Early Action, Applied Research & Collaboration to Combat COVID-19: María Guadalupe Guzmán MD PhD DSc

Director, Reference Center for Research & Diagnosis, Pedro Kourí Tropical Medicine Institute, Havana

Gisele Coutin MD MS and Conner Gorry MA


E. Añé

Virologist Dr María Guadalupe Guzmán is recognized as a global leader in dengue research and heads the Pedro Kourí Tropical Medicine Institute's work as a WHO/PAHO Collaborating Center for the Study of Dengue and Its Vector. The Institute (IPK) was founded in 1937 and is now Cuba's national reference center for the diagnosis, treatment, control and prevention of communicable diseases. Dr Guzmán is also president of the Cuban Society of Microbiology and Parasitology and directs IPK's Scientific Council, which is responsible for setting the Institute's research priorities. A recent h-index analysis found that Dr Guzmán is among the most widely-published and cited Cuban researchers.

As part of the National Intersectoral Commission for COVID-19, IPK was integral to the design of Cuba's COVID-19 Prevention and Control Plan, approved in February 2020, more than a month before the first cases were confirmed in Cuba. This included the three-tiered biosafety training program for frontline health professionals, designed and launched at IPK, which built on the institution's experience preparing Cuban doctors who served in West Africa with the Henry Reeve Emergency Medical Contingent during the 2014–2016 Ebola outbreak. As of this writing, the Contingent has served in 39 countries fighting COVID-19. Prior to departure, members were trained in biosafety at IPK.

Today, IPK conducts COVID-19 testing and research and provides patient care. The institution is supported by an integrated national network of diagnostic laboratories, hospitals and isolation centers. In addition to research related to the clinical evolution and epidemiology of COVID-19, IPK has several studies under way on its diagnosis, pathogenesis, kinetics, immunity and genetics. In July 2020, Dr Guzmán, along with 7 other Cuban specialists, was appointed to the InterAcademy Partnership's (IAP) COVID-19 Expert Group, a 60-member, multi-disciplinary group comprised of researchers from around the world. The group is designed to promote knowledge sharing and regional and international collaborations concerning the coronavirus using a multisector approach that takes into account the health, social and environmental factors related to the disease. This ***MEDICC Review*** interview took place in early July, a few days before the Cuban IAP appointments were announced.

MEDICC Review: **Latin America has become an epicenter of the COVID-19 pandemic, with some of the highest per capita infection rates in the world. Yet Cuba and Uruguay stand out as examples of containment, with lower rates. What might Cuba's experience offer in this context?**

María Guadalupe Guzmán: The situation in the region is indeed complex, with an alarming rise in confirmed cases and COVID-19 fatalities—according to WHO data as of July 5, Latin America had registered over 5.5 million cases. Cuba took early action with a national plan aimed at controlling SARS-CoV-2 transmission and its impact on the country (between March 11 and September 17, 2020, Cuba administered over 520,000 real-time polymerase chain reaction (RT-PCR) tests, with 5004 people testing positive for COVID-19. Of those, 4249 recovered, 111 died, and 2 were evacuated; 642 cases were still active, Eds).

The main measures contributing to Cuba's more favorable situation as compared to some other countries in the region include: comprehensive stay-at-home messaging and obligatory mask mandates; early hospitalization of people fitting the clinical parameters of possible infection; quarantining people who had

contact with confirmed cases in isolation centers equipped for this purpose; and active screening across the country, including in workplaces and among high-risk groups.

I think Cuba's COVID-19 experience can be useful in the following areas: clinical case management; epidemiological measures designed to identify hot spots and better contain and control transmission; treatment protocols and products developed and produced by Cuba's biotech sector; laboratory diagnostics; and international collaboration—our specialists are serving in many countries where COVID-19 has created complex health situations.

MEDICC Review: **Research is indicating that SARS-CoV-2 is much more contagious than other human coronaviruses including SARS-CoV and MERS-CoV. How is this indicator playing out in Cuba?**

María Guadalupe Guzmán: This virus's highly contagious nature is one reason why COVID-19 has spread so far, so fast and to so many countries. Several articles have described that each infected person can transmit the virus to three more people. Slowing transmission requires lowering the disease's reproduction number (R-value).

Since the first cases in Cuba, scientists here have been working on transmission forecasts using mathematical models based on time-varying reproduction numbers (R_t; effective reproduction). As opposed to R_0, which is the basic reproduction number quantifying a disease's transmission potential at the start of an epidemic, R_t numbers change over time and depend on the population's actual susceptibility to the disease. At the beginning of the epidemic, we were seeing high R_t numbers—near 5, which is consistent with the exponential transmission dynamic seen in other countries. After 15 days, that number steadily dropped to just above 1 and by the seventh week, it fell below the R_t 1 target. This indicator has fluctuated with periodic local transmission events, but once prevention and control measures contain the outbreak, the R_t number falls below 1 again—underscoring the importance of maintaining these measures to slow transmission.

