)
Washington, DC	33 (4.9)	25 (3.7)
Maryland	(<3.0)	220 (3.7)
New York	763 (3.9)	768 (3.9)
Texas	1333 (4.9)	1250 (4.5)
California	2130 (5.5)	2073 (5.3)
Alaska	68 (9.2)	57 (7.7)
Hawaii	127 (8.9)	119 (8.3)
Cuba[c] (province)		
Camagüey	20 (2.6)	23 (3.0)
Matanzas	26 (3.7)	22 (3.1)
Guantánamo	24 (4.7)	16 (3.1)
Sancti Spíritus	27 (5.8)	17 (3.6)
Cienfuegos	32 (7.8)	16 (3.9)
Pinar del Río	29 (4.9)	25 (4.3)
Holguín	45 (4.3)	46 (4.4)
Artemisa	20 (4.0)	26 (5.1)
Santiago de Cuba	46 (4.4)	55 (5.2)
Villa Clara	70 (8.9)	52 (6.6)
Granma	45 (5.4)	57 (6.8)
Las Tunas	29 (5.4)	40 (7.4)
Havana	199 (9.4)	200 (9.4)
Ciego de Ávila	46 (10.7)	45 (10.4)
Mayabeque	34 (8.9)	47 (12.3)

[a]≥3/100,000 population selected as baseline because 2015 national TB incidence in the USA was 3/100,000 population
[b]number of reported cases (US National Tuberculosis Surveillance System) divided by midyear population estimates (US Census Bureau)
[c]number of reported cases (Cuban Ministry of Public Health National Medical Records and Health Statistics Division) divided by population estimates (Cuban Ministry of Public Health statistical yearbooks)
incidence: new and relapse cases in past year
TB: tuberculosis
Sources: references 1,10,11

PROPOSED COLLABORATION

Background This proposed bilateral collaboration in TB control originated from four scientific exchanges since 2014, all with Cuban government approval. In March 2014, participation in the American Public Health Association–Medical Education Cooperation with Cuba (APHA–MEDICC) delegation provided an immersion experience to gain insight into Cuba's universal health coverage as it functions at the primary care level. Following this exchange, the Cuban Hygiene and Epidemiology Society's Pulmonary Health Executive Board and the Pedro Kourí Tropical Medicine Institute (IPK), a PAHO/WHO collaborating center, successfully conducted two TB symposia at international conferences in Havana in 2015 and 2016: the International TB Symposium 2015 (Towards TB Elimination 2016–2050),[12] at Cuba Salud 2015 in April 2015, and the International Symposium on Pulmonary Health and TB Elimination (TB Elimination: Accelerating the Pace), held in conjunction with the International

Forum on Hygiene and Epidemiology, in November 2016. Both symposia were instrumental in stimulating dialogue on continued efforts towards TB elimination by 2050.[12] Finally, in April 2017, Cuban health leaders and invited international researchers participated in the workshop, Epidemiologic and Operational Research on TB, at IPK.

These events provided opportunities for fruitful scientific and technical exchange among clinicians and health researchers at IPK and the University of Florida (UF), with two notable results: First, Helena Chapman, then a UF doctoral student, received a three-week cross-cultural training in clinical and epidemiologic aspects of TB, mentored by respected clinicians and researchers at IPK and other Cuban Ministry of Public Health (MINSAP) institutions. Second, a collaborative manuscript was published that described the outcomes of the International TB Symposium 2015.[12] Such academic exchanges are evidence of strong commitment to scientific discovery, research and practice en route to TB control and elimination.

The proposed collaboration can strengthen future scientific advances in TB prevention and control efforts, which would be beneficial locally, nationally and internationally, and serve as a model for other countries that aim to build scientific capacity, better understand the epidemiology of TB transmission and reach optimal indicators for population health related to TB control.

Participating Institutions UF, located in Gainesville, Florida, was founded in 1853 and has recently been ranked as one of the USA's top ten public universities. The Division of Infectious Diseases and Global Medicine forms part of the UF Health Science Center, the largest health education center in the southeastern USA.[13] In addition to academic training and clinical responsibilities in medicine and patient care, scientific research collaborations among various disciplines are fundamental at the UF Health Science Center, UF Emerging Pathogens Institute, Southeastern National TB Center (SNTC), and UF One Health Center of Excellence. SNTC itself provides services to the southeastern USA, including Puerto Rico and the US Virgin Islands. Together, these academic centers provide broad research expertise and potential for collaboration in basic, clinical and social sciences related to spread of emerging infectious diseases that influence human, animal and environmental health in Florida communities.

Located in Havana, IPK was founded in 1937 and has become an internationally renowned scientific institution for undergraduate and graduate academic training, medical care, laboratory diagnostics and research.[14] As part of MINSAP, IPK's main objectives are to provide optimal medical services to patients, conduct laboratory diagnostics of infectious pathogens, educate Cuban and international students in multiple scientific disciplines, and develop research initiatives on prevention and control of tropical and other infectious diseases. Collaborating departments include the National Tuberculosis, Leprosy and Mycobacteria Reference and Research Laboratory, IPK Hospital, Department of Epidemiology and the National Clinical Reference Center for AIDS Treatment.

Proposed activities Through this proposed collaboration, binational activities between UF and IPK clinicians and researchers in basic, clinical and social sciences related to TB control efforts can identify research gaps and develop innovative projects to strengthen the scientific knowledge base about *M. tuberculosis*. Notably, these internationally recognized institutions, with robust clinical and research capacities in infectious diseases, have geographic proximity that would facilitate such joint work over the long term. In order to maximize scientific rigor and communication throughout an established research timeline, several activities can facilitate open dialogue, rapport among researchers, task efficiency, adherence to deadlines and overall transparency.

We propose a US-Cuban collaboration to develop a long-range strategy for research into TB epidemiology as it relates to the geographic catchment area of each institution, an accounting of best practices that have emerged in each area, analyses of persistent problems and innovative proposals to address these challenges, and a publication agenda to share findings with the scientific and public health communities. Working methods would include conference calls, web-based seminars, academic exchanges, research collaborations and joint publications.

ANALYSIS

Strengths Since NTPs were founded in the USA and Cuba, efforts towards TB elimination have integrated essential components of TB control. Political commitment can be described in the context of government responsibility, accountability and rapid responses to TB epidemics.[15,16] The US Public Health Service's NTP was established in 1944, eventually transitioning financial support from local and state governments to the federal level.[15] In Cuba, the national TB surveillance system was initiated in 1953.[16] Cuba's NTP was established in 1959, and national policies and guidelines were implemented in 1963 and 1964, focusing on population-based health promotion and disease prevention for TB control.[16] Notably, neonatal BCG vaccination has been a routine preventive measure in Cuba,[17] but not in the USA.

All countries have encountered challenges in managing MDR-TB, diagnosing and treating LTBI, and identifying and preventing TB transmission in high-risk population groups. However, rapid and effective responses to these challenges by NTPs in the USA and Cuba have demonstrated successful identification of TB cases, reduction of TB incidence and mortality, and increased treatment success rates.[18,19] Over time, robust *M. tuberculosis* monitoring and surveillance systems; universal access to directly observed treatment, short-course; and contact followup have proven to be strengths for rapid outbreak control. Strict *M. tuberculosis* infection control practices and continued research and international collaboration to understand TB dynamics complement the structure and function of these two systems. Also, promotion of human rights and ethical treatment of TB patients has aimed to reduce social stigma and discrimination that may hinder access to TB service delivery or negatively influence health-seeking behaviors.

Challenges In addition to the global challenges, TB control in low-incidence countries such as the USA and Cuba presents unique hurdles to continuing to improve TB indicators. Sustained innovative programs and collaborations that target these challenges will facilitate TB elimination.

LTBI and risk of TB reactivation Prompt identification of population groups at high risk for TB infection or disease is essential for TB control. Certain groups have risk factors for *M.*

tuberculosis exposure, such as those with occupational risks (e.g., health care workers), compromised immune systems (e.g., HIV/AIDS), comorbidities (e.g., diabetes) or toxic behaviors (e.g. tobacco use) that also lead to higher risk for TB infection or reactivation.[8]

Migration from high-burden to low-burden countries Low-incidence countries, which have less active TB transmission than high-incidence countries, have documented TB transmission based on immigration.[8] Migrants may have previous *M. tuberculosis* exposure from their country of origin; their latent infections can progress to active TB disease following a stressful relocation and settlement process, and further increase population risk of exposure.