MEDICC Review: **Given how contagious SARS-CoV-2 has proven to be, how is Cuba managing testing, contact tracing and treatment?**

María Guadalupe Guzmán: One fundamental action we've taken is administering and analyzing a large number of tests to identify both symptomatic and asymptomatic cases. (According to the website of Cuba's Ministry of Public Health, between August 17 and September 17, Cuba was processing an average of 6010 RT-PCR tests daily and at the time of this writing had performed 524,374 tests since March, Eds). This allows for early diagnosis, tracing of all available contacts for each confirmed case and remittance to isolation centers.

Applied research from Cuba's biotech sector is another important element. Adding Cuban biotech products to treatment protocols; sample collection; implementing case management policies; and assuring we have the necessary equipment and materials for treating critical patients by switching production lines at some plants to produce personal protective equipment, ventilators and diagnostic kits, are some ways our biotech sector is helping us confront the epidemic.

MEDICC Review: **You mentioned that Cuba performs RT-PCR tests—several thousand a day. Where do these come from and where are they processed? Are labs in Cuba equipped and prepared for this kind of diagnostic load?**

María Guadalupe Guzmán: At the moment our RT-PCR tests are imported, though the Immunoassay Center in Havana (CIE) is working on standardizing a molecular diagnostic kit and several population studies are already underway using the CIE's system for detecting COVID-19 antibodies.

In terms of laboratories diagnosing COVID-19, we currently have 7. Those processing tests for Havana are located at the Provincial Hygiene, Epidemiology and Microbiology Center and the Hermanos Ameijeiras Clinical-Surgical Teaching Hospital, plus the Genetic Engineering and Biotechnology Center (CIGB) and Civil Defense laboratories. The laboratory here at IPK processes tests for the capital, plus the western region of the country, while the Ministry of Public Health's lab in Villa Clara handles testing from Cuba's central region and the one in Santiago de Cuba processes those from the eastern region. Four additional labs are currently being equipped in the provinces for processing tests as well and should be up and running soon. (Two labs, in Holguín and Matanzas provinces, will be operable by the end of September, and the other two, in Ciego de Ávila province and the Isle of Youth, soon thereafter. Since this interview, Havana has added five more labs to process RT-PCR tests, Eds). IPK is charged with evaluating these labs, plus training and assessing the personnel working there.

In addition to training lab personnel to process these tests, IPK evaluates the kits and technologies used in coronavirus diagnosis, as well as the transportation mechanisms used to collect patient samples, the equipment introduced to strengthen case diagnosis, and serological systems used for patient screening. IPK is also responsible for periodic quality control of samples to corroborate results from other laboratories around the country.

MEDICC Review: **Was this all put into place with the advent of COVID-19?**

María Guadalupe Guzmán: No. As a WHO/PAHO Collaborating Center for the Study of Dengue and Its Vector, IPK has a long, strong work history related to the clinical, epidemiological, laboratory, training, entomology-vectors and research components concerning arboviruses. Our collaborating center works on these issues as part of the PAHO-led Integrated Management Strategy for Arboviral Diseases and helped draft several guidelines used regionally today. These include clinical case management for dengue; diagnosis and treatment of patients with possible arbovirus infections; and diagnostic algorithms for laboratory surveillance of dengue, Zika and chikungunya.

In 2008, the Arbovirus Diagnosis Laboratory Network of the Americas (RELDA) was established to strengthen laboratory diagnostic and surveillance capabilities in the region (The WHO/

PAHO Coordinating Center at IPK headed RELDA from 2010–2018, with Dr Guzmán as president, Eds). It's also designed to systematize best practices and foster collaboration among labs in the region. To this end, RELDA holds training courses in new diagnostic technologies, develops protocols and guidelines, coordinates the exchange of reagents between labs, performs serological and molecular proficiency testing to verify the reliability of laboratory diagnostics, standardizes diagnostic systems and more. Today, 32 laboratories in 26 countries are part of this network—many are also WHO/PAHO Collaborating Centers.

> **It's crucial that countries devise strategies for dealing with coexisting dengue and COVID-19 epidemics**

The work creating and strengthening these labs, their infrastructure and training capacities, plus our regional experience with the 2009 flu pandemic, means we were better prepared and equipped to pivot from arboviruses to COVID-19. RELDA and the labs in its network have worked diligently to face this emergency—and laboratory diagnosis of COVID-19 has proven challenging for all countries—without slowing the diagnosis and surveillance of arboviruses. In fact, we're expecting an increase in dengue transmission this year and RELDA has been discussing how to manage both at once. It's crucial that countries devise strategies for dealing with coexisting dengue and COVID-19 epidemics; controlling dengue-related deaths while maintaining measures implemented in recent years to lower dengue fatalities in the midst of COVID-19…it's quite a complex situation.

MEDICC Review: **SARS-CoV-2 has shown to be highly lethal, with a 13% patient fatality rate in some countries and around 6% in Latin America. How has Cuba, with its aging population and heavy chronic disease burden—not to mention the US embargo—been able to keep its rate well below 5%?**

María Guadalupe Guzmán: I think early action is one of the main factors. Active screening in neighborhoods everywhere in the country, along with hospitalization of all suspected cases and timely attention to them—in health institutions with separate areas specially equipped and staffed—has helped us keep fatality rates here below 5%. Application of different treatment protocols, which are showing good results, is another factor. Our health messaging strategy, alerting and keeping the population informed, and their collaboration in active screening is one more. Staying informed about COVID-19 and continuing to observe health measures, including using masks, is imperative.

It's important to underscore the role of our primary care system in this regard. Primary care professionals here are community-based, have direct contact with the people they serve in the neighborhoods where they live, and are actively looking for and diagnosing cases.

MEDICC Review: **Cuba's biotech products and treatment protocols are showing good results, as you mentioned. As part of the team that sets IPK's research priorities, what is the Institute's research agenda for COVID-19?**

María Guadalupe Guzmán: IPK is pursuing several research initiatives, including in the following areas:

- COVID-19 etiology;
- Morphology of SARS-CoV-2 (in collaboration with CEAC);
- Nucleotide sequence (whole genome) and molecular characterization;
- Viral shedding kinetics in clinical samples; Ultrastructural tissue damage, identifying immunological biomarkers associated with severe clinical prognosis, immune system response associated with protection/severity, and genetic and epigenetic influences on the progression of the infection (in collaboration with CEAC);
- Evaluation of reagents, materials and equipment (in collaboration with the National Biopreparations Center, BIOCEN, as well as MEDICUBA and the National Biomedical Engineering Center);
- Evaluation of serologic diagnostic kits and PCR tests (in collaboration with the Immunoassay Center; CIE);
- Development of a biosensor to diagnose COVID-19 in cooperation with the Cuban Center for Advanced Studies (CEAC);
- Epidemiological studies of asymptomatic infections, outbreaks themselves, and socioeconomic factors related to the disease; and
- Clinical characterization of critical and non-critical patients, and clinical follow-up of symptomatic and asymptomatic patients.

Several of these research avenues are already showing results. We've characterized the clinical features of the first COVID-19 patients in Cuba, identified the immunological biomarkers for disease severity, and have a deeper understanding of those patients and asymptomatic carriers who maintain positive RT-PCR tests over time. We've also evaluated serologic diagnostic kits, including those produced in Cuba using UMELISA technology, currently in use in screening studies.

MEDICC Review: **Cuba is known globally for its overseas medical cooperation, while IPK is known for its biennial International Course on Dengue, Zika and Other Emerging Arboviruses. How important is cooperation—locally, regionally, internationally—in fighting COVID-19?**

María Guadalupe Guzmán: The role of international organizations like PAHO and WHO cannot be overstated. From best practices and recommendations for confronting the epidemic to donations of reagents and materials, their collaboration has been fundamental. Other organizations including the Global Fund and MediCuba Europe have also provided necessary support.

Also important is participation in thematic networks to exchange ideas, such as those organized by the Community of Latin

American and Caribbean States (CELAC), the International Association of National Public Health Institutes (IANPHI) and the Ibero-American Science and Technology for Development Program (CYTED).

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I also see a broad range of opportunities for collaboration between Cuba and the United States. Exchanging findings on each country's COVID-19 policies and lessons learned—what has worked and what hasn't—is one place to start. Sharing clinical case experiences and the use of different treatment protocols is another. Joint research to develop a better diagnostic kit or vaccine, to deepen our understanding of the disease and its viral agent or effective prevention measures…these are all potential areas for collaboration, as is joint publishing on findings. Even global medical cooperation, in which Cuba has vast experience, could be on the table.

For more on the research, clinical practices and diagnostic systems of the Pedro Kourí Tropical Medicine Institute (IPK), see Cuba's Pedro Kourí Tropical Medicine Institute: Battling COVID-19 One Study, One Test, One Patient at a Time, in MEDICC Review April 2020, Vol 22, No 2.

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