Delayed identification and treatment of TB cases Delays in health care service delivery to diagnose TB can be attributed to health providers (e.g., medical error) or patients (e.g., reduced health care-seeking behavior due to stigma, mistrust of authorities or lack of service availability or access to health institutions).[18] It is thus essential to avoid missed opportunities to identify TB infection or disease in the general population.

Expertise in TB control Low TB incidence may result in fewer professionals having direct experience with TB, which may lead to gaps in health professions education and training, contributing to medical errors, lapses in infection control practices, or inadequate outbreak control and contact followup.[18] Existence of and adherence to administrative, environmental and respiratory protection controls in *M. tuberculosis* are crucial to reduce nosocomial TB transmission in health institutions.

Type of institution Although UF and IPK are both institutions that focus on scientific advances in clinical and research capacities, they have differing characteristics. UF is a public (state) academic institution of higher learning, forming part of Florida's state university system, and includes SNTC's state and regional scope. IPK is a public (national government) institution, under MINSAP, with academic functions as well as clinical responsibilities at municipal, provincial and national levels.

US embargo against Cuba In 1961, the US Congress passed legislation forbidding assistance to communist countries, including Cuba, and authorized the President to embargo all trade with Cuba. The embargo was formally declared on February 3, 1962 and has since limited direct interactions between the two countries, impeding trade and commerce, economic relations, and aid and development, and making scientific collaboration challenging.[20] Despite such restrictions, academic exchanges in clinical practice and research activities over the past decade have fostered an open scientific dialogue between US and Cuban scientists.

Next steps and recommendations Challenges in TB control encountered in low-incidence countries will continue, so collaborative efforts between the USA and Cuba need to take a holistic approach towards reducing TB burden, emphasizing the importance of understanding all determinants that influence physical and psychosocial health outcomes related to TB, is imperative for clinicians and researchers leading efforts towards TB elimination. Hence, targeted efforts to reduce risk of *M. tuberculosis* transmission can be multidisciplinary in nature in clinical and community settings. Passive and active surveillance of active TB cases can rapidly identify persons with TB infection or disease, reducing diagnostic delay, enabling timely preventive or curative therapy as needed, and increasing the proportion of cases successfully treated. Likewise, rapid identification of social or structural barriers in health care service delivery can improve understanding of TB dynamics and serve to strengthen established TB control policies. Next steps in TB control, incorporating scientific evidence to inform policy, include:

Renewal of political commitment to TB elimination It is essential to understand the structural determinants of TB control based on federal or national policies and directives that drive legal regulations and budget allocation. NTPs require administrative leadership and financial resources to maintain universal access to and availability of TB service delivery in all institutions and communities.

Implementation of new technologies to facilitate TB diagnostics and treatment Development of new technologies, whether in laboratory diagnostics or more effective treatment regimens, is key to prompt diagnosis and treatment of TB infection and disease.

Promotion of sustainable training and evaluation Continued training in basic, clinical and social sciences can advance scientific and social understanding of *M. tuberculosis* and transmission dynamics, yet can be difficult in the face of an epidemic with decreasing incidence rates. Highlighting barriers among health care workers or community members that may hinder components of TB service delivery can support formulation of more efficient designs or alternative approaches for holistic care.

Quality assurance of monitoring and evaluation in TB control Close examination of TB control through monitoring and evaluation procedures can identify poor quality or gaps in practice so that they can be modified. By identifying discrepancies in TB burden among states or provinces, preventive actions and prioritized medical attention can be concentrated on the geographic sites most in need.

Focus on LTBI Current TB control efforts and economic development have helped reduce active TB incidence, but to ultimately eliminate TB, a much greater focus on testing and effective treatment of LTBI is critical. Scaling up LTBI services will require operational and clinical research to inform new policies.

CONCLUSIONS

Countries with low TB incidence, such as the USA and Cuba, have made successful strides in the move to eliminate TB by 2050. Their collaboration can serve as a model for other countries that intend to reach population health targets for TB, improve understanding of TB epidemiology, and strengthen academic capacity-building and training of basic, clinical and social scientists. With close geographic proximity, research capacity and shared health priority for TB elimination, the two nations can collaborate and share clinical, laboratory and community health experiences to accelerate TB elimination throughout the Americas Region.

